CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **21-196**

Submission Date: **10/5/01,**

OCPB Receipt Date: **10/12/01**

Drug:	**Xyrem (γ-hydroxybutyrate; sodium oxybate, GHB)**
Strength(s):	**500 mg/ml oral solution**
Indication:	**Cataplexy, Narcolepsy**
Applicant:	**Orphan Medical, Inc., Minnetonka, Minnesota**
Type:	**'1P' NDA**
Date of Review:	**2/28/02**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**

Background and Summary of Current Submission:

Orphan Medical, Inc. is seeking approval of Xyrem for the treatment of cataplexy attacks, resulting from patients with narcolepsy. Xyrem is an oral solution that is a neuroactive agent with a variety of CNS pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a GHB receptor and possesses neuromodulatory properties with significant effects on dopamine and GABA. As a result, studies have suggested that sodium oxybate improves REM sleep of narcoleptics in contrast to the antidepressant drugs. The recommended starting dose is 4.5 grams divided into 2 equal doses of 2.25 grams, the first taken at bedtime and the second taken 2.5-4 hours later while sitting in bed. The starting dosage can be decreased to 3.0 g/d or increased to as high as 9.0 g/d in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and to minimize side effects.

Based on *in vitro studies*, the inhibitory potential of GHB on CYP450 isozymes was tested across a concentration range of 3 – 300 μM. The IC_{50} was determined to be greater than 300 μM (37.8 μg/ml) from these studies. Plasma concentrations that were achieved clinically following a dose of 4.5 g were approximately 100 μg/ml. Thus, further studies were requested by the Agency in order to assess completely the entire concentration range observed clinically. The original NDA was granted an approvable status on 7/2/01. This submission is a response to one of the Clinical Pharmacology deficiencies identified at that time. The other Clinical Pharmacology deficiencies will be addressed as Phase IV commitments following approval of the drug. The results of the additional study are as follows:

1. *In Vitro* Studies

Title: Inhibitory Potential Of γ-Hydroxybutyrate (GHB) Towards Human Hepatic Microsomal Cytochrome P450 Isozymes.

Objective:

The goal of this study was to determine the potential inhibitory activity of GHB on various CYP450 enzymes *in vitro*.

Study Design and Methods:

Briefly, pooled, human liver microsomes from ten individuals were obtained [redacted] The activity of each isozyme was determined in the presence (concentrations ranging from 300 – 3000 μM) and absence of GHB. The positive control inhibitors used for each isozyme included 100 nM α-naphthoflavone for CYP1A2, 5 μM sulfaphenazole for CYP2C9, 60 μM tranylcypromine for CYP2C19, 0.75 μM quinidine for CYP2D6, 100 μM diethyldithiocarbamate for CYP2E1, and 100 μM troleandomycin for CYP3A.

Results:

Table 1: Inhibitory Potential of Xyrem on Various CYP450 Enzymes.

Assay	P450 Isoenzyme	IC_{50} (μM)
7-Ethoxyresorufin O-deethylase	CYP1A2	>3000
Tolbutamide 4-methyl hydroxylase	CYP2C9	>3000
S-Mephenytoin 4'-hydroxylase	CYP2C19	>3000
Dextromethorphan O-demethylase	CYP2D6	>3000
p-Nitrophenol hydroxylase	CYP2E1	>3000
Erythromycin N-demethylase	CYP3A	>3000

For all of the CYP450 enzymes, the GHB concentration needed to inhibit 50% of the enzyme activity exceeded 3000 μM (378 μg/ml).

Conclusion:

Following a dose of 4.5 g (highest to be marketed dose), plasma concentrations of Xyrem are approximately 100 μg/ml. Thus, it appears that Xyrem will not inhibit any of the CYP450 enzymes (1A2, 2C9, 2C19, 2D6, 2E1, and 3A) at concentrations that will be achieved clinically.

Recommendation:

The information supporting the lack of inhibitory potential of GHB on various CYP450 isozymes is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. These findings should be incorporated into the proposed labeling. In addition, the labeling comments are attached at the end of this review. The sponsor is advised to incorporate the proposed labeling changes under the following sections of the label.

Gerald J. Fetterly, Ph.D. _____

RD/FT Initialed by Vanitha Sekar, Ph.D. _____

cc: NDA 21,196, HFD-120 (Harmonnay), HFD-860 (Mehta, Uppoor, Sekar, Fetterly), Central Document Room (Clin. Pharm./Biopharm. File)

2. OCPB Labeling Comments.

R_x only

CIII

Xyrem® (sodium oxybate) oral solution

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5-1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7 fold as dose is doubled from 4.5 to 9 grams. The pharmacokinetics are not altered with repeat dosing.

Absorption

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%. The average peak plasma concentrations (1^{st} and 2^{nd} peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 micrograms/ml respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increased more than proportionally with increasing dose. Single doses greater than 4.5 grams have not been studied. Administration of sodium oxybate immediately after a high fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (C_{max}) by a mean of 58% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190-384 ml/kg. At sodium oxybate concentrations ranging from 3 to 300 micrograms/ml, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyses the conversion of sodium oxybate to

succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyses the conversion to succinic semialdehyde in the presence of alpha-ketoglutarate. An alternate pathway of biotransformation involves beta-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 micrograms/ml). These levels are considerably higher than levels achieved with therapeutic doses.

Elimination.

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

Special Populations

Geriatric

The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.

Pediatric

The pharmacokinetics of sodium oxybate in pediatric patients under the age of 18 years have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 grams.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic Disease

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites, (Child's Class A) and half with ascites (Child's Class C) were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 ml/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean $T_{½}$ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (see Dosage and Administration).

Drug-Drug Interaction

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out.

INDICATIONS AND USAGE

Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy.

In Xyrem clinical trials approximately 80% patients maintained concomitant stimulant use (see BLACK BOX WARNINGS).

CONTRAINDICATIONS

Sodium oxybate is contraindicated in patients being treated with sedative hypnotic agents,

Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism.

PRECAUTIONS

Sodium Intake

Daily sodium intake in patients taking sodium oxybate ranges from 0.5 g (for a 3 g sodium oxybate dose) to 1.6 g (for a 9 g sodium oxybate dose). This should be considered in patients with heart failure, hypertension or compromised renal function.

Hepatic Insufficiency

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate (see **Pharmacokinetics** The starting dose should therefore be decreased by one-half, and response to dose increments monitored closely (see Dosage and Administration).

Renal Insufficiency

No studies have been conducted in renal failure . Because less than 5% of sodium oxybate is excreted via the kidney, no dose adjustment should be necessary in patients with renal impairment. The sodium load associated with administration of sodium oxybate should be considered in patients with renal insufficiency.

Information for Patients

Drug Interactions

Interactions between sodium oxybate and three drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline HCl, and modafinil) have been evaluated in formal studies. Sodium oxybate, in combination with these drugs, produced no significant pharmacokinetic changes for either drug (see **Pharmacokinetics and Metabolism**). However, pharmacodynamic interactions cannot be ruled out. Nonetheless, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

DOSAGE AND ADMINISTRATION

Because food significantly reduces the bioavailability of sodium oxybate, consistent timing of dosing with relation to food is advised for each patient to minimize variability in response **(see Pharmacokinetics and Metabolism). Whether sodium oxybate is taken in the fed or fasted state may affect both its efficacy and safety.**

Xyrem is required to be taken at bedtime and again 2.5-4 hours later. The recommended starting dose of Xyrem 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 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.

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.

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

/s/

Gerald Fetterly
3/5/02 04:15:29 PM
BIOPHARMACEUTICS

Vanitha Sekar
3/5/02 04:20:47 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860)** **Tracking/Action Sheet for Formal/Informal Consults**

n: Gerald Fetterly, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND submission**	
DATE: **6/29/01**	IND No.: Serial No.:	NDA No. **21-196**	DATE OF DOCUMENT **5/4/01**	TREATMENT **Cataplexy**
NAME OF DRUG **GHB (Xyrem) Oral Solution**	PRIORITY CONSIDERATION		Date of Formal Consult: **5/6/01** JUN 29 2001	

NAME OF THE SPONSOR: Orphan Medical, Inc. IO COMPLETED JUN 29 2001

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
- ☐ PHASE III PROTOCOL
- ☐ DOSING REGIMEN CONSULT
- ☐ PK/PD- POPPK ISSUES
- ☐ PHASE IV RELATED
- ☐ DISSOLUTION/IN-VITRO RELEASE
- ☐ BIOAVAILABILITY STUDIES
- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☐ OTHER *(SPECIFY BELOW)*:

Response to Biopharmaceutics Question Conveyed to Sponsor

REVIEW ACTION

- ☒ NAI (No action indicated)
- ☐ E-mail comments to:

☐Medical ☐Chemist ☐Pharm-Tox ☐ Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)

- ☐ Oral communication with Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]
- ☐ Formal Review/Memo (attached)
- ☐ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor has responded to the agency's question about ascertaining the potential pharmacodynamic interactions in narcoleptic patients with other commonly used drugs in this patient population, such as methylphenidate. As a result, OMC-GHB-2 was the only controlled trial where the patients maintained stable doses of stimulants. The sponsor's analysis of the data concluded that 85% of the patient population were on stable stimulant doses. Since 85% of the patients with cataplexy in the sponsor's major clinical trial (OMC-GHB-2) were on chronic stimulant therapy, the potential for pharmacodynamic interactions between GHB and concomitant medications cannot be ruled out.

SIGNATURE OF REVIEWER: /S/ Date 6/29/01

SIGNATURE OF TEAM LEADER: /S/ Date 6/29/01

CC.: NDA 21-196; HFD-120; TL: R. Uppoor; DD: M. Mehta
ıtral Document Room (Clin. Pharm./Biopharm. Files)

Project Manager: _____ **Date** _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860)** **Tracking/Action Sheet for Formal/Informal Consults**

m: Gerald Fetterly, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND submission**	
DATE: **6/29/01**	IND No.: Serial No.:	NDA No. **21-196, SN 058**	DATE OF DOCUMENT **4/19/01**	TREATMENT **Cataplexy**
NAME OF DRUG **GHB (Xyrem) Oral Solution**	PRIORITY CONSIDERATION		Date of Formal Consult: **4/23/01**	JUN 29 2001

NAME OF THE SPONSOR: Orphan Medical, Inc. COMPLETED JUN 29 2001

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- ☐ PRE-IND
- ☐ ANIMAL to HUMAN SCALING
- ☐ IN-VITRO METABOLISM
- ☐ PROTOCOL
- ☐ PHASE II PROTOCOL
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- ☐ PK/PD- POPPK ISSUES
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- ☐ IN-VIVO WAIVER REQUEST
- ☐ SUPAC RELATED
- ☐ CMC RELATED
- ☐ PROGRESS REPORT
- ☐ SCIENTIFIC INVESTIGATIONS
- ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ ANNUAL REPORTS
- ☐ FAX SUBMISSION
- ☐ OTHER *(SPECIFY BELOW)*:

Response to Biopharmaceutics Question Conveyed to Sponsor

REVIEW ACTION

- ☒ NAI (No action indicated)
- ☐ E-mail comments to:

☐Medical ☐Chemist ☐Pharm-Tox ☐ Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)

- ☐ Oral communication with Name: [ ]
- ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]
- ☐ Formal Review/Memo (attached)
- ☐ See comments below
- ☐ See submission cover letter
- ☐ OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor has provided an explanation regarding the agency's question on the identical precision and accuracy observed in the three drug interaction studies. For clarification, the values obtained during the analyses of each study were similar but not identical in these three studies (See Attached Table 1). With respect to the method validation for GHB, a single report was prepared to describe the validation of the — assay used in all three studies to measure GHB. This response is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

SIGNATURE OF REVIEWER: /S/ Date 6/29/01

SIGNATURE OF TEAM LEADER: /S/ Date 6/29/01

CC.: NDA 21-196; HFD-120; TL: R. Uppoor; DD: M. Mehta
Central Document Room (Clin. Pharm./Biopharm. Files)

Project Manager: _____ **Date** _____

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860)** **Tracking/Action Sheet for Formal/Informal Consults**

m: Gerald Fetterly, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND submission**	
DATE: **6/28/01**	IND No.: Serial No.:	NDA No. **21-196, SN 056**	DATE OF DOCUMENT **4/11/01**	TREATMENT **Cataplexy**
NAME OF DRUG **GHB (Xyrem) Oral Solution**	PRIORITY CONSIDERATION		Date of Formal Consult: **4/12/01**	JUN 29 2001

NAME OF THE SPONSOR: Orphan Medical, Inc.

ID COMPLETED JUN 29 2001

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
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☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: Response to Biopharmaceutics Question Conveyed to Sponsor
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)		☐ See submission cover letter
		☐ OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

As a result of the food effect on the bioavailability of GHB, we requested that the sponsor submit the calorie intake and food content of all meals consumed in the pharmacokinetic studies in order to support labeling recommendations about drug administration. The sponsor has stated that in the six studies conducted in healthy volunteers, subjects were fed in the same sequence and interval at which they were dosed. In all studies involving either multiple cohorts or crossover designs, the same menu was used for each period within a given study (See Attachments). Thus, food consumption effected the bioavailability of GHB in each pharmacokinetic study. As a result of these findings, administration of Xyrem should be conducted in the fasted state in order to maximize efficacy or at least consistently (with or without food for both doses) throughout the treatment period.

SIGNATURE OF REVIEWER: /S/	Date 6/29/01
SIGNATURE OF TEAM LEADER: /S/	Date 06/29/01
cc: NDA 21-196; HFD-120; TL: R. Uppoor; DD: M. Mehta **Central Document Room (Clin. Pharm./Biopharm. Files)**	**Project Manager:** _____ **Date**

Food Consumption in All Pharmacokinetic Studies.

OMC-SXB-8 (Gender Study):

Subjects were dosed beginning at 8 pm (20:00hr) two hours after a dinner beginning at 6 pm (18:00hr) and consisting of:

Hamburger patty (3 oz. ground beef)		- 240 cal
Hamburger bun		- 123
Lettuce, tomato, condiments (est.)		- 80
Pasta salad, ½ cup		- 189
Caffeine-free soda, 12 oz.		- 150
	Total	782 cal

The following morning at 7 am (07:00) a light breakfast was offered consisting of:

One apple, raw, medium		- 81 cal
Milk, whole, 8 oz.		- 150
	Total	- 231 cal

OMC-SXB-9 (Dose Proportionality Study):

Subjects were dosed beginning at 8 pm (20:00hr) two hours after a dinner beginning at 6 pm (18:00hr) and consisting of:

Hamburger patty (3 oz. ground beef)		- 240 cal
Hamburger bun		- 123
Lettuce, tomato, condiments (est.)		- 80
Pasta salad, ½ cup		- 189
Caffeine-free soda, 12 oz.		- 150
	Total	782 cal

The following morning at 7 am (07:00) a light breakfast was offered consisting of:

One apple, raw, medium		- 81 cal
Milk, whole, 8 oz.		- 150
	Total	- 231 cal

OMC-SXB-10 (Acute vs Chronic Study in Patients):

The same standardized dinner was given to the patients prior to both the acute and 8 week test doses of Xyrem. The dinner was given beginning at 8 pm (20:00) two hours prior to beginning dosing at 10 pm (22:00). The dinner consisted of:

KFC fried chicken, breast or leg & thigh	- 400
Mashed potatoes & gravy, 1 serving	- 120
Cole slaw, 1 serving	- 180
Biscuit, 1 w/butter	- 180
Total	880 cal

OMC-SXB-11 (Food Effect Study)

A snack consisting of a cinnamon roll (300 cal) and 8 oz. of whole milk (150 cal) was given at 9 pm (21:00hr) the evening before dosing the next morning beginning at 7 am (07:00hr). On the study day when the high fat meal (breakfast) was served, the meal began at 6:30 am (06:30hr) thirty minutes prior to dosing and was consumed within 15 minutes. The meal consisted of:

2 eggs fried in butter	- 184 cal	14g fat
2 strips of bacon	- 72	6g
4 oz. hash browns, fried	- 160	11g
2 slices white toast, buttered	- 220	8g
8 oz. whole milk	- 150	8g
8 oz. orange juice	- 110	0
Total	896 cal	47g fat

Beginning at 11 am (11:00hr) after the 4 hour blood draw, the subjects were given lunch which consisted of:

Smoked turkey croissant sandwich	- 372 cal
Soup, chicken noodle, 1.5 cup	- 195
Caffeine-free soda, 12 oz.	- 150
Total	717 cal

OMC-SXB-12 (Zolpidem Interaction Study):

A snack was offered at 9 pm (21:00hr) the night before dosing at 7 am (07:00hr) the following morning while fasted overnight. The snack consisted of one vanilla pudding cup (130 cal), a fruit bar (140 cal) and 8 oz of whole milk (150 cal). Four hours after (7am) dosing, lunch was served beginning at 11 am (11:00hr) consisting of the following:

Lasagna, w/meat, ~12 oz.		- 530 cal
Scalloped potatoes, ~1 cup		- 211
Lettuce salad w/dressing		- 90
Roll w/butter		- 140
8 oz. fruit punch		- 110
	Total	1081

Dinner was given beginning at 5 pm (17:00hr) and consisted of:

Smoked turkey croissant sandwich		- 272 cal
Potato chips, 1 oz. bag		- 150
Caffeine-free soda, 12 oz.		- 150
	Total	572 cal

OMC-SXB-14 (Protriptyline Interaction Study):

A snack was offered at 10 pm (22:00hr) the night before dosing. The snack consisted of one vanilla pudding cup (130 cal), a fruit bar (140 cal) and 8 oz of whole milk (150 cal). At 6 am (06:00hr) a light breakfast was served two hours before dosing at 8 am (08:00)hr). This consisted of:

One cinnamon roll		- 300 cal
8 oz. whole milk		- 150
	Total	450 cal

Five hours after the first (8am) dosing and one hour after the second (12 noon) dosing, if applicable, lunch was served beginning at 1 pm (13:00hr) consisting of the following:

Lasagna, w/meat, ~12 oz.		- 530 cal
Scalloped potatoes, ~1 cup		- 211
Lettuce salad w/dressing		- 90
Roll w/butter		- 140
8 oz. fruit punch		- 110
	Total	1081

Dinner was given beginning at 5 pm (17:00hr) and consisted of:

Smoked turkey croissant sandwich		- 272 cal
Potato chips, 1 oz. bag		- 150
Caffeine-free soda, 12 oz.		- 150
	Total	572 cal

OMC-SXB-17 (Modafinil Interaction Study):

A snack was offered at 9 pm (21:00hr) the night before dosing at 7 am (07:00hr) the following morning while fasted overnight. The snack consisted of one vanilla pudding cup (130 cal), a fruit bar (140 cal) and 8 oz of whole milk (150 cal). Four hours after (7am) dosing, lunch was served beginning at 11 am (11:00hr) consisting of the following:

Lasagna, w/meat, ~12 oz.		- 530 cal
Scalloped potatoes, ~1 cup		- 211
Lettuce salad w/dressing		- 90
Roll w/butter		- 140
8 oz. fruit punch		- 110
	Total	1081

Dinner was given beginning at 5 pm (17:00hr) and consisted of:

Smoked turkey croissant sandwich		- 272 cal
Potato chips, 1 oz. bag		- 150
Caffeine-free soda, 12 oz.		- 150
	Total	572 cal

COMPLE... MAR 27 2001

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

MAR 27 2001

General Information About the Submission

	Information		Information
NDA Number	21-196	**Brand Name**	Xyrem
OCPB Division (I, II, III)	DPE 1	**Generic Name**	Sodium Oxybate
Medical Division	Neuropharmacology	**Drug Class**	
OCPB Reviewer	Gerald Fetterly	**Indication(s)**	Narcolepsy, Cataplexy
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Solution (500 mg/ml)
		Dosing Regimen	Starting dose: 4.5 g/day. 3, 4.5, 6, 7.5 and 9 g/day divided into 2 equal doses administered 4 h apart.
Date of Submission	9/30/00	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	3/12/00	**Sponsor**	Orphan Medical, Inc.
PDUFA Due Date	4/2/00	**Priority Classification**	P – 6 month
Division Due Date			

A. Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	No			
Isozyme characterization:	X	1	1	cP450 Inhibition Studies
Blood/plasma ratio:	N/A			
Plasma protein binding:	X			Literature data
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	No			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3	3	
In-vivo effects of primary drug:	X	3 (same as above)	3 (same as above)	
In-vitro:	No			
Subpopulation studies -				
ethnicity:	No			
gender:	X			Data is encompassed within studies
pediatrics:	No			
geriatrics:	No			
renal impairment:	N/A			
hepatic impairment:	X	1	1	Literature Data
PD:				

Phase 2:	X			Dose/Clinical Response (4 studies were submitted in the Clinical Section)
Phase 3:	X			
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:	No			
Phase 3 clinical trial:	No			
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:	No			
Data sparse:	No			
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	No			
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:	X			Solution is also the test formulation.
Alternate formulation as reference:	N/A			
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:	N/A			
replicate design; single / multi dose:	N/A			
Food-drug interaction studies:				
Dissolution:	N/A			
(IVIVC):	N/A			
Bio-wavier request based on BCS	N/A			
BCS class	N/A			
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:	N/A			
Chronopharmacokinetics	N/A			
Pediatric development plan	N/A			
Literature References	X			
Total Number of Studies	[redacted]	10	10	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	A mass balance study was not performed. The sponsor suggests that a radiolabeled mass balance and metabolic fate study in human volunteers would be unethical due to the possibility of the radiolabel becoming incorporated into the amino acid pool.
QBR questions (key issues to be considered)		1. What is the effect of food on the pharmacokinetics of GHB? As a result, does the timing of administration following food intake influence the bioavailability of the drug. 2. What is the effect of Hepatic Impairment on the pharmacokinetics of GHB? 3. What is the effect of antacid administration on the bioavailability of GHB?
Other comments or information not included above		
Primary reviewer Signature and Date		/S/ 3/26/01
Secondary reviewer Signature and Date		/S/ - 03/26/01

CC: NDA 21-196, HFD-850(Electronic entry - Lee), HFD-120(CSO: Homonnay), HFD-860(Uppoor, Mehta), CDR(Clin. Pharm./Biopharm)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **21-196**

Submission Dates: **9/30/00,**
10/13/00,
12/7/00

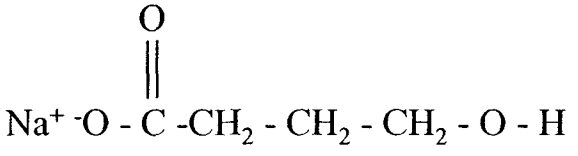
OCPB Receipt Dates: **11/1/00**
12/18/00

Drug:	**Xyrem (γ-hydroxybutyrate; sodium oxybate, GHB)**
Strength(s):	**500 mg/ml oral solution**
Indication:	**Cataplexy, Narcolepsy**
Applicant:	**Orphan Medical, Inc., Minnetonka, Minnesota**
Type:	**'1P' NDA**
Date of Review:	**3/12/01**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**

Table of Contents.

Executive Summary:

Orphan Medical, Inc. is seeking approval of Xyrem for the treatment of cataplexy attacks, resulting from patients with narcolepsy. Xyrem is an oral solution that is a neuroactive agent with a variety of CNS pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a GHB receptor and possesses neuromodulatory properties with significant effects on dopamine and GABA. As a result, studies have suggested that sodium oxybate improves REM sleep of narcoleptics in contrast to the antidepressant drugs. The recommended starting dose is 4.5 grams divided into 2 equal doses of 2.25 grams, the first taken at bedtime and the second taken 2.5-4 hours later while sitting in bed. The starting dosage can be decreased to 3.0 g/d or increased to as high as 9.0 g/d in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and to minimize side effects.



γ-hydroxybutyrate (GHB) has high aqueous solubility (500 mg/ml) and its chemical structure (shown above) possesses acidic components. As a result, the drug is ionized in the GI tract, which may explain the erratic absorption observed in the clinical trials. The intake of food can have a pronounced effect on the absorption of the drug by altering the pH of the GI tract.

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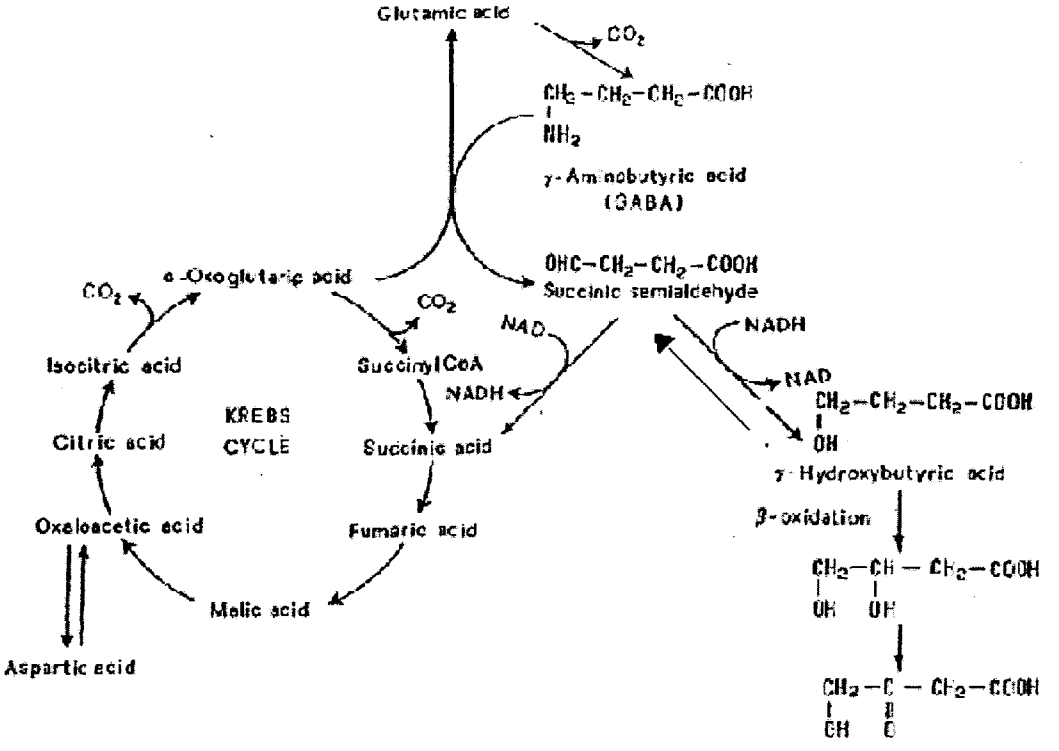
Figure 1. Biosynthesis and Metabolism of GHB.



Several studies in the literature have shown that GHB has a high first pass effect following oral administration, resulting in poor bioavailability (F) of 30%. In the liver, GHB primarily is metabolized by two pathways. The principal biotransformation pathway involves the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid (TCA) cycle. Oxybate also can be metabolized through β-oxidation. Following metabolism, the ultimate form is CO_2 in expired air. When GHB is administered exogenously, the liver is responsible for metabolizing 90% of the drug while less than 10% is excreted in the urine. As a result of the body internally catabolizing GHB, no mass balance studies were performed. In addition, the drug is not bound to plasma proteins.

In the NDA, the applicant conducted 8 pharmacokinetic studies in drug development Phases 1-2 following oral administration of GHB. These studies included single dose studies in healthy volunteers and narcoleptic patients, a food effect study, and three drug interaction studies with Ambien (zolpidem), Vivactil (protriptyline), and Provigil (modafinil). In addition, *in vitro* inhibition studies of CYP450 isozymes and a published article in patients with hepatic impairment were submitted. This NDA also included pivotal clinical trials to ascertain the safety and efficacy of GHB in narcoleptic patients with cataplexy.

Following oral administration of 4.5 g of GHB in both normal volunteers and narcoleptic patients, single-dose studies revealed a wide variability in pharmacokinetic parameters. Mean C_{max} ranged from 85 –146 μg/ml and mean AUC ranged from 226 – 302 μg-h/ml. When 3 g of the drug was administered, C_{max} was approximately 84 μg/ml

compared with healthy volunteers. In cirrhotic patients without ascites, C_{max} and AUC increased by 1.5- and 2-fold. The apparent oral clearance decreased 2-fold and the percent of administered dose recovered in urine was doubled. In patients with ascites, the total systemic exposure (AUC) doubled and CL_{po} decreased 2-fold. $T_{1/2}$ and MRT increased by more than 2-fold. The results of this study suggest that dose adjustment is warranted in patients that are hepatically impaired.

Based on the results of the clinical studies, three doses (3, 6, and 9g) of Xyrem were considered to be effective in decreasing the incidence of cataplexy attacks. The sponsor has suggested that the starting dose would be 4.5 g divided into two equivalent doses 4 h apart. But, a wide range of variability in the clinical outcomes was observed hindering the overall effect of the drug.

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General Comments.

1. The clinical study database should be investigated to ascertain potential pharmacodynamic interactions in narcoleptic patients with other drugs, such as methylphenidate.
2. In the food effect study, the data showed that food has a significant effect on GHB bioavailability and that considerable absorption is occurring up to 4 h following administration of the drug. This pronounced effect of food on the bioavailability of GHB suggests that timing of food intake relative to administration is crucial in obtaining the maximum bioavailability of the drug. In addition, the pharmacokinetic parameters were quite variable across studies. This variability could be explained by differences in meal content and timing in relation to drug administration. As a result, information in the clinical database that is associated with calorie intake, fat content of food, and timing of meals should be provided in order to determine appropriate labeling recommendations with respect to food consumption.
3. As a result of the food effect on the bioavailability of GHB, calorie intake and food content of all meals consumed in the pharmacokinetic studies should be provided in order to support labeling recommendations about drug administration.
4. The results of the hepatic impairment study suggested that the GHB dose should be decreased by one-half in this patient population, which should be reflected in the labeling.
5. Although no pharmacokinetic drug interactions were observed with the drugs studied in this submission, a pharmacodynamic interaction cannot be ruled out especially when GHB is administered at a daily dose of 9 g/day. This information should be incorporated into the labeling.
6. The sponsor should provide information on the assay performance/validation for GHB in the 3 drug interaction studies. Current submissions showed identical precision and accuracy information in all 3 studies, which is highly unlikely.

Phase IV Recommended Studies:

7. Drug interaction studies with pharmaceutical agents that alter gastric pH, such as antacids, proton-pump inhibitors, and H-2 blockers, should be performed since GHB is ionized in the GI tract, which may affect the bioavailability of the drug.
8. Xyrem appears to not inhibit any of the CYP450 enzymes at the concentrations tested up to 300 μM (38 μg/ml). Clinically, plasma concentrations that were achieved following a dose of 4.5 g exceeded 100 μg/ml. Thus, further studies should be performed to ensure proper coverage of the entire clinical plasma concentrations achieved following administration of the drug.

Recommendations.

The pharmacokinetic studies provided an understanding of the systemic exposure of γ-hydroxybutyrate and are considered acceptable for this NDA from the Clinical Pharmacology and Biopharmaceutics view provided the sponsor adequately addresses the general and labeling comments. In addition, the sponsor needs to make commitments to conduct the above recommended studies (Phase IV/post-approval). The General

Comments given above and the Labeling Comments (p. 55) should be conveyed to the sponsor.

Gerald J. Fetterly, Ph.D. /S/ 3/26/01

RD/FT Initialed by Ramana Uppoor, Ph.D. /S/ 3/26/01

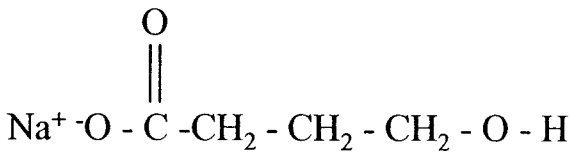
CC: NDA 21-196, HFD-120, HFD-850 (PLee, LLesko), HFD-860 (Mehta, Uppoor, Fetterly), CDR(Clin. Pharm./Biopharm.)

Question Based Review

A. What Are The Highlights Of The Chemistry And Physicochemical Properties Of The Drug?

Structure

The chemical name for sodium oxybate is γ-hydroxybutyric acid (GHB), sodium. The molecular formula is $NaC_4H_7O_3$ and the molecular weight is 126.1 grams/mole. The chemical structure is:



Formulation

Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem oral solution contains 500 mg of sodium oxybate per milliliter of USP purified water, neutralized to pH 7.5 with malic acid.

B. What Is The Proposed Mechanism Of Action And Therapeutic Indication?

Xyrem is a neuroactive agent with a variety of CNS pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a GHB receptor and possesses neuromodulatory properties with significant effects on dopamine and GABA. As a result, studies have suggested that sodium oxybate improves REM sleep of narcoleptics in contrast to the antidepressant drugs. The proposed indication for Xyrem is to reduce the incidence of cataplexy and improve daytime sleepiness in patients with narcolepsy.

C. What Is the Proposed Dosage Regimen?

The recommended starting dose is 4.5 g divided into 2 equal doses of 2.25 g, the first taken at bedtime and the second taken 2.5-4 h later while sitting in bed. The starting dosage can be decreased to 3.0 g/d or increased to as high as 9.0 g/d in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and to minimize side effects.

I. Clinical Pharmacology

A. What Were the Clinical Endpoints Measured?

The clinical endpoint measured was the total number of cataplexy attacks which is the sum of complete and partial cataplexy attacks that occurred. Other efficacy measures such as daytime sleepiness and improvement in inadvertent naps were measured along with reduction in the number of episodes of cataplexy attacks.

not be apparent based on the short half life of the drug. In these studies, AUC also increased disproportionately from 296 – 518 μg-h/ml. This information also may provide evidence of nonlinear absorption and elimination, or a possible food effect since a light meal was administered within 2 h of dosing in some studies.

Metabolism

In the liver, GHB primarily is metabolized by two pathways. The principal biotransformation pathway involves the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid (TCA) cycle. Oxybate also can be metabolized through β-oxidation. Following metabolism, the ultimate form is CO_2 in expired air. When GHB is administered exogenously, the liver is responsible for metabolizing 90% of the drug while less than 10% is excreted in the urine. As a result of the body internally catabolizing GHB, no mass balance studies were performed. In addition, the drug is not bound to plasma proteins.

Elimination

Across all the studies, the terminal $t_{1/2}$ ranged from ——— Following oral administration of 4.5 g of GHB in both normal volunteers and narcoleptic patients, single-dose studies revealed a wide variability in pharmacokinetic parameters. C_{max} ranged from ——— and AUC ranged from ——— When 3 g of the drug was administered, C_{max} was approximately 84 μg/ml while AUC was 136 μg-h/ml. This disproportional increase in AUC with respect to dose suggests nonlinear elimination of the drug.

What is the effect of Food on the pharmacokinetics of GHB?

Across all of the studies, GHB concentration-time profiles in various patients revealed two peaks, supporting nonlinear or site-specific absorption of the drug. The results of the effect of food on the bioavailability of GHB showed that C_{max} and AUC_{inf} decreased by 59% and 37%, respectively. Absorption of sodium oxybate appeared to be slower following food consumption, resulting in a later t_{max} of 2.00 hr compared to 0.75 hr. The data showed that considerable absorption is occurring up to 4 h following administration of the drug. This pronounced effect of food on the bioavailability of GHB suggests that timing of food intake relative to administration is crucial in obtaining the maximum bioavailability of the drug. As a result of this effect on the oral absorption of GHB, the drug should not be taken with food.

In addition, the pharmacokinetic parameters were quite variable across studies. This variability could be explained by differences in meal content and timing in relation to drug administration. Thus, further studies may need to be performed to assess the pharmacokinetic differences of GHB that are associated with calorie intake and fat content of food.

Do drug interactions exist between GHB and commonly administered drugs in the treatment of narcolepsy?

Potential pharmacokinetic interactions were investigated between GHB and commonly administered drugs for the treatment of narcolepsy. These drugs included Ambien (zolpidem; hypnotic), Vivactil (protriptyline; tricyclic antidepressant), and

Provigil (modafinil; stimulant). The results of all these studies revealed no clinically significant alteration in both C_{max} and AUC of GHB or the other drug in that particular study. These results were not surprising based on the metabolic profile of GHB. Thus, the sponsor has shown no drug interaction from a pharmacokinetic view. However, pharmacodynamic interactions cannot be ruled out.

Is there a gender effect on the pharmacokinetics of GHB?

Following a single 4.5 g dose of GHB, no gender effects were observed on various pharmacokinetic parameters.

What is the inhibitory potential of GHB on various CYP450 isozymes?

Based on *in vitro* studies, the inhibitory potential of GHB on CYP450 isozymes was tested across a concentration range of 3 – 300 μM. As a result, the IC_{50} was determined to be greater than 300 μM (37.8 μg/ml). Contrastly, plasma concentrations that were achieved clinically following a dose of 4.5 g exceeded 100 μg/ml. Thus, further studies will be useful to assess the entire concentration range observed clinically.

What is the effect of hepatic impairment on the pharmacokinetics of GHB?

In the hepatic impairment study following administration of GHB, various pharmacokinetic parameters differed significantly in patients with hepatic impairment compared with healthy volunteers. In cirrhotic patients without ascites, C_{max} and AUC increased by 1.5- and 2-fold. The apparent oral clearance decreased 2-fold and the percent of administered dose recovered in urine was doubled. In patients with ascites, the total systemic exposure (AUC) doubled and CL_{po} decreased 2-fold. $T_{1/2}$ and MRT increased by more than 2-fold. The results of this study suggest that the administered dose should be decreased by one-half in patients that are hepatically impaired.

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Summary of Pharmacokinetic Studies.

Table 2: Protocol OMC-GHB-4

Pilot or Background Study

Study Number	Route	Study Design	Formulation	Dose	Batch Number	Number of Subjects	Date Original Protocol Submitted to FDA	Previous Agency Response and Date
OMC-GHB-4	Oral	Open Label Single Center Single Cohort PK Study	Unit 3 g GHB doses Comprised of twin foil pouch (one pouch containing 3 g GHB and the other containing flavor excipient blend) Contents of unit dose were dissolved in 2 oz of water prior to ingestion	Two consecutive 3 g doses, administered 4 hours apart (with the first dose ingested just prior to bedtime and the second dose 4 hours later)	Lot 615203	6 adult narcoleptic patients (who were receiving nightly GHB dose for 2 to 13 years)	20 Oct 96	None

Sponsor's Biopharmaceutic Conclusions

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

Table 3: Protocol OMC-SXB-8

Study Title: A study to examine the pharmacokinetics of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) oral solution in male and female normal healthy volunteers

Subject Type	Route Number of Subjects	Formulation	Dose g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg	Urinary Recovery %	CL_R mL/hr
Healthy volunteers	Oral 36 subjects (18 female and 18 male) in a single center, open-label, single treatment design.	Xyrem (sodium oxybate) oral solution	4.5 g single dose	Male 88.3 ± 21.4 Female 93.0 ± 18.7	Male 1.25 ± 0.66 Female 1.14 ± 0.49	Male 0.65 ± 0.23 Female 0.61 ± 0.12	Male 241 ± 81.7 Female 233 ± 81.5	Male 3.8 ± 1.3 Female 4.2 ± 1.6	Male 202 ± 61.4 Female 218 ± 86.6	Male 3.1 ± 1.3 Female 3.1 ± 1.8	Male 494 ± 185 Female 510 ± 276

Results expressed as arithmetic mean ± standard deviation.

C_{max} = Observed maximum plasma concentration; T_{max} = Time to observed maximum plasma concentration from dosing; $T_{1/2}$ = Apparent half-life; AUC_{inf} = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; V_z/F = Apparent volume of distribution divided by absolute bioavailability; **Urinary Recovery** = Percent recovery of unchanged sodium oxybate in the urine; CL_r = Absolute renal clearance.

Table 4: Protocol OMC-SXB-9

Study Title: A study to examine the pharmacokinetics of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate)oral solution in normal healthy volunteers following doses of two times 2.25 grams and two times 4.5 grams

Subject Type	Route Number of Subjects	Formulation	Dose g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg	Urinary Recovery %	CL_R mL/hr
Healthy volunteers	Oral 13 subjects (3 female and 10 male) in a single center, open-label, 2 period, 2 treatment, crossover, randomized design**	Xyrem (sodium oxybate) oral solution	4.5 g in 2 divided doses	Dose-1 26.6 ± 8.6 Dose-2 60.1 ± 17.5	Dose-1 0.85 ± 0.36 Dose-2 0.64 ± 0.31	0.59 ± 0.13	138 ± 49.8	6.6 ± 2.1	325 ± 78.5	1.4 ± 0.8	388 ± 156
			9.0 g in 2 divided doses	Dose-1 77.6* ± 24.4 Dose-2 142 ± 49.3	Dose-1 1.17 ± 0.54 Dose-2 0.72 ± 0.45	0.83* ± 0.19	518* ± 195	3.6 ± 1.3	249 ± 89.0	3.6* ± 2.8	496 ± 282

Results expressed as arithmetic mean ± standard deviation.

C_{max} = Observed maximum plasma concentration; **T_{max}** = Time to observed maximum plasma concentration from dosing; **$T_{1/2}$** = Apparent half-life; **AUC_{inf}** = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; **V_z/F** = Apparent volume of distribution divided by absolute bioavailability; **Urinary Recovery** = Percent recovery of unchanged sodium oxybate in the urine; **CL_R** = Absolute renal clearance.

* Significantly different from the 4.5g result ($p<0.05$). C_{max} and AUC_{inf} were dose normalized for this analysis.

** One subject did not return for period 2 because of AEs in period 1 consisting of headache, nausea, and diarrhea. All data analyses were performed on the 12 patients that completed both trial phases.

Table 5: Protocol OMC-SXB-10

Study Title: A study to examine the pharmacokinetics of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) oral solution in narcoleptic patients following a single dose and after eight weeks of Xyrem® treatment

Subject Type	Route Number of Subjects	Formulation	Dose g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg
Patients with a diagnosis of narcolepsy	Oral 13 subjects (10 female and 3 male) in a single center, open-label, 2 period, 2-treatment design. First treatment consists of initial Xyrem dose and second treatment after 8 weeks of Xyrem treatment.	Xyrem (sodium oxybate) oral solution	4.5 g single dose on initial night of treatment	90.0* ± 30.8	0.75^	0.67 ± 0.17	226* ± 74.6	4.0 ± 1.1	226 ± 65.4
			4.5 g single dose on after 8 weeks of treatment	104 ± 31.3	0.50	0.67 ± 0.21	254 ± 78.5	3.5 ± 1.1	197 ± 67.5

Results expressed as arithmetic mean ± standard deviation. T_{max} is expressed as a median.

C_{max} = Observed maximum plasma concentration; **T_{max}** = Time to observed maximum plasma concentration from dosing; **$T_{1/2}$** = Apparent half-life; **AUC_{inf}** = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; **V_z/F** = Apparent volume of distribution divided by absolute bioavailability.

* Significantly different results for the 2 treatments ($p<0.05$)

^ Not significantly different based on the signed-ranks test.

Table 6: Protocol OMC-SXB-11

Study Title: A study to examine the effect of food on the bioavailability of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) oral solution in normal healthy volunteers

Subject Type	Route Number of Subjects	Formulation	Dose g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg	Urinary Recovery %	CL_R mL/hr
Healthy volunteers	Oral 36 female subjects in a single center, open-label, 2 period, 2 treatment, crossover, randomized design to examine the effect of food on the bio-availability of Xyrem**	Xyrem (sodium oxybate) oral solution	4.5 g after a high fat meal	60.1* ± 20.1	2.00*	0.68 ± 0.22	188* ± 80.0	6.2 ± 3.2	384 ± 324	3.8 ± 2.0	826 ± 462
			4.5 g after an overnight fast	142 ± 34.2	0.75	0.57 ± 0.30	289 ± 109	3.7 ± 1.4	192 ± 193	3.5 ± 1.9	490 ± 251

Results expressed as arithmetic mean ± standard deviation. Median is reported for T_{max}.

C_{max} = Observed maximum plasma concentration; T_{max} = Time to observed maximum plasma concentration from dosing; $T_{1/2}$ = Apparent half-life; AUC_{inf} = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; V_z/F = Apparent volume of distribution divided by absolute bioavailability; **Urinary Recovery** = Percent recovery of unchanged sodium oxybate in the urine; CL_R = Absolute renal clearance.

* Significantly Different results for the 2 treatments ($p<0.05$)
** Thirty-four (34) patients completed the study. One subject did not return for period 2 because of AEs in period 1 consisting of dizziness, nausea, vomiting, apnea, hypoventilation, and involuntary defecation. Another subject did not return for period 2 because of an illness that was not related to study drug administration.

Table 7: OMC-SXB-12

Study Title: A study to determine the interaction potential of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) with Ambien® (zolpidem tartrate) in normal healthy volunteers

Subject Type	Route Number of Subjects	Xyrem Formulation	Dose Xyrem g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg
Healthy volunteers	Oral 15 subjects (5 female and 10 male) in a single center, open-label, 2 period, 3 treatment, crossover, randomized design to determine the interaction potential of Xyrem with Ambien	Xyrem (sodium oxybate) oral solution	3.0 g Xyrem	83.8 ± 24.6	0.50	0.74 ± 0.22	136 ± 43.2	4.3 ± 1.3	260 ± 72.2
			3.0g Xyrem with 5 mg Ambien	93.5 ± 27.8	0.75	0.73 ± 0.18	143 ± 48.1	4.4 ± 2.3	281 ± 231
		Ambien Formulation	**Dose Ambien** **mg**	**C_{max}** **ng/mL**	**T_{max}** **hr**	**$T_{1/2}$** **hr**	**AUC_{inf}** **ng•hr/mL**	**CL/F** **mL/min/kg**	**Vz/F** **mL/kg**
		Ambien (zolpidem tartrate) tablets	5 mg Ambien	107 ± 47.5	0.75	3.35 ± 1.88	420 ± 216	2.6 ± 1.3	643 ± 225
			5 mg Ambien with 3.0g Xyrem	96.3 ± 35.9	0.50	3.34 ± 1.59	424 ± 230	2.8 ± 1.9	640 ± 165

Results expressed as arithmetic mean ± standard deviation. Median is reported for T_{max}.
C_{max} = Observed maximum plasma concentration; T_{max} = Time to observed maximum plasma concentration from dosing; $T_{1/2}$ = Apparent half-life; AUC_{inf} = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; V_z/F = Apparent volume of distribution divided by absolute bioavailability.

Administration of Xyrem® and Ambien® together had no clinically significant effect on the pharmacokinetics of sodium oxybate or zolpidem tartrate.

Table 8: Protocol OMC-SXB-14

Study Title: A study to determine the interaction potential of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) with Vivactil® (protriptyline hydrochloride) in normal healthy volunteers

Subject Type	Route Number of Subjects	Xyrem Formulation	Dose Xyrem g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg
Healthy volunteers	Oral 12 subjects (7 female and 5 male) in a single center, open-label, 3 period, 3 treatment, crossover, randomized design to determine the interaction potential of Xyrem with Vivactil**	Xyrem (sodium oxybate) oral solution	4.5g divided dose of Xyrem	Dose 1 55.1 ± 14.5 Dose 2 64.6 ± 15.2	Dose 1 0.75 Dose 2 0.50	0.57 ± 0.19	178 ± 72.6	5.7 ± 2.5	246 ± 44.8
			6.5g divided dose of Xyrem with 10mg Vivactil	Dose 1 55.5 ± 18.8 Dose 2 58.3 ± 22.9	Dose 1 0.63 Dose 2 0.75	0.57[Δ] ± 0.18	183[Δ] ± 79.5	5.9[Δ] ± 3.3	263[Δ] ± 98.6
		Vivactil Formulation	**Dose Vivactil** **mg**	**C_{max}** **ng/mL**	**T_{max}** **hr**	**$T_{1/2}$** **hr**	**AUC_{inf}** **ng•hr/mL**	**CL/F** **L/hr/kg**	**Vz/F** **L/kg**
		Vivactil (protriptyline hydrochloride) tablets	10mg Vivactil	4.7 ± 1.4	8.00	72.1 ± 38.2	452 ± 334	0.41 ± 0.28	32.0 ± 11.6
			10mg Vivactil with 4.5g divided dose of Xyrem	5.0 ± 1.3	8.00	68.2 ± 39.1	463 ± 311	0.40 ± 0.30	30.6 ± 17.5

Results expressed as arithmetic mean ± standard deviation. Median is reported for T_{max}.

C_{max} = Observed maximum plasma concentration; **T_{max}** = Time to observed maximum plasma concentration from dosing; **$T_{1/2}$** = Apparent half-life; **AUC_{inf}** = Area under the curve from time zero to time infinity for the first oral dose; **CL/F** = Apparent oral clearance divide by absolute bioavailability; **V_z/F** = Apparent volume of distribution divided by absolute bioavailability.

[Δ] n=11
** One subject withdrew prior to completing period 3

Administration of Xyrem® and Vivactil® together had no clinically significant effect on the pharmacokinetics of sodium oxybate or protriptyline hydrochloride.

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Table 9: Protocol OMC-SXB-17

Study Title: A study to determine the interaction potential of Xyrem® (sodium oxybate, sodium γ-hydroxybutyrate) with Provigil® (modafinil) in normal healthy volunteers

Subject Type	Route Number of Subjects	Formulation	Dose Xyrem g	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg
Healthy volunteers	Oral 13 subjects (6 female and 7 male) in a single center, open-label, 2 period, 3 treatment, crossover, randomized design to determine the interaction potential of Xyrem with Provigil®	Xyrem (sodium oxybate) oral solution	4.5g Xyrem Alone	146 ± 30.4	0.50	0.76 ± 0.18	302 ± 116.3	3.1 ± 0.9	190 ± 29.8
			4.5g Xyrem with 200mg Provigil	135 ± 35.1	0.50	0.76 ± 0.21	294 ± 164.8	3.4 ± 1.3	205 ± 41.7
		Formulation	**Dose Provigil** **mg**	C_{max} µg/mL	T_{max} hr	$T_{1/2}$ hr	AUC_{inf} µg•hr/mL	CL/F mL/min/kg	Vz/F mL/kg
		Provigil (modafinil) tablets	200mg Provigil Alone	5.5 ± 1.7	2.00	12.3 ± 2.3	71.8 ± 18.7	0.66 ± 0.14	690 ± 141
			200mg Provigil with 4.5g Xyrem	5.2 ± 1.4	1.00	12.0 ± 1.8	74.2 ± 19.7	0.64 ± 0.13	657 ± 135

Results expressed as arithmetic mean ± standard deviation. Median is reported for T_{max}.

C_{max} = Observed maximum plasma concentration; T_{max} = Time to observed maximum plasma concentration from dosing; $T_{1/2}$ = Apparent half-life; AUC_{inf} = Area under the curve from time zero to time infinity for the first oral dose; CL/F = Apparent oral clearance divide by absolute bioavailability; V_z/F = Apparent volume of distribution divided by absolute bioavailability.

Administration of Xyrem and Provigil together had no clinically significant effect on the pharmacokinetics of sodium oxybate and modafinil.

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Analysis of Studies

1. *In Vitro* Studies

Title: Inhibitory Potential Of γ-Hydroxybutyrate (GHB) Towards Human Hepatic Microsomal Cytochrome P450 Isozymes.

Objective:

The goal of this study was to determine the potential inhibitory activity of GHB on various CYP450 enzymes.

Study Design and Methods:

Briefly, pooled, human liver microsomes from ten individuals were obtained ——— The activity of each isozyme was determined in the presence (concentrations ranging from 3 – 300 μM) and absence of GHB. The positive control inhibitors used for each isozyme included 100 nM α-naphthoflavone for CYP1A2, 5 μM sulfaphenazole for CYP2C9, 60 μM tranylcypromine for CYP2C19, 0.75 μM quinidine for CYP2D6, 1000 μM diethyldithiocarbamate for CYP2E1, and 100 μM troleandomycin for CYP3A.

Results:

Table 10: Inhibitory Potential of Xyrem on Various CYP450 Enzymes.

Activity Assay	P450 Isozyme	IC_{50} (μM)
Ethoxyresorufin O-deethylase	CYP1A2	>300
Tolbutamide methyl hydroxylase	CYP2C9	>300
S-Mephenytoin 4'-hydroxylase	CYP2C19	>300
Dextromethorphan O-demethylase	CYP2D6	>300
p-Nitrophenol hydroxylase	CYP2E1	>300
Erythromycin N-demethylase	CYP3A	>300

IC_{50} The concentration of GHB that inhibits 50% of the activity of an isozyme specific assay.

For all of the CYP450 enzymes, the GHB concentration needed to inhibit 50% of the enzyme activity exceeded 300 μM (37.8 μg/ml).

Conclusion:

Xyrem appears to not inhibit any of the CYP450 enzymes at the concentrations tested. Clinically, plasma concentrations that were achieved following a dose of 4.5 g exceeded 100 μg/ml. Thus, further studies may need to be performed to ensure proper coverage of the entire clinical plasma concentrations achieved following administration of the drug.

2. Protocol OMC-SXB-4: Multiple-Dose Pharmacokinetics of Xyrem in Narcoleptic Patients on Chronic Therapy.

Title: Phase I, Open-Label Pharmacokinetic Study of Orally Administered Xyrem™ (Gamma-Hydroxybutyrate) in Narcoleptic Patients

Investigator: Martin Scharf, Ph.D.
Study Center: The Center for Research in Sleep Disorders
1275 East Kemper Road
Cincinnati, OH 45246

Objective:

The objective of this pilot study was to assess the pharmacokinetics of GHB after oral administration of two consecutive single doses of GHB (3 g per dose; 4 hours apart) to narcoleptic patients who were maintained on a chronic regimen of GHB.

Methodology:

This study consisted of an open-labeled, phase I pharmacokinetic study including: the first 3 g GHB dose administered immediately prior to bedtime at 10 p.m.; the second 3 g GHB dose administered four hours later. The first dose was administered within 3 h of eating. Sequential plasma samples were collected over 10 hours (from first dosing) and were analyzed for GHB concentrations.

Subjects:

Six narcoleptic patients (4 males and 2 females; 19 to 62 years of age) who were receiving GHB nightly for 2 to 13 years were enrolled. All six participants completed the study in its entirety. A nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) verified the diagnosis of narcolepsy in each patient.

Test Product, Dose, and Mode of Administration (Batch No):

Unit 3 g GHB doses (Lot PK1) were provided by the sponsor; each unit dose was comprised of twin foil pouch: one pouch containing 3 g GHB and the other containing the flavor excipient blend. Within 30 minutes prior to the first oral administration to each patient, the contents of one twin pouch was emptied into a dosing cup to which two ounces of water was added. After replacing the lid, the dosing cup was gently shaken to dissolve GHB and the excipient. Immediately prior to bedtime, the patient ingested the oral solution. Likewise, the second GHB dosing solution was prepared and ingested by the patient at hour 4.

Criteria for Pharmacokinetic Evaluation:

Each patient's plasma GHB concentration data was analyzed non-compartmentally to yield estimates for the following pharmacokinetic parameters: C_{max}, t_{max}, $t_{1/2}$, AUC_{inf}, V_z/F, and CL/F. Descriptive statistics (mean, median, standard deviation, maximum, and minimum) were computed for pertinent pharmacokinetic parameters.

Assay Validation:

The assay used to quantitate GHB was a [redacted] assay. For both plasma and urine, the calibration curve was linear for the concentration range from [redacted] with a lower limit of quantitation (LLOQ) of [redacted] The between day variability did not exceed 16% for the QC samples of 15, 75, and 150 μg/ml. For the accuracy of the method, the deviations from the mean were 11.7% for the low QC sample, 9.4% for the intermediate QC sample, and 15.8% for the high QC sample. The recovery of GHB from human plasma was 21.9% at 15 μg/ml, 39.7% at 75 μg/ml, and 48.6% at 150 μg/ml.

Results.

Figure 2: Plasma Pharmacokinetics of GHB in one Narcoleptic Patient

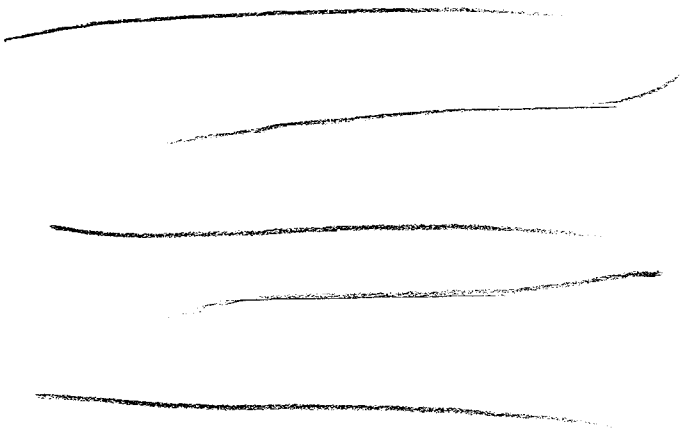

Table 11: Pharmacokinetic Parameters of GHB in Narcoleptic Patients

PK Parameter	Xyrem
Dose-1 C_{max} (μg/ml)	62.8 (27.4)
Dose-1 T_{max} (min)	40 (6.2)
Dose-2 C_{max} (μg/ml)	91.2 (25.6)
Dose-2 T_{max} (min)	35.7 (7.0)
T1/2 (min)	53.0 (19.3)
AUC_{inf} (μg/ml-min)	17732 (4867)
CL/F (ml/min/kg)	4.23 (0.99)
V_z/F (ml/kg)	307 (96.1)
MRT (min)	249 (56.1)

Capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB. As a result, C_{max} increased by 50% following the second dose of GHB. Nonlinear absorption also was observed, resulting in the two peaks in the plasma concentration – time profile.

Conclusions:

Capacity-limited pharmacokinetics may have developed as a result of the patients being on chronic therapy of GHB.

Note: The results of this PK study may be inaccurate due to the variability in recovery of GHB in the QC samples.

3. Protocol OMC-SXB-8: Single Dose Pharmacokinetic Study of Xyrem in Healthy Volunteers

Title: A Study To Examine The Pharmacokinetics Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) Oral Solution In Male And Female Normal Healthy Volunteers

Study Center:

Objectives:

The purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate assay) following a 4.5 g dose of sodium oxybate oral solution to male and female volunteers. In addition, the safety and tolerability of gamma-hydroxybutyrate was assessed.

Study Design and Methods:

This Phase I study utilized a single-center, open-label, single treatment design. Each subject qualified for study entry based on medical history and the inclusion/exclusion criteria. Each subject received the assigned treatment at approximately 8 p.m. Approximately 2 h prior to dosing and 11 h after dosing, the subjects had a light meal. Serial plasma samples were collected pre-dose and up to 8 h following Xyrem dosing for the determination of pertinent pharmacokinetic parameters. All urine voided was collected up to 8 h post-dose and a 25 ml aliquot was frozen for later analysis.

Subjects:

Eighteen male and 18 female volunteers were selected on the basis of general good health as confirmed by physical examination, medical history, and clinical laboratory evaluations. The male volunteers were 18 to 54 years of age; 60 to 96 kg in weight; 16 were Caucasian, 1 was Hispanic, and 1 was Multiracial. The female volunteers were 18 to 55 years of age; 57 to 84 kg in weight; 16 were Caucasian, one was Asian, and one was Hispanic. If a female subject was of childbearing potential, a negative serum pregnancy test was required prior to study entry. Subjects were excluded if they had any disease or condition that could impact absorption, distribution, metabolism or elimination of the study drug.

Test Product, Dose, and Mode of Administration (Batch No):

Xyrem was supplied as an oral solution containing 500 mg sodium oxybate per milliliter. It was supplied by Orphan Medical in bottles of 180 ml. (Lot No: EH75). The treatment in this study was a single oral dose of 4.5 g sodium oxybate solution

administered at approximately 2000 hours (8 p.m.). Each dose was diluted with 60 ml room-temperature water and the dosing cup was rinsed with another 60 ml water.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{inf}), oral plasma clearance (CL/F), elimination half-life ($t_{1/2}$), percentage of dose excreted unchanged in urine and renal clearance (CL_r). Non-compartmental methods were used in the determination of various pertinent pharmacokinetic parameters. Descriptive statistics (mean, median, standard deviation, coefficient of variation, maximum, and minimum) were computed for pertinent pharmacokinetic parameters for each gender. The comparison of pharmacokinetic parameters for men and women was accomplished by an unpaired t-test of log transformed AUC_{inf}, log transformed C_{max}, t_{max}, CL/F, $t_{1/2}$, percentage of dose excreted unchanged in urine and apparent renal clearance.

Assay Validation:

The assay used to quantitate GHB was an [redacted] assay. For plasma and urine, the calibration curves were linear for the concentration range from [redacted] with a lower limit of quantitation (LLOQ) of [redacted] The within-day variability ranged from 2.1 to 6.7% for the QC samples of 15, 75, and 150µg/ml. For the accuracy of the method, the deviations from the mean were –8.5% for the low QC sample, -5.9% for the intermediate QC sample, and -4.7% for the high QC sample. Comparatively for urine, the deviations from the mean were –1% for the low QC sample, -8.8% for the intermediate QC sample, and -3.4% for the high QC sample.

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Results:

Figure 3: Single Dose PK of GHB in Male and Female Volunteers

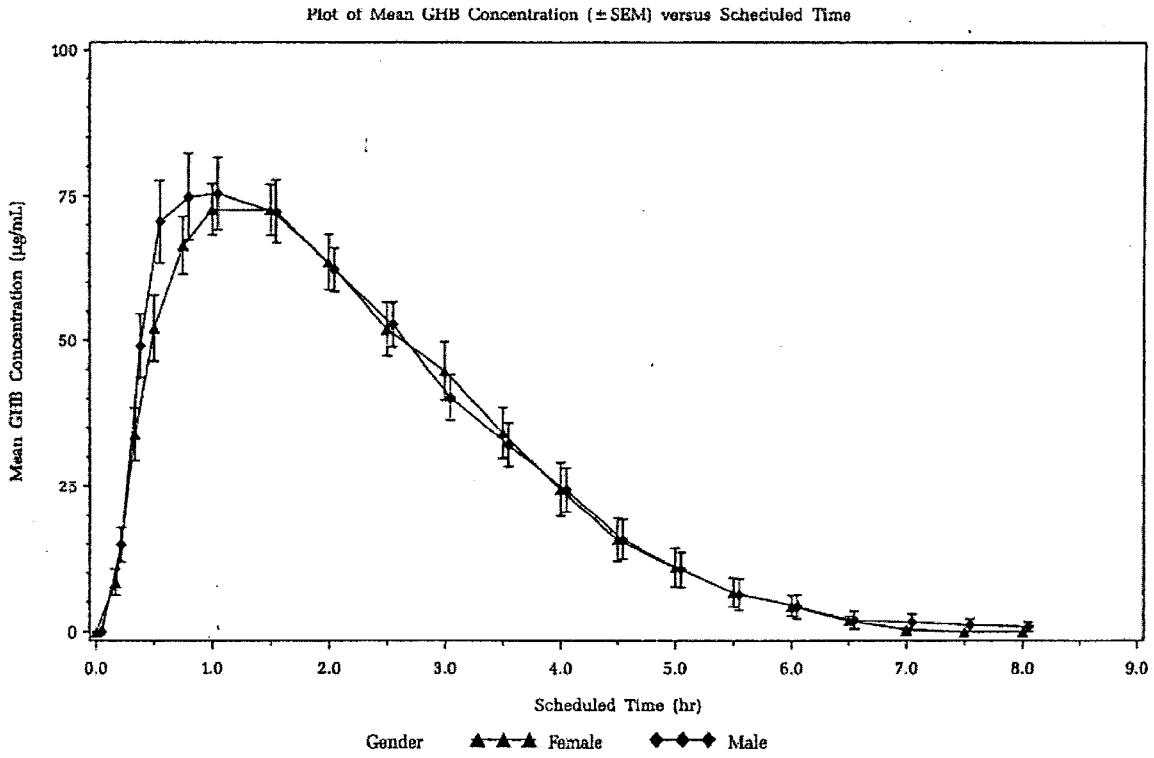

Table 12

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

[Mean (±SD)]

Parameter (units)	Male Subjects (n=18)	Female Subjects (n=18)
C_{max} (µg/mL)	88.3 (21.4)	83.0 (18.7)
T_{max} (hr)	1.25 (0.66)	1.14 (0.49)
$T_{1/2}$ (hr)	0.65 (0.23)	0.61 (0.12)
AUC_{inf} (µg.hr/mL)	241 (81.7)	233 (81.5)
CL/F (mL/min/kg)	3.8 (1.3)	4.2 (1.6)
V_z/F (mL/kg)	202 (61.4)	218 (86.6)
Urinary Recovery (%)	3.1 (1.3)	3.1 (1.8)
CL_r (mL/hr)	484 (185)	510 (276)

No difference in the systemic exposure of GHB in male and female human subjects was observed, resulting in a mean AUC_{inf} of 241 μg-hr/ml in men and 233 μg-hr/ml in women. There was no difference in C_{max}, t_{max}, oral clearance, $t_{1/2}$, the percent of dose excreted unchanged, or renal clearance between men and women. The half-life of GHB was 39 minutes in men and 37 minutes in women, resulting in very low concentrations by 6 hours after a 4.5 g dose. Urinary excretion of unchanged drug was a minor elimination pathway (1-7%) in men and women. According to the sponsor, sodium oxybate administered as a single oral 4.5 g dose was well-tolerated by healthy adult male and female volunteers.

Conclusions:

No clinically significant gender differences in the plasma pharmacokinetics of Xyrem were observed.

4. Protocol OMC-SXB-9: Multiple-Dose Pharmacokinetics of Xyrem in Healthy Volunteers.

Title: A Study To Examine The Pharmacokinetics Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) Oral Solution In Normal Healthy Volunteers Following Doses Of Two Times 2.25 Grams And Two Times 4.5 Grams

Study Center:

Objectives:

The purpose of this study was to describe the plasma pharmacokinetics and dose proportionality of gamma-hydroxybutyrate assay) after total doses of Xyrem oral solution of 4.5 and 9 g. Doses were administered in two equal portions 4 h apart. In addition, the safety and tolerability of gamma-hydroxybutyrate was determined.

Study Design and Methods:

This Phase I study utilized a single-center, open-label, two-period, two-treatment, crossover, randomized design. After qualifying for study entry based on medical history and satisfying the inclusion/exclusion criteria, each subject was randomized to one of two treatment sequences. Each subject received a standard full meal 2 h prior to treatment. During period 1, each subject received half of the assigned treatment at approximately 8 p.m. The second half was administered 4 h later at about midnight. There was a 7-day washout between periods 1 and 2. During period 2, each subject received the other treatment, which was administered in the same fashion (the first half at about 8 p.m. and the second half at approximately midnight). Serial plasma samples were collected pre-dose and up to 10 h following the start of Xyrem dosing. All urine was collected in two-hour increments up to 10 h post-dose.

Subjects:

Three female and 10 male volunteers (all Caucasian; 19 to 47 years of age; 61 to 90 kg in weight) were selected on the basis of general good health as confirmed by physical examination, medical history, and clinical laboratory evaluations. If a female subject was of childbearing potential, a negative serum pregnancy test was required prior to study entry. Subjects were excluded if they had any disease or condition that could impact absorption, distribution, metabolism or elimination of the study drug.

Test Product, Dose, and Mode of Administration (Batch No):

Xyrem was supplied as an oral solution containing 500 mg sodium oxybate (sodium gamma-hydroxybutyrate) per milliliter. It was supplied by Orphan Medical in bottles of 180 ml. (Lot No: EH75). The 2 treatments compared in this study were daily oral doses containing 4.5 and 9 g of sodium oxybate. Each daily dose was administered in two equal portions. Half the daily dose was administered at approximately 2000 hours (8 p.m.) and the second half was administered 4 hours later at about midnight. Each portion was diluted with 60 ml room temperature water and the dosing cup was rinsed with another 60 ml water.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration after each portion of a dose (dose-1 C_{max} and dose-2 C_{max}), corresponding peak times (dose-1 t_{max} and dose-2 t_{max}), area under the curve (AUC_{inf}), oral plasma clearance (CL/F), elimination half-life ($t_{1/2}$), percentage of dose excreted unchanged in urine and renal clearance (CL_r). Non-compartmental methods were used in the determination of various pertinent pharmacokinetic parameters and semi-log coordinates. Descriptive statistics (mean, median, standard deviation, coefficient of variation, maximum, and minimum) were computed for pertinent pharmacokinetic parameters for both doses. Dose proportionality was determined by ANOVA of AUC_{inf}, dose-1 C_{max}, dose-2 C_{max}, $t_{1/2}$, percentage of dose excreted unchanged in urine and apparent renal clearance. Statistical comparison was performed on AUC_{inf}, dose-1 C_{max}, and dose-2 C_{max} after these three parameters for the high dose (9 g) had been normalized to the low dose (4.5g) and logarithmically transformed.

Assay Validation:

The assay used to quantitate GHB was an ——— assay. For plasma and urine, the calibration curves were linear for the concentration range from ——— with a lower limit of quantitation (LLOQ) ——— The between-day variability did not exceed 12.3% for the QC samples of 15, 75, and 150µg/ml. For the accuracy of the method, the deviations from the mean were –1.8% for the low QC sample, -6.3% for the intermediate QC sample, and -4.4% for the high QC sample. Comparatively for urine, the deviations from the mean were –11.9% for the low QC sample, -4.2% for the intermediate QC sample, and –2.7% for the high QC sample.

Results:

Figure 4

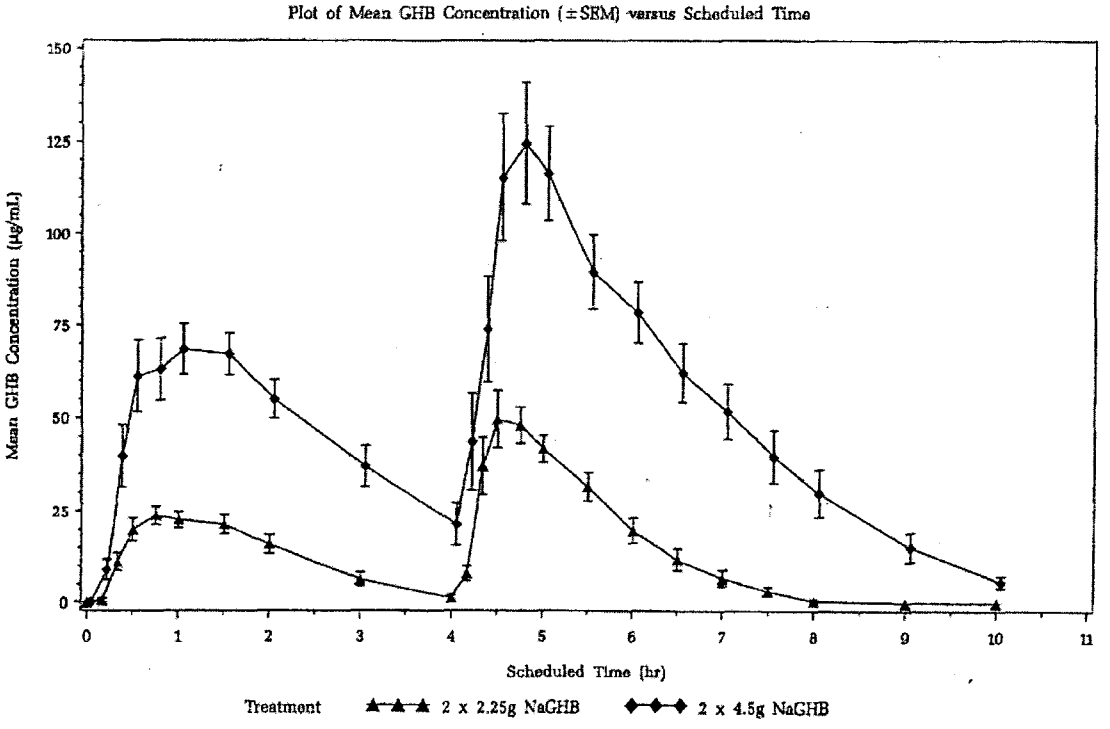

Table 13

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

4.5 gram Dose (n = 12)

Parameter (units)	Mean	SD	CV	Minimum	Maximum
Dose-1 C_{max} (µg/mL)	26.6	8.6	32.3		
Dose-1 T_{max} (hr)	0.85	0.36	42.3		
Dose-2 C_{max} (µg/mL)	60.1	17.5	29.1		
Dose-2 T_{max} (hr)	0.64	0.31	49.1		
$T_{1/2}$ (hr)	0.59	0.13	21.5		
AUC_{inf} (µg.hr/mL)	138	49.8	36.2		
CL/F (mL/min/kg)	6.6	2.1	31.8		
V_z/F (mL/kg)	325	78.5	24.2		
Urinary Recovery (%)	1.4	0.8	56.2		
CL_r (mL/hr)	388	156	40.1		

Table 14

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

9 gram Dose (n = 12)

Parameter (units)	Mean	SD	CV	Minimum	Maximum
Dose-1 C_{max} (µg/mL)	77.6*	24.4	31.5		
Dose-1 T_{max} (hr)	1.17	0.54	46.0		
Dose-2 C_{max} (µg/mL)	142	49.3	34.8		
Dose-2 T_{max} (hr)	0.72	0.45	62.8		
$T_{1/2}$ (hr)	0.83*	0.19	23.1		
AUC_{inf} (µg.hr/mL)	518*	195	37.7		
CL/F (mL/min/kg)	3.6	1.3	37.6		
V_z/F (mL/kg)	249	89.0	35.8		
Urinary Recovery (%)	3.6*	2.8	76.5		
CL_r (mL/hr)	496	282	56.8		

*Significantly different from the 4.5 g result (α=0.05); C_{max} and AUC_{inf} were dose normalized for this analysis.

The systemic exposure of human subjects to gamma-hydroxybutyrate increased disproportionately with dose, indicating capacity limited elimination. Doubling of the nightly oral dose from 4.5 to 9 g resulted in a 3.8-fold increase in AUC_{inf}. Maximum concentrations of gamma-hydroxybutyrate were higher after the second half of the nightly dose administered 4 h after the first half of the dose. The apparent half-life of gamma-hydroxybutyrate was less than 1 h, resulting in very low concentrations by 10 h after the start of this dosing regimen. Urinary excretion of unchanged drug was less than 10%, representing a minor elimination pathway. According to the sponsor, sodium oxybate at dosages of 4.5 and 9 g administered orally on separate occasions (with each treatment administered in two divided portions 4 h apart) were well-tolerated by healthy adult male and female volunteers.

Conclusions:

The pharmacokinetic profile of GHB in normal volunteers was nonlinear. The change in C_{max} following two equivalent doses may be explained by a pronounced food effect on the oral absorption of the drug. Thus, food intake suppresses the oral absorption of GHB, which is supported by Study OMC-SXB-11. Clinically, close monitoring of GHB plasma levels may be warranted as a result of disproportional increases in AUC and C_{max}.

5. Protocol OMC-SXB-10: Pharmacokinetics of Xyrem after Single and Chronic Dosing

Title: A Study To Examine The Pharmacokinetics Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) Oral Solution In Narcoleptic Patients Following A Single Dose and After Eight Weeks Of Xyrem® Treatment.

Study Center: Investigator: Martin Scharf
The Center for Research in Sleep Disorders
1275 East Kemper Road,
Cincinnati, OH 45246

Objectives:

The purpose of this study was to characterize the pharmacokinetics of sodium gamma-hydroxybutyrate assay) after the first 4.5 g daily dose of Xyrem oral solution administered to narcoleptic patients and after 8 weeks of individualized Xyrem treatment. In addition, the safety and tolerability of Xyrem was assessed.

Methodology:

This Phase I study utilized a single-center, open-label, two-treatment (single and multiple dose) design. After qualifying for study entry based on medical history and satisfying the inclusion/exclusion criteria, each patient was assigned a patient number. All patients entered the study facility approximately 3 h prior to administration of the nighttime dose. Serial plasma samples were collected pre-dose and up to 7 h following Xyrem dosing for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of time.

Subjects:

Thirteen otherwise healthy narcoleptic patients (10 women and 3 men; 12 Caucasian and 1 Black; 18 years of age or above; 51 to 99 kg in weight) were selected on the basis of general good health as confirmed by physical examination, medical history, and clinical laboratory evaluations.

Test Product, Dose, and Mode of Administration (Batch No):

Xyrem was supplied as an oral solution containing 500 mg sodium oxybate per milliliter (ml). It was supplied by Orphan Medical in bottles of 180 ml. (Lot No: EH76A). The 2 treatments compared in this study were single oral doses of 4.5 grams sodium oxybate administered to naïve patients and following 8 weeks of Xyrem treatment. The dose was administered at approximately 2200 hours (10 p.m.).

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak plasma concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{inf}), oral plasma clearance (CL/F) and elimination half-life ($t_{1/2}$). Non-compartmental methods were used in the determination of various pertinent pharmacokinetic parameters. Descriptive statistics (mean, median, standard deviation, coefficient of variation,

maximum, and minimum) were computed for pertinent pharmacokinetic parameters for both treatments. The effect of time on GHB pharmacokinetics was determined by a paired t-test of logarithmically transformed AUC_{inf} and C_{max}, and a nonparametric comparison of t_{max}.

Assay Validation:

The assay used to quantitate GHB was an l ——— assay. For plasma and urine, the calibration curves were linear for the concentration range from with a lower limit of quantitation (LLOQ) of ~~—~~ The within-day variability ranged from 2.1 to 6.7% for the QC samples of 15, 75, and 150µg/ml. For the accuracy of the method, the deviations from the mean were –8.5% for the low QC sample, -5.9% for the intermediate QC sample, and -4.7% for the high QC sample.

Results:

Figure 5

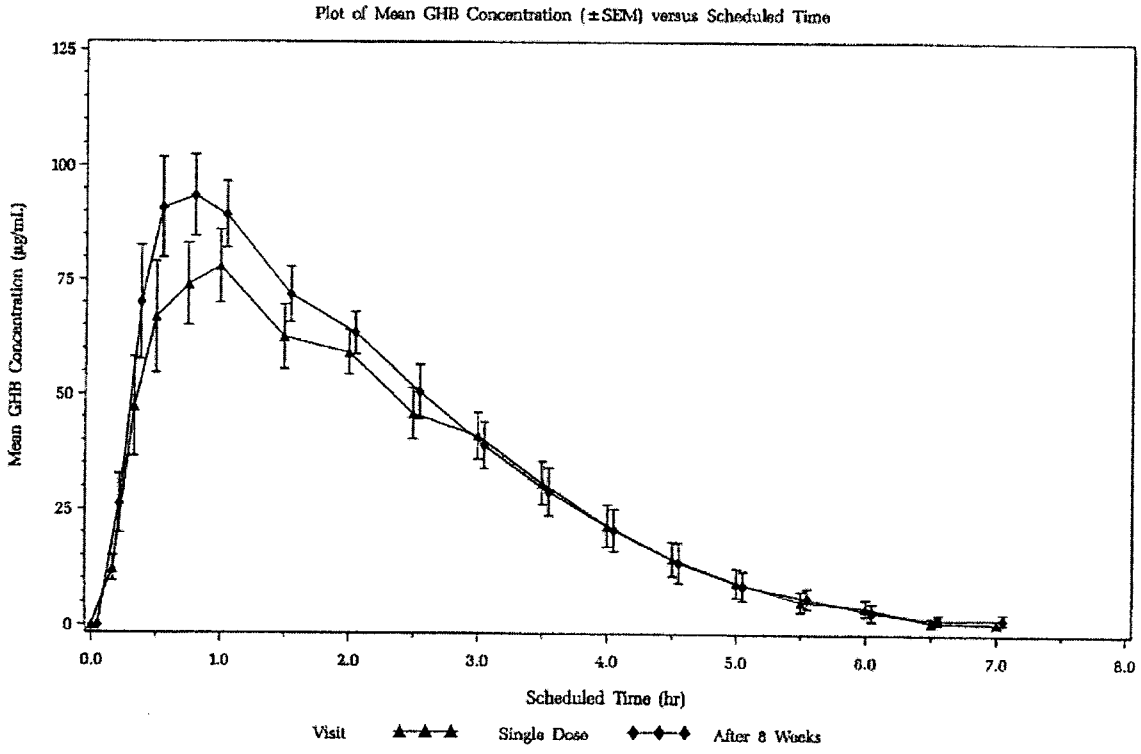

Table 15

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Initial Dose (n=13)	After 8 weeks of Xyrem Treatment (n=13)
C_{max} (µg/mL)	90.0* (30.8)	104 (31.3)
T_{max} (hr)	0.75^	0.50
$T_{1/2}$ (hr)	0.67 (0.17)	0.67 (0.21)
AUC_{inf} (µg.hr/mL)	226* (74.6)	254 (78.5)
CL/F (mL/min/kg)	4.0 (1.1)	3.5 (1.1)
V_z/F (mL/kg)	226 (65.4)	197 (67.5)

** Median is reported for T_{max}

* Significantly different results for the 2 treatments ($p<0.05$)

^ Not significantly different based on the signed-ranks test

On average the nightly treatment of narcoleptic patients with Xyrem for 8 weeks resulted in a 13% increase in systemic exposure of GHB (AUC) and a 16% increase in peak concentration (C_{max}). While statistically significant, these modest changes were not considered to be clinically significant. On an individual patient basis, the increase in GHB exposure was <25% for 11 of the 13 patients (85%). Over the 8 weeks of the study, within subject variability in C_{max} and AUC_{inf} was low (<15%) when the same dose of Xyrem was administered. The apparent half-life of GHB was less than 1 hour before and after 8 weeks of Xyrem treatment. The pharmacokinetics of GHB in narcoleptic patients did not appear to differ from the pharmacokinetics of GHB in healthy volunteers. Chronic Xyrem treatment did not result in auto-induction (self-induction of metabolism). Few adverse events were experienced after the first dose of Xyrem and none was experienced following the same 4.5 g dose administered after 8 weeks of Xyrem treatment. According to the sponsor, all of the adverse events were well tolerated by the patients and resolved without sequelae.

Conclusions:

According to the results of this study, the plasma pharmacokinetics were relatively unchanged following chronic single dosing of the drug. No food effect was apparent in this study due to the lack of information on the timing of the dose following food intake. The dosage regimen (once daily) used in this study was different form the proposed dosage regimen (2 equivalent doses/day administered 2.5 – 4 h apart).