6. Protocol OMC-SXB-11: Effect of Food on the Pharmacokinetics of GHB.

Title:

A Study to Examine the Effect of Food on the Bioavailability of Xyrem Oral Solution in Healthy Volunteers.

Objective:

The main purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate (using an ——— assay) following a 4.5 g dose of Xyrem oral solution administered after a standardized high fat meal and after an overnight fast. In addition, the safety and tolerability of the drug were evaluated.

Study Design and Methods:

This study utilized a single-center, single-dose, open-label, two-period, two-treatment, crossover, randomized design. After qualifying for the study, each subject was randomized to one of two treatment sequences. All subjects spent the night before dosing at the study facility. During the morning of period 1, half the subjects ingested 4.5 g of the study drug following a standardized high fat breakfast served half an hour before dosing; the other subjects ingested an equivalent dose of the study drug in a fasting state. There was a 7-day washout between periods 1 and 2. During period 2, individual subjects crossed over to the other treatment. Serial plasma samples were collected pre-dose and up to 10 hours following Xyrem dosing for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of administration with food. All urine voided was collected in two-hour increments up to 10 hours post-dose. Throughout the treatment phase, each volunteer was monitored for the occurrence of adverse events (AEs) and changes in vital signs.

Subjects:

Thirty-six healthy female volunteers (34 Caucasian and 2 Hispanic; 18 to 55 years of age; 52 to 84 kg in weight) enrolled in the study and 34 completed the study. If a female subject was of childbearing potential, a negative serum pregnancy test was required prior to study entry. 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 (not related to study drug administration).

Test Product, Dose and Mode of Administration:

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).

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. The effect of food was determined by ANOVA of logarithmically transformed AUC_{inf} and C_{max} and computation

of the 90% confidence interval about the ratio of the mean results observed after a high fat meal and after an overnight fast. A non-parametric comparison (Wilcoxon rank sum test) was used in the comparison of fed and fasting t_{max} values.

Assay Validation:

The assay used to quantitate GHB was an ——— assay. For both plasma and urine, the calibration curve was linear for the concentration range from with a lower limit of quantitation (LLOQ) of ——— The between day variability did not exceed 10% for the QC samples of 15, 75, 150, and 400 µg/ml. For the accuracy of the method, the deviations from the mean were –7.1% for the low QC sample, -5.7% for the intermediate QC sample, -3.2% for the high QC sample, and 0.9% for the over the curve 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.

Results:

Figure 6. Effect of Food on the Plasma Concentrations of GHB Following a 4.5 g oral dose.

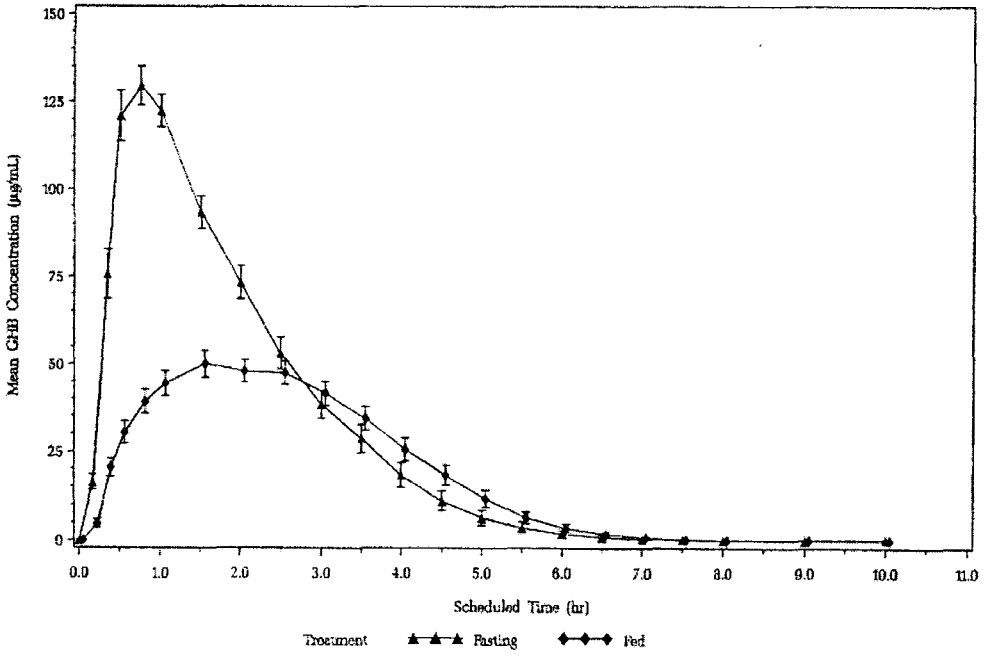

Figure 7. Cumulative Renal Excretion of GHB Following an oral dose of 4.5 g.

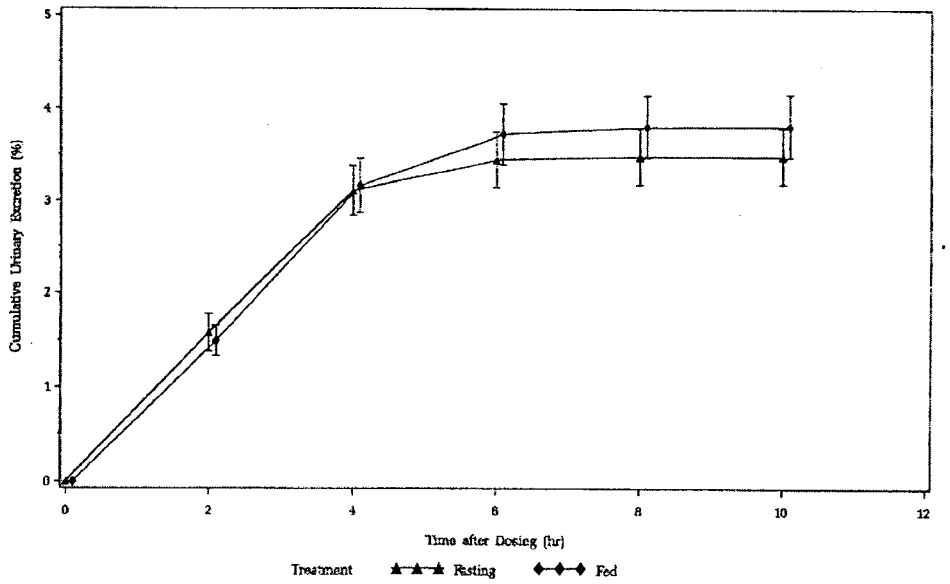

Table 16: GHB Pharmacokinetic Parameters

[Arithmetic Mean (±SD)**]

Parameter (units)	Fed (n=34)	Fasting (n=34)
C_{max} (µg/mL)	60.1* (20.1)	142 (34.2)
T_{max} (hr)	2.00 *	0.75
$T_{1/2}$ (hr)	0.68 (0.22)	0.57 (0.30)
AUC_{inf} (µg.hr/mL)	188* (80.0)	289 (109)
CL/F (mL/min/kg)	6.2 (3.2)	3.7 (1.4)
V_z/F (mL/kg)	384 (324)	192 (193)
Urinary Recovery (%)	3.8 (2.0)	3.5 (1.8)
CL_r (mL/hr)	826 (462)	490 (251)

*Statistically significant at $p < 0.05$.
**Median is reported for t_{max}.

Table 17: Gamma-Hydroxybutyrate Pharmacokinetic Parameters: Effect of Food (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	Fed (n=34)	Fasting (n=34)		
C_{max} (μg/ml)	56.5	137.9	0.41	0.37 – 0.46
AUC_{inf} (μg-hr/ml)	168.7	269.4	0.63	0.57 – 0.69

On average C_{max} decreased by 59% and AUC_{inf} decreased by 37%. The 90% confidence intervals were outside the reference ranges (0.80 – 1.25 for both C_{max} and AUC_{inf}) that indicate bioequivalence. Absorption of sodium oxybate appeared to be slower following food consumption, resulting in a later t_{max} of 2 hr compared to 0.75 hr. The t_{max} values for fed and fasting states were significantly different (p=0.0001). The apparent half-life of GHB was less than 1 h for both dosing conditions. Urinary excretion of unchanged drug was a minor elimination pathway and unaffected by the treatment conditions (means were 3.5% [fasting] and 3.8% [fed]). More adverse events were experienced when Xyrem was administered after an overnight fast than when it was administered after a high fat meal, probably as a result of the higher plasma concentrations of drug observed when Xyrem was administered after a fast. According to the sponsor, all of the adverse events were well tolerated by healthy adult volunteers and resolved without sequelae.

Conclusion:

Food decreased the systemic exposure of gamma-hydroxybutyrate with decreases in C_{max} and AUC of 59% and 37%, respectively. In addition, the data showed that considerable absorption occurred 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. Therefore, Xyrem should be taken in the fasted state.

7. Effect of Hepatic Impairment on the Pharmacokinetics of GHB.

Title: Effect of moderate or severe liver dysfunction on the pharmacokinetics of γ-hydroxybutyric acid.

Objective:

Since GHB is primarily metabolized by the liver, a hepatic impairment study would be warranted. The sponsor has submitted a previously published study (Ferrara et al, 1996) to support labeling recommendations in this special population. The main

purpose of this study was to assess the effect of moderate or severe liver dysfunction on the pharmacokinetics of γ-hydroxybutyric acid.

Subjects:

Sixteen male patients with biopsy-proven liver cirrhosis (8 with ascites and 8 without ascites) were studied (mean age; 55 and 60 yrs.). All nonascitic patients were categorized as Child's Pugh class A (score of 5), whereas ascitic patients were Child's class C (score of 15). Exclusion criteria included a history of hypersensitivity to the administered drugs, recent history of GI bleeding, severe encephalopathy, a $CL_{CR} < 50$ ml/min, and presence of any other disease. None of the patients were heavy smokers. All of the patients abstained from alcohol and other drugs two weeks prior to the study, apart from those used to treat cirrhosis: diuretics, H2-blockers, and vitamin supplements.

Study Design and Methods.

A liver metabolic function of each patient was evaluated by measuring antipyrine clearance and the formation rate of lidocaine metabolite, monoethylglycinexylidide (MEGX). GHB, lidocaine, and antipyrine were administered at 8 a.m. following an overnight fast. On day 1, each patient underwent a MEGX liver function test. Lidocaine was infused over 2 min. and serial blood samples were collected up to 1 h. On day 3, antipyrine was administered orally at a dose of 10 mg/kg. Subsequently, blood samples were collected over 48 h. On day 8, GHB, dissolved in black cherry syrup was administered orally at a dose of 25 mg/kg (1.75 g). Blood samples were collected at serial time points up to 6 h. In addition, urine was collected before and up to 24 h following administration of the drug.

Analytical Methods.

GHB was quantitated in plasma and urine using a previously described ——— assay (Data to support assay validation was not included in the study). The limit of detection for the assay was ——— The calibration curve had a correlation coefficient of 0.997 over the relevant concentration range up to 50 μg/ml. The intra- and interassay coefficients of variation were both below 3% at 5 μg/ml and 2% at 50 μg/ml.

Pharmacokinetic Analysis.

Noncompartmental approaches were used to estimate various pharmacokinetic parameters, including the maximum observed plasma concentration (C_{max}), observed time to C_{max} (t_{max}), terminal half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC), area under the first moment of the plasma concentration-time curve (AUMC), mean residence time (MRT), apparent oral clearance (CL_{po}), renal clearance (CL_r), and apparent volume of distribution following oral administration (V_z/f).

Results.

Figure 8. Semilogarithmic plot of mean (SEM) plasma concentrations of GHB vs. time. Filled circles; cirrhotics without ascites, open circles; cirrhotics with ascites.

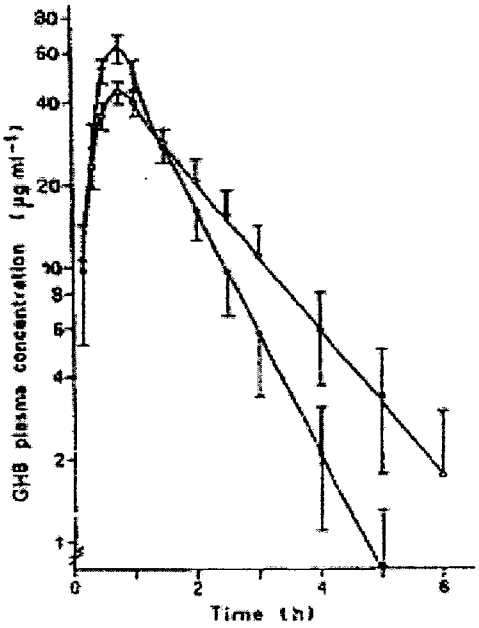

Table 18. Mean (SD) pharmacokinetic parameters of GHB after oral administration of 25 mg/kg.

	Healthy volunteers[a]	Cirrhotics without ascites	Cirrhotics with ascites
C_{max} (μg·ml^{-1})	46 (22)	68 (19)*	47 (10)
t_{max} (min)	30 (20–45)[b]	45 (30–45)[b]**	45 (30–60)[b]**
AUC (μg·ml^{-1}·min)	2542 (1120)	5125 (1850)**	5643 (2566)**
CL_o (ml·min^{-1}·kg^{-1})	9.1 (4.0)	4.5 (1.5)**	4.1 (1.6)**
V_z/f (ml·kg^{-1})	335 (114)	198 (55)*	285 (62)
$t_{½}$ (min)	22 (3)	32 (10)*	56 (29)**
MRT (min)	53 (9)	77 (20)*	110 (45)**
Urinary recovery (% dose)	0.83 (0.50)	1.63 (0.64)**	0.43 (10)
CL_R (ml·min^{-1}·kg^{-1})	0.067 (0.043)	0.068 (0.030)	0.013 (0.009)***

[a] Data from ref. [10] (V_z/f, urinary recovery and CL_R not presented therein)
[b] Median value (range); *$P < 0.05$, **$P < 0.01$ or ***$P < 0.001$ vs healthy volunteers

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.

Conclusion:

The results of this study suggest that the GHB dose should be decreased by one-half in patients that are hepatically impaired. [1]**(Note: According to the reference used, the healthy subjects (22 – 26 yrs.) were not age-matched with the patients in this study).**

[1]Palatini et al, 1993. Dose-dependent absorption and elimination of GHB in healthy volunteers. *Eur J. Clin. Pharmacol.*, 45:353-6.

8. Protocol OMC- SXB-12: Pharmacokinetic Interaction of GHB with Zolpidem

Title: A Study To Determine The Interaction Potential Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) With Ambien® (Zolpidem Tartrate) In Normal Healthy Volunteers.

Objectives:

The purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate [redacted] assay) and zolpidem [redacted] assay) in normal healthy human subjects. In addition, the safety and tolerability of sodium oxybate administered as an oral solution alone or in combination with 5 mg of zolpidem tartrate as a tablet (Ambien) were compared.

Study Center: [redacted]

Study Design and Methods:

This Phase I study utilized a single-center, open-label, three-period, three-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 three treatment sequences. All subjects spent the night before dosing at the study facility. During the morning of period 1, one third of the subjects ingested 3 g of Xyrem following an overnight fast; one third of the subjects ingested a 5 mg Ambien tablet after an overnight fast; and one third of the subjects ingested both 3 g Xyrem and a 5 mg Ambien tablet after an overnight fast. There was a 7-day washout between periods 1, 2 and 3. During periods 2 and 3, individual subjects crossed over to the other treatments according to the sequence to which they had been randomized. Serial plasma samples were collected pre-dose and up to 24 h following dosing for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of co-administration. Throughout the treatment phase, each volunteer was monitored for the occurrence of adverse events (AEs) and changes in vital signs.

Subjects:

Fifteen healthy volunteers (five female; 14 Caucasian and one Multiracial; 19 to 51 years of age; 56 to 98 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:

Xyrem was supplied as an oral solution containing 500 mg sodium oxybate (gamma-hydroxybutyrate) per milliliter. It was supplied by Orphan Medical in bottles of 180 ml [Lot No: EH75]. Ambien was supplied as tablets containing 5 mg zolpidem tartrate (equivalent to 4.02 mg zolpidem base) [Lot No: 9L474]. The 3 treatments compared in this study were single oral doses of 3 grams sodium oxybate administered alone, 5 mg Ambien tablet administered alone and the combination of 5 mg Ambien tablet and 3 grams sodium oxybate. Each treatment was administered after an overnight fast. The dose was administered at approximately 0700 hours (7 a.m.). Each Xyrem dose was diluted with 60 ml room-temperature water and the dosing cup was rinsed with another 180 ml water. Each Ambien dose was administered with 240 ml water. For the combination treatment the Ambien tablet was administered with the 60 ml Xyrem dose and followed by the 180 ml dosing cup rinsings.

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 ($t_{1/2}$) of gamma-hydroxybutyrate and of zolpidem when administered alone and in combination. 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 co-administration of zolpidem tartrate on gamma-hydroxybutyrate pharmacokinetics was determined by an ANOVA of logarithmically transformed AUC_{inf} and C_{max} and computation of the 90% confidence interval about the ratio of the mean results observed after administration in combination and alone. A non-parametric analysis (Wilcoxon signed rank test) was used in the comparison of t_{max} values.

Assay Validation:

The assay used to quantitate GHB was an [redacted] assay. For plasma, the calibration curve was 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.

For zolpidem, the assay used for quantitation was a [redacted] assay. The within-day variability ranged from 0.91 to 7.8% for the QC samples of 3, 30, and 300 ng/ml. For the accuracy of the method, the deviations from the mean for all the QC samples were all within 5.8% when the samples were processed manually. Using an automated sample-processing unit, the deviations from the mean for all the QC samples

were all within 10.8%. The calibration curve was linear for the concentrations ranging from [redacted] with a lower limit of quantitation (LLOQ) of [redacted]

Results:

Figure 9: Plasma Concentration-Time Profile of GHB Following Co-administration of Ambien.

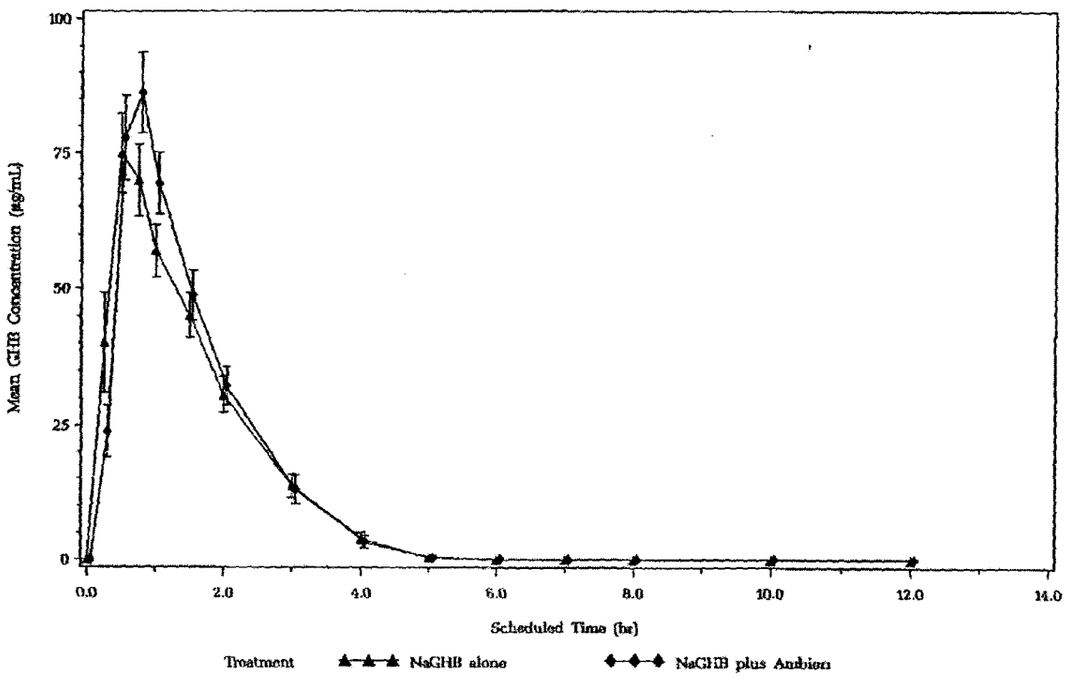

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Table 19

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Xyrem Alone (n=15)	Xyrem With Ambien (n=15)
C_{max} (µg/mL)	83.8 (24.6)	93.5 (27.8)
T_{max} (hr)	0.50	0.75
$T_{1/2}$ (hr)	0.74 (0.22)	0.73 (0.18)
AUC_{inf} (µg.hr/mL)	136 (43.2)	143 (48.1)
CL/F (mL/min/kg)	4.3 (1.3)	4.4 (2.3)
V_z/F (mL/kg)	260 (72.2)	281 (231)

** Median is reported for T_{max}.

There were no significant effects of co-administration of Ambien with Xyrem (p>0.05).

Table 20: Gamma-Hydroxybutyrate Pharmacokinetic Parameters: Effect of Ambien Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Ambien (n=15)	Alone (n=15)		
C_{max} (µg/ml)	85.5	81.0	1.06	0.85 – 1.31
AUC_{inf} (µg-hr/ml)	133.4	130.0	1.03	0.93 – 1.14

Figure 10: Effect of GHB on the Plasma Pharmacokinetics of Zolpidem

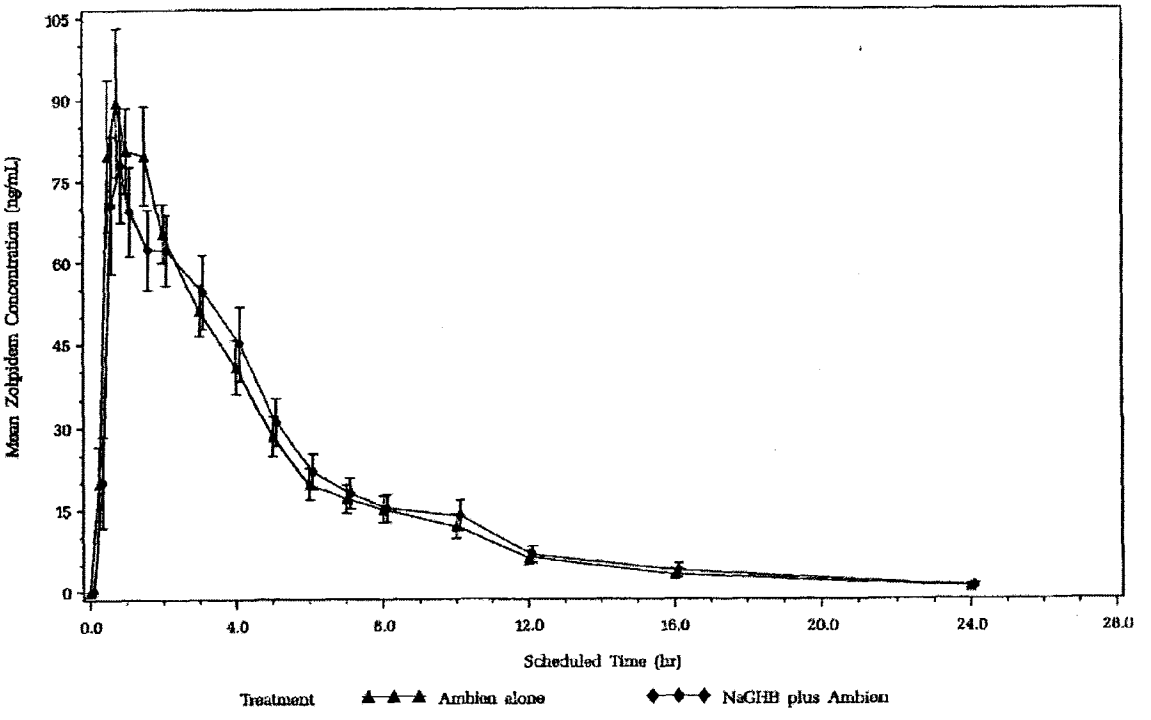


Table 21

Zolpidem Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Ambien Alone (n=15)	Ambien With Xyrem (n=15)
C_{max} (ng/mL)	107 (47.5)	96.3 (35.9)
T_{max} (hr)	0.75	0.50
$T_{1/2}$ (hr)	3.35 (1.88)	3.34 (1.59)
AUC_{inf} (ng.hr/mL)	420 (216)	424 (230)
CL/F (mL/min/kg)	2.6 (1.3)	2.8 (1.9)
V_z/F (mL/kg)	643 (225)	640 (165)

** Median is reported for T_{max}.

Table 22: Zolpidem Pharmacokinetic Parameters:

Effect of Xyrem Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Xyrem (n=15)	Alone (n=15)		
C_{max} (ng/ml)	90.0	98.0	0.92	0.78 – 1.08
AUC_{inf} (ng-hr/ml)	368.4	375.8	0.98	0.85 – 1.13

The systemic exposure to gamma-hydroxybutyrate following co-administration with Ambien was equivalent to the systemic exposure when Xyrem was administered alone. The gamma-hydroxybutyrate C_{max} increased by 6% and AUC_{inf} increased by 3% in the presence of Ambien. The systemic exposure to zolpidem following co-administration with Xyrem was equivalent to the systemic exposure when Ambien was administered alone. In the presence of Xyrem, the zolpidem C_{max} and AUC_{inf} decreased by 8% and 2%, respectively. According to the sponsor, the frequency and severity of adverse events was the same when Xyrem and Ambien were administered together as when Xyrem was administered alone. One adverse event was experience when Ambien was administered alone. All of the adverse events were well tolerated by healthy adult volunteers and resolved without sequelae.

Conclusions:

When Xyrem and Ambien were administered together, no clinically significant pharmacokinetic changes were observed for either drug. A pharmacodynamic interaction cannot be ruled out, especially when 9 g/day of Xyrem and 10 mg of zolpidem are administered. The results of the assay validation may be suspect because the tables submitted for this study were identical to the tables in the Modafinil and Vivactil drug interaction studies.

9. Protocol OMC- SXB-14: Pharmacokinetic Interaction of GHB with Vivactil (Protriptyline).

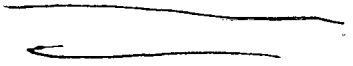
Title: A Study To Determine The Interaction Potential Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) With Vivactil® (Protriptyline Hydrochloride) In Normal Healthy Volunteers

Objectives:

The purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate [redacted] assay) and protriptyline [redacted] assay) in normal healthy subjects following administration of

Xyrem and Vivactil alone and in combination after an overnight fast. In addition, the safety and tolerability of sodium oxybate was assessed when administered alone and in combination to healthy volunteers.

Study Center:



Study Design and Methods:

This study utilized a single-center, open-label, three-period, three-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 three treatment sequences. All subjects spent the night before dosing at the study facility. During the morning of period 1, one third of the subjects ingested 2 x 2.25 g Xyrem 4 h apart, following a light breakfast; one third of the subjects ingested one 10 mg Vivactil tablet after a light breakfast; and one third of the subjects ingested both 2 x 2.25 g Xyrem and a 10 mg Vivactil tablet after a light breakfast. Lunch, dinner and a snack were given to the subjects at 5, 9, and 14 h following administration of GHB. There was a 3-week washout between periods 1, 2 and 3. During periods 2 and 3, individual subjects crossed over to the other treatments according to the sequence to which they had been randomized. Serial plasma samples were collected pre-dose and up to 312 h after the Vivactil dose, in combination treatment, and up to 8 h after Xyrem dosed alone. Appropriate samples were analyzed for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of co-administration. Throughout the treatment phase, each volunteer was monitored for the occurrence of adverse events (AEs) and changes in vital signs.

Subjects:

Twelve healthy volunteers (five male and seven female; 11 Caucasian and one Asian; 19 to 55 years of age; 56 to 89 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 (gamma-hydroxybutyrate) per milliliter. It was supplied by Orphan Medical in bottles of 180 ml [Lot No: EH75]. Vivactil was supplied as tablets containing 10 mg protriptyline hydrochloride (equivalent to 8.78 mg protriptyline base) [Lot No: H6740]. The 3 treatments compared in this study were a divided oral dose of 2 x 2.25 g sodium oxybate administered 4 h apart, a single oral dose of one 10 mg Vivactil tablet administered alone and the combination of a 10 mg Vivactil tablet and 2 x 2.25 g sodium oxybate. Each treatment was administered 2 h after a light breakfast. The doses were started at approximately 0800 hours (8 a.m.). Each Xyrem dose was diluted to 60 ml with room-temperature water and the dosing cup was rinsed with another 60 ml water. Each Vivactil dose was administered with 120 ml water. For the combination treatment the

Vivactil tablet was administered with the 60 ml Xyrem dose and followed by the 60 ml dosing cup rinsings.

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 ($t_{1/2}$) of gamma-hydroxybutyrate (GHB) and of protriptyline when administered alone and in combination. Dose-1 C_{max} and dose-2 C_{max} and the corresponding t_{max} were determined for the 2 portions of each Xyrem dose. 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 all treatment groups. The effect of co-administration of protriptyline hydrochloride on gamma-hydroxybutyrate pharmacokinetics was determined by an ANOVA of logarithmically transformed AUC_{inf}, dose-1 C_{max} and dose-2 C_{max} and computation of the 90% confidence interval for the ratio of the mean results observed after administration in combination and alone. A non-parametric analysis (Wilcoxon signed rank test) was used in the comparison of t_{max} values. The effect of co-administration of Xyrem on protriptyline AUC_{inf} and C_{max} were determined in the same manner.

Assay Validation:

The assay used to quantitate GHB and protriptyline was an ——— assay. For plasma GHB, the calibration curve was 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.

For protriptyline, the within-day variability ranged from 4.1 to 9% for the QC samples of 0.06, 2.00, and 40 ng/ml. For the accuracy of the method, the deviations from the mean were –0.5% for the low QC sample, -1.1% for the intermediate QC sample, and –0.9% for the high QC sample. The calibration curve was linear for the concentration range from ——— with a lower limit of quantitation (LLOQ) of ———

Results:

Figure 11: Effect of Vivactil on the Plasma Concentration-Time Profile of GHB

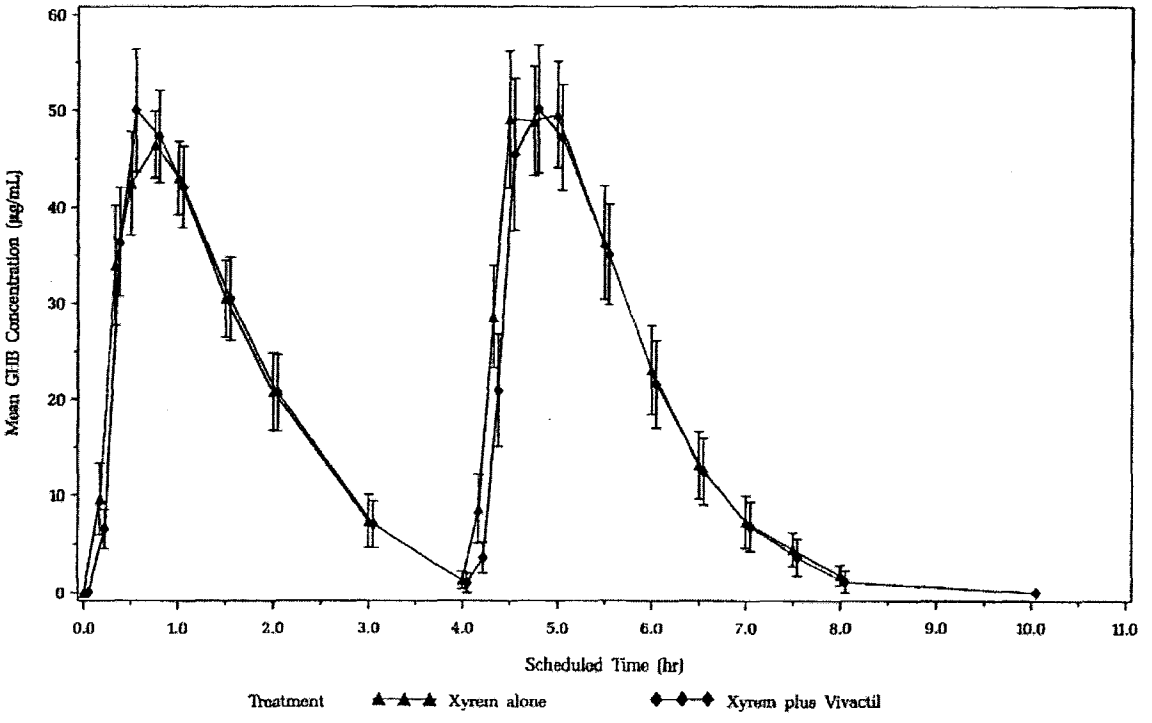


Table 23

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Xyrem Alone (n=12)	Xyrem With Vivactil (n=12)
Dose-1 C_{max} (µg/mL)	55.1 (14.5)	55.5 (18.8)
Dose-1 T_{max} (hr)	0.75	0.63
Dose-2 C_{max} (µg/mL)	64.6 (15.2)	58.3 (22.9)
Dose-2 T_{max} (hr)	0.50	0.75
$T_{1/2}$ (hr)	0.57 (0.19)	0.57* (0.18)
AUC_{inf} (µg.hr/mL)	178 (72.6)	183* (79.5)
CL/F (mL/min/kg)	5.7 (2.5)	5.9* (3.3)
V_z/F (mL/kg)	248 (44.8)	263* (98.6)

** Median is reported for T_{max}.

* n=11

There were no significant effects of co-administration of Vivactil with Xyrem ($p \geq 0.05$).

Table 24: Gamma-Hydroxybutyrate Pharmacokinetic Parameters: Effect of Vivactil Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Vivactil (n=12)	Alone (n=12)		
Dose-1 C_{max} (µg/ml)	52.5	53.5	0.98	0.85 – 1.14
Dose-2 C_{max} (µg/ml)	52.7	62.8	0.84	0.64 – 1.09
AUC_{inf} (µg-hr/ml)*	158.8	163.3	0.97	0.89 – 1.07

* n=11

Figure 12: Vivactil Plasma Pharmacokinetics Following Co-administration with GHB

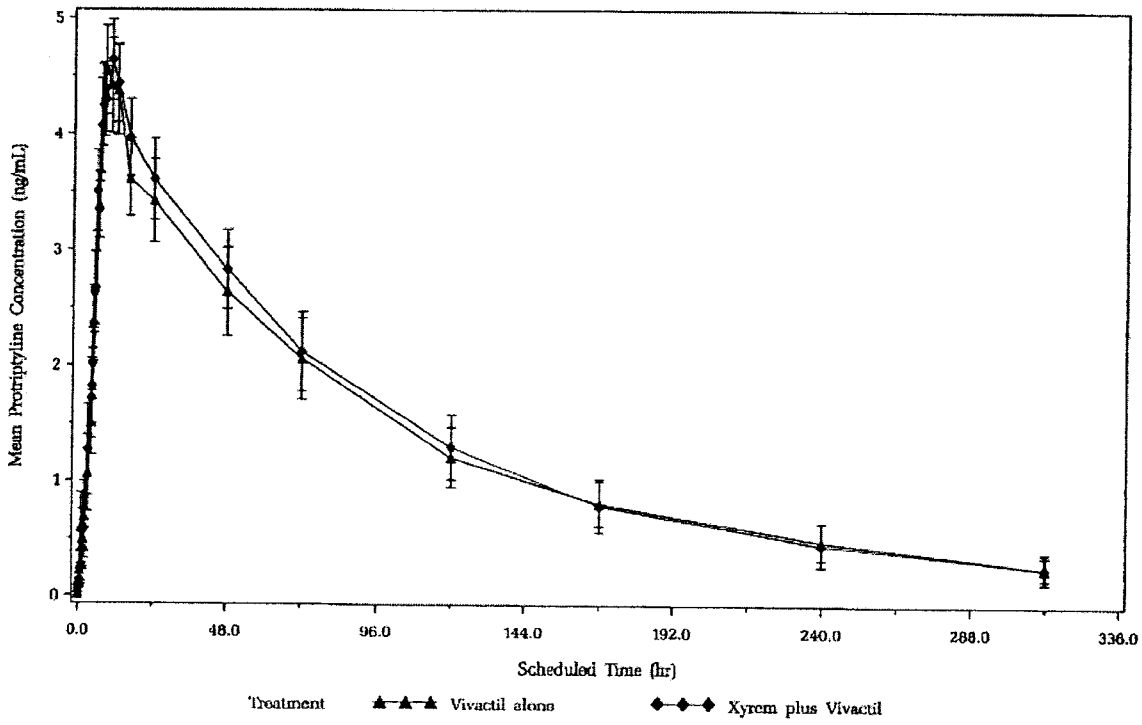


Table 25

Protriptyline Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Vivactil Alone (n=12)	Vivactil With Xyrem (n=12)
C_{max} (ng/mL)	4.7 (1.4)	5.0 (1.3)
T_{max} (hr)	8.00	8.00
$T_{1/2}$ (hr)	72.1 (38.2)	68.2 (39.1)
AUC_{inf} (ng.hr/mL)	452 (304)	463 (311)
CL/F (L/hr/kg)	0.41 (0.28)	0.40 (0.30)
V_z/F (L/kg)	32.0 (11.6)	30.6 (17.5)

Table 26: Protriptyline Pharmacokinetic Parameters:

Effect of Xyrem Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Xyrem (n=12)	Alone (n=12)		
C_{max} (ng/ml)	4.81	4.51	1.07	0.99 – 1.15
AUC_{inf} (ng-hr/ml)	377.5	367.7	1.03	0.96 – 1.09

On average, C_{max} decreased by 2% and 16% after the first and second portions of the Xyrem dose respectively and AUC_{inf} decreased by 3% following co-administration with Vivactil. The systemic exposure of protriptyline following co-administration with Xyrem was equivalent to the systemic exposure when Vivactil was administered alone. For protriptyline, the C_{max} increased by 7% and AUC_{inf} increased by 3% following co-administration with Xyrem. Thus, no clinically significant pharmacokinetic changes were observed for either drug. According to the sponsor, all of the adverse events were mild and well tolerated by healthy adult volunteers and resolved spontaneously without sequelae. The frequency of adverse events was greater when Xyrem and Vivactil were administered together compared to when Xyrem was administered alone but the severity of adverse events was similar. Only one adverse event was experienced when Vivactil was administered alone.

Conclusion:

The systemic exposure of human subjects to gamma-hydroxybutyrate when Xyrem was administered with Vivactil was equivalent to the systemic exposure when Xyrem was administered alone. The results of the assay validation may be suspect because the tables submitted for this study were identical to the tables in the Ambien and Modafinil drug interaction studies.

10. Protocol OMC SXB-17: Pharmacokinetic Interaction of GHB with Provigil

Title: A Study To Determine The Interaction Potential Of Xyrem® (Sodium Oxybate, Sodium γ–Hydroxybutyrate) With Provigil® (Modafinil) In Normal Healthy Volunteers

Objectives:

The purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate [redacted] assay) and modafinil [redacted] assay) following single doses of Xyrem and Provigil alone and in combination after an overnight fast. In addition, the safety and tolerability of sodium oxybate and modafinil were assessed alone and in combination.

Study Center: [redacted]

Study Design and Methods:

This study utilized a single-center, open-label, three-period, three-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 three treatment sequences. All subjects spent the night before dosing at the study facility. During the morning of period 1, one third of the subjects ingested 4.5 g of Xyrem following an overnight fast; one third of the subjects ingested a 200 mg Provigil tablet after an overnight fast; and one third of the subjects ingested both 4.5 g of Xyrem and a 200 mg Provigil tablet after an overnight fast. There was a 7-day washout between periods 1, 2 and 3. During periods 2 and 3, individual subjects crossed over to the other treatments according to the sequence to which they had been randomized. Serial plasma samples were collected pre-dose and up to 48 h following dosing for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of co-administration.

Subjects:

Thirteen healthy volunteers (six female and seven male; all Caucasian; 19 to 51 years of age; 59 to 88 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:

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). Provigil was supplied as tablets containing 200 mg modafinil. (Lot No. 918201) The 3 treatments compared in this study were a single oral dose of 4.5 g sodium oxybate administered alone, a 200 mg Provigil tablet administered alone and the combination of a 200 mg Provigil tablet and 4.5 g of sodium oxybate. Each treatment was administered after an overnight fast. The dose was administered at approximately 0700 hours (7 a.m.). Each Xyrem dose was diluted to 60 ml with room-temperature water and the dosing cup was rinsed with another 180 ml water. Each Provigil dose was administered with 240 ml water. For the combination treatment the Provigil tablet was administered with the 60 ml Xyrem dose and followed by the 180 ml dosing cup water rinsings.

Criteria for Evaluation:

Safety and pharmacokinetic parameters were the primary end-points of this pharmacokinetic and drug interaction study. Safety evaluations included physical examination, vital signs measurements (blood pressure, pulse, respiratory rate), electrocardiogram (ECG) assessment, clinical laboratory evaluation, and adverse events (AEs) assessment. 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 ($t_{1/2}$) of gamma-hydroxybutyrate and of modafinil when administered alone and in combination. 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 all of the treatment groups. The effect of co-administration of modafinil on gamma-hydroxybutyrate pharmacokinetics was determined by ANOVA of logarithmically transformed AUC_{inf} and C_{max} and computation of the 90% confidence interval about the ratio of the mean results observed after administration in combination and alone. A non-parametric comparison (Wilcoxon signed rank test) was used in the comparison of t_{max} values. The effect of co-administration of Xyrem on modafinil pharmacokinetics was determined in the same manner.

Assay Validation:

The assay used to quantitate GHB was an [redacted] assay. For plasma, the calibration curve was linear for the concentration range from . 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.

For modafinil, the [redacted] assay with UV detection was used for quantitation. The within-day variability ranged from 3.3 to 4.6% for the QC samples of 0.3, 2.0, and 18 µg/ml. For the accuracy of the method, the deviations from the mean were 8.5% for modafinil, and 7.7% for modafinil acid and sulfone. The calibration curve was linear for the concentration range from [redacted] with a lower limit of quantitation (LLOQ) of [redacted]

Results:

Figure 13: Effect of Provigil on the Plasma Pharmacokinetics of Xyrem

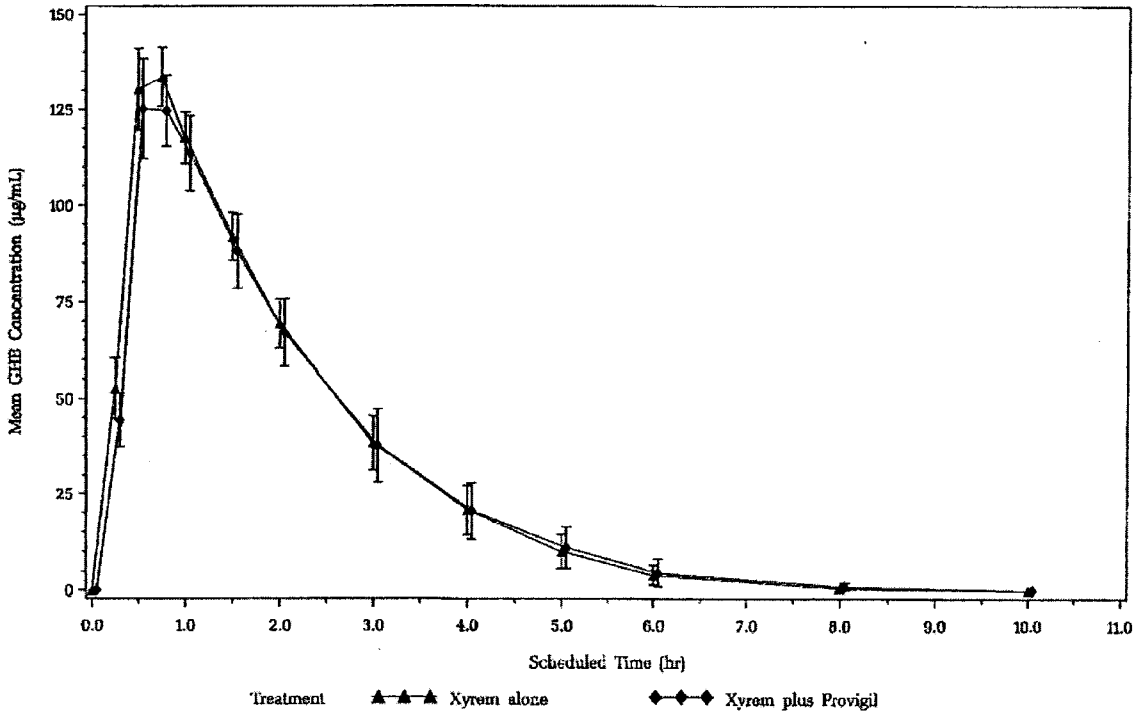


Table 27:

Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Xyrem Alone (n=12)	Xyrem With Provigil (n=12)
C_{max} (µg/mL)	146 (30.4)	135 (35.1)
T_{max} (hr)	0.50	0.50
$T_{1/2}$ (hr)	0.76 (0.18)	0.76 (0.21)
AUC_{inf} (µg.hr/mL)	302 (116.3)	294 (164.8)
CL/F (mL/min/kg)	3.1 (0.9)	3.4 (1.3)
V_z/F (mL/kg)	190 (29.8)	205 (41.7)

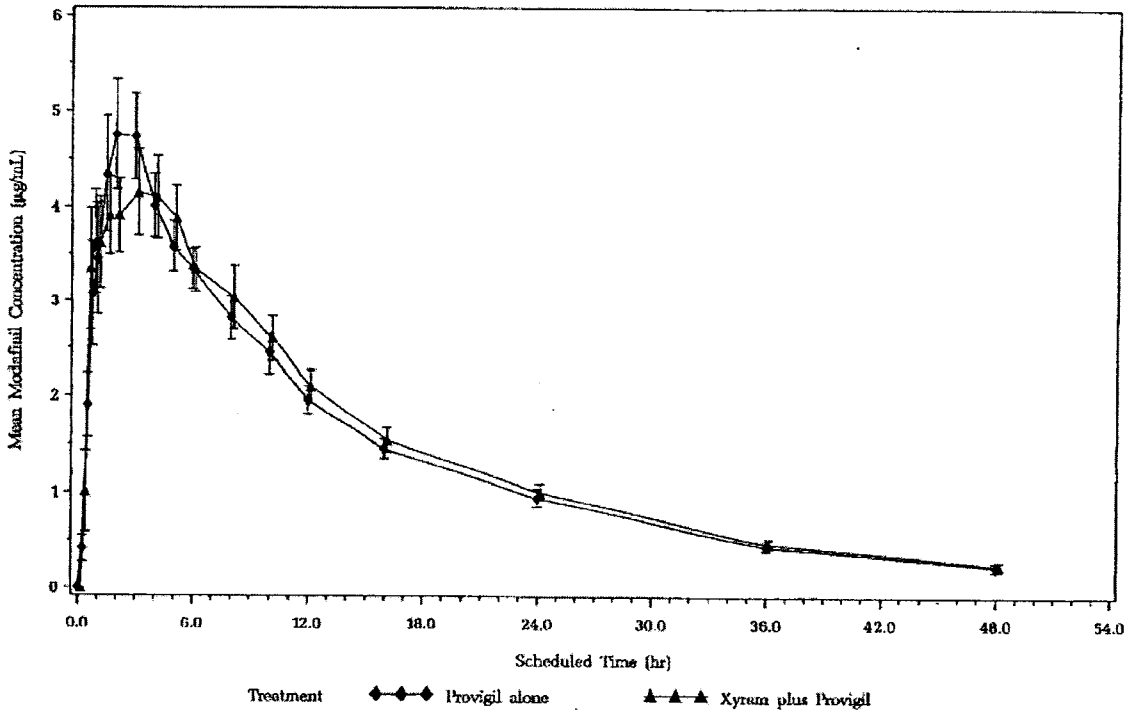
** Median is reported for T_{max}.

Table 28: Gamma-Hydroxybutyrate Pharmacokinetic Parameters:

Effect of Provigil Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Provigil (n=12)	Alone (n=12)		
C_{max} (µg/ml)	130	141	0.92	0.85 – 1.01
AUC_{inf} (µg-hr/ml)	263	282	0.93	0.85 – 1.01

Figure 14: Effect of Xyrem on the Plasma Pharmacokinetics of Modafinil



APPEARS THIS WAY
ON ORIGINAL

Table 29

Modafinil Pharmacokinetic Parameters:

[Arithmetic Mean (±SD)]**

Parameter (units)	Provigil Alone (n=12)	Provigil with Xyrem (n=12)
C_{max} (µg/mL)	5.5 (1.7)	5.2 (1.4)
T_{max} (hr)	2.00	1.00
$T_{1/2}$ (hr)	12.3 (2.3)	12.0 (1.8)
AUC_{inf} (µg.hr/mL)	71.8 (18.7)	74.2 (19.7)
CL/F (mL/min/kg)	0.66 (0.14)	0.64 (0.13)
V_z/F (mL/kg)	690 (141)	657 (135)

** Median is reported for T_{max}.

Table 30: Modafinil Pharmacokinetic Parameters:

Effect of Xyrem Co-Administration (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	With Xyrem (n=12)	Alone (n=12)		
C_{max} (µg/ml)	5.05	5.37	0.94	0.80 – 1.10
AUC_{inf} (µg-hr/ml)	72.0	69.1	1.04	0.98 – 1.11

The systemic exposure of human subjects to gamma-hydroxybutyrate (oxybate) when Xyrem was administered with Provigil was equivalent to the systemic exposure when Xyrem was administered alone. The GHB C_{max} and AUC_{inf} decreased by 8% and 7%, respectively. The systemic exposure of human subjects to modafinil when Provigil was administered with Xyrem was equivalent to the systemic exposure when Provigil was administered alone. The modafinil C_{max} decreased by 6% and AUC_{inf} increased by 4%. All of the adverse events were mild in severity, well tolerated by healthy adult volunteers and resolved without sequelae. Neither drug alone nor in combination had any clinically significant effects on heart rate, blood pressure or respiration rate.

Conclusions:

Xyrem and Provigil when administered together presented no clinically significant pharmacokinetic changes. The results of the assay validation may be suspect

because the tables submitted for this study were identical to the tables in the Ambien and Vivactil drug interaction studies.

Literature (Protein Binding and Absolute Bioavailability *via* cross study comparison)

According to literature data, less than 1% of GHB is bound to plasma proteins. In addition, the absolute bioavailability of GHB was determined to be 30%, as a result of cross study comparisons of literature results.

22 page(s) of revised draft labeling has been redacted from this portion of the review.

Body as a whole

Abdominal
hangover effect,
neck rigidity.

Cardiovascular system

Digestive system

constipation,
mouth ulceration,
stomatitis,

Hemic and lymphatic system

Anemia, ecchymosis,
leukocytosis,
lymphadenopathy,
polycythemia.

Metabolic and nutritional

Alkaline phosphatase increased,
hypercholesteremia, hyperglycemia,

Musculoskeletal system

Arthritis,
leg cramps,

Nervous system

Agitation, convulsion,

stupor.

Respiratory system

Skin and appendages

Acne, alopecia, rash,

Special senses

taste loss,

Urogenital system

albuminuria, hematuria, urine frequency,

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Xyrem is classified as a Schedule III controlled substance by Federal law. Non-medical uses of sodium oxybate are classified under Schedule I.

Abuse, Dependence, and Tolerance

Abuse

Dependence

Tolerance

[redacted]

OVERDOSAGE

Human Experience

Information regarding overdose with sodium oxybate is derived [redacted] from [redacted] describing [redacted]

Signs and Symptoms

[redacted]

Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if coingestants are suspected. [redacted] emesis [redacted] presence of [redacted] appropriate posture (left lateral recumbent position) or protection of the airway by intubation should be [redacted] Although the gag reflex may be absent in deeply comatose patients, even unconscious

In ten other cases, GHB was not used alone. In six of these cases, the deaths were possibly related to the use of GHB. The medical examiners in two cases concluded that the cause of death was GHB intoxication. Both patients had a history of alcohol abuse, mental illness *(depression, bipolar, respectively)*, and had taken other medications at the time of the death. GHB level in the blood was 380 mg/L in one patient. In both cases, GHB was used for recreational purposes, but it is concerning that one of the deaths occurred in January 2002. How this patient acquired this drug was unknown. In a third case, an autopsy report stated that GHB in combination with opiates and benzodiazepines caused the death of a 23 year old male in an accidental manner. Two reports noted the use of alcohol as one of the concomitant drugs. GHB level in the blood was 190 mg/L in one patient. The final patient had a history of using multiple over-the-counter supplements *(e.g. Ma Huang)* and steroids for body building.

The remaining four cases of death were very confounded, and therefore, a possible association with GHB seemed unlikely. In two elderly patients, the reported causes of death were Lyell's Syndrome and circulatory shock in one patient, and encephalopathy and pneumonia in the other. GHB was listed as one of the many concomitant drugs without additional information. In the third case, the patient may have been using small doses of arsenic and had a history of alcohol abuse. He had used large doses of GHB as a sleeping agent for 8-9 months. Prior to death, he experienced seizures, hyponatremia, and cerebral edema. In the last case, two weight-loss supplements *("Absorbit-All plus", "Slim-again")* may have been used concomitantly. The autopsy report indicated that the cause of death was probable idiopathic cardiac arrhythmia. Other significant condition was listed as drug-induced sleep produced by Renewtrient *(GHB-containing substance)*, but the GHB level in her blood was moderate (170 mg/L). The husband of the deceased did not think that other prescription or OTC medications were used within 72 hours prior to her death. See the table below for further details:

	Age/ Sex/Yr	Concomitant Medications	Drug levels	GHB used	Cause of Death	Significant Medical Hx
1	27 M (2000)	Not stated ---	---	Enliven	"Suicide when attempting to stop using" Enliven *(per family)*	Healthy body builder, not drug user
2	55 M (1998)	Prozac, Lipitor, HCTZ, Xanax, vitamins, garlic, aspirin, diphenhydramine, terpin hydrate, acetaminophen, nicotine propoxyphene (norpropoxyphene)	GHB(blood) -380 mg/L GHB(urine) ≈5100mg/L	GHB	Cause: GHB intoxication	Alcoholic, depression, HTN, ↑ chol
3	24 M (2002)	Unisom	GHB(urine) -15583mg/L	GHB	Cause: GHB intoxication	Attempted suicide 6 mos prior, bipolar, depression, alcoholic, hx of seizures and drug abuse
4	23 M (2000)	Oxycodone, hydrocodone, benzodiazepine	---	GHB	Cause: respiratory failure due to multi-drug combination, (accidental)	---

5	20 M (1999)	Alcohol (for increased intoxication)	GHB(blood) - 190 mg/L GHB(urine) - 690 mg/L EtoH- 0.15%	Invigorate	Not stated, experienced coma prior to death	Frequent alcohol use
6	42 F (1999)	Alcohol, Revia, Augmentin, possibly Zoloft and Trazodone	---	NRG3	Cause: Ingestion of NRG3 *(per family)*, found dead hrs later	Alcohol abuse, depression, smoker
7	23 M (1999)	Rippled Fuel *(contains Ma Huang)*, various dietary supplements, naproxen, possibly steroids and other GHB containing substances	---	Blue Nitro	Not stated, found dead next morning in bed	Body builder, previous ER visits for adverse events from GHB use
8	65 F (1998)	Diprostene, amoxicillin, tetrazepam, estradiol, medroxyprogesterone, zolpidem, meprobamate, bromazepam, piascledin (avocado/soya oil), sodium uridine, paracetamol	---	Renutryl 500	Cause: Lyell's syndrome, circulatory shock	Arthrosis, rhinitis
9	82 M (1997)	Miconazole, cisapride, glibenclamide, tianeptine, algeldrate,	---	Renutryl	Cause: B/L pneumonia and encephalopathy	Angina, right hemi-laminectomy
10	52 M (1999)	Small amount of arsenic?	---	Zen and Rest Eze	Not stated, experienced seizures, hyponatremia, and cerebral edema prior to death	Hx of alcohol abuse
11	29 F (1998)	Possibly have taken weight-loss supplements *("Absorbit-All plus", "Slim-again")* at time of death Not taken other prescription or OTC meds within 72 hrs prior to death *(per husband)*. List of meds included, Prozac, Biaxin, Diazepam, Imitrex, promethazine	GHB(blood) -170 mg/L	Renewtrient	Cause: Probable idiopathic cardiac arrhythmia Significant condition: drug-induced sleep by Renewtrient	hx of Phen-Phen use *(heart valves unremarkable)* obesity, tuberculosis,

In conclusion, six of 11 cases of death may have been associated with the use of GHB, but in all six cases, the concomitant use of other drugs was noted.

Lauren Lee, Pharm.D.
Post-Marketing Safety Evaluator

Concur:

Susan Lu, R.Ph.
Team Leader

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

/s/

Lauren Lee
6/7/02 04:33:07 PM
PHARMACIST

Julie Beitz
6/7/02 05:01:10 PM
DIRECTOR

MEMORANDUM

To: File, NDA 21-196

Through: Robert Temple, M.D., ODE I Office Director
Russell Katz, M.D., Division Director, Neuropharmacologic Drug Products
Barry Rosloff, Ph.D., Pharmacology Supervisor, HFD-120
Anna Marie Hommonay R.Ph., Project Manager, HFD-120

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

Subject: NDA 21-196, Xyrem®, sodium oxybate (sodium gamma hydroxybutyrate)
Tertiary Review of Pharmacology/Toxicology Data

Date: April 8, 2002

The preclinical pharmacology and toxicology data submitted in support of the approval of Xyrem suggest that the chronic administration of gamma hydroxybutyrate (GHB) to animals was associated minimal systemic toxicity. Therefore, I concur with Dr Rosloff's recommendation that the NDA is approvable.
Preclinical studies submitted in support of the NDA include complete genotoxicity and reproductive toxicity batteries and 6-month rat and 12-month dog oral toxicity studies with GHB. The published results of 2-year oral carcinogenicity studies conducted by the National Toxicology Program (NTP) with gamma-butyrolactone (GBL) in mice and rats were also provided . GBL is extensively converted to GHB *in vivo*. A separate 2-year rat carcinogenicity study with GHB has been recently completed and the results will be submitted as a Phase 4 commitment.

The genotoxic potential of GHB was evaluated in an Ames test, an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and an *in vivo* rat micronucleus assay. GHB tested negative in all three assays. The NDA review (p.102) suggests that higher doses of GHB could have been utilized in the rat micronucleus assay. However, the high dose of 2000 mg/kg/day is considered the maximum required dose for testing in the *in vivo* micronucleus assay. Therefore, the completed genotoxicity battery is adequate.

The only drug-related adverse effects observed in the chronic oral toxicity studies were hypoactivity and mild decreases in food consumption and body weight gain in high dose rats and high dose dogs. The high doses tested, namely 1000 mg/kg/day in rats and 600/900 mg/kg/day in dogs, produce exposures comparable to (1-2 times) therapeutic exposures with the maximum recommended human dose of 9 grams/day. The animal to human exposure ratios (safety margins) are comparable regardless of whether the comparison is based on body surface area (mg/M^2) or actual pharmacokinetics (AUC) .

The effects of GHB on fertility, reproductive performance, embryo-fetal and postnatal development were evaluated in the standard battery of studies which included a rat fertility study, rat and rabbit embryo-fetal toxicity studies, and a rat pre/postnatal development study.
No compound-related reproductive or developmental adverse effects were observed in any of the studies. Similar to the oral toxicity studies, the highest doses evaluated in the reproductive toxicity studies produce drug exposures in animals comparable to human therapeutic exposures. The high dose of 1200 mg/kg/day utilized in the rabbit teratology study was associated with decreased food consumption and significant decreases in maternal weight gain supporting the

adequacy of the doses tested in the rabbit. Data were not provided in the NDA review to demonstrate that the 1000 mg/kg/day high dose evaluated in the rat studies was adequately high (i.e., associated with minimal maternal toxicity).

The rodent carcinogenicity studies conducted by the NTP evaluated gamma butyrolactone(GBL) , which is extensively converted to GHB *in vivo*.
2-Year Study in B6C3F1 mice: Doses evaluated were 0, 262, and 525 mg/kg/day in both sexes. (50/sex/dose). There was no evidence of carcinogenic potential associated with chronic oral administration of GBL.
The high dose of 525 mg/kg/day GBL exceeded the maximum tolerated dose (MTD) in male mice since significant mortality was observed (76% at HD vs. 30% in controls) . The high dose of 525 mg/kg/day GBL also represented the MTD in female mice since the final mean body weights were reduced 14-17% in HD female mice. A separate study was conducted to determine the plasma GHB exposures (AUC) after direct dosing with the MTD of GHB in mice (1000 mg/kg/day) or the high dose of 525 mg/kg/day GBL tested in the 2-year mouse CA study (see NDA review, p. 93). This was performed to determine adequacy of the completed mouse study with GBL to assess the carcinogenic potential of GHB . This evaluation demonstrated that GHB exposures after dosing with the high dose of 525 mg/kg/day GBL in mice were approximately 50% in males and 70% in females of those achieved after direct dosing with gamma hydroxybutyrate at the MTD . Therefore, it was concluded that the mouse study with GBL could be considered an adequate carcinogenicity assessment since it was conducted at GHB exposures in mice equivalent to 50% of those attained with the maximum tolerated dose of gamma hydroxybutyrate. (Carcinogenicity studies conducted at half the MTD are generally accepted as adequate).

2-Year Study in F344 rats: Doses evaluated were 0, 112, 225 mg/kg/day in males; 0, 225, 525 mg/kg/day in females (50/sex/dose). GBL produced no increases in neoplastic or non-neoplastic lesions in this study. However, doses of GBL evaluated in the rat did not represent a maximum tolerated dose (MTD) since they were not associated with excess mortality, decreased mean body weight, or any significant increase in tissue pathology or tumors.
In addition, the GHB exposures in rats after administration of the high doses of GBL were only fractions of the AUC exposure to GHB associated direct dosing of the maximum tolerated dose of GHB to rats (8% in males, 35% in females; NDA review p. 96). It was concluded that the rat study with GBL was not an adequate assessment of the carcinogenic potential of GHB. A 2-year rat study with GHB was conducted at FDA request. The 2-year rat carcinogenicity study with GHB has been completed and the sponsor has stated that no evidence of carcinogenic potential was observed. The Division has agreed to accept the results of the 2- year rat study with GHB as a Phase 4 commitment.

Assessments of carcinogenic potential are generally required prior to approval. The Division's decision to allow post-approval submission of the rat carcinogenicity study results for GHB appears reasonable based on the other available data suggesting a minimal carcinogenic risk. These supportive data include:
1) the absence of evidence of genotoxic potential
2) the absence of tissue proliferative effects in chronic toxicity studies (i.e., no evidence for potential carcinogenic effects via non-genotoxic mechanisms)
3) no evidence of carcinogenic potential in a 2-year mouse study with GBL (at GHB exposures half the MTD for GHB).

A labeling review has been conducted (NDA review pp. 103 and 104) and accurately represents the study findings.

MEMORANDUM

DATE: April 4, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-196

SUBJECT: Recommendation for action on NDA 21-196, for the use of Xyrem (Sodium Oxybate) in narcoleptic patients with cataplexy

NDA 21-196, for the use of Xyrem (Sodium Oxybate) as treatment for cataplexy and excessive daytime sleepiness in narcoleptic patients with cataplexy, was submitted by Orphan Medical, Inc., on 9/30/00. The Agency issued an Approvable letter on 7/2/01; in the draft labeling accompanying that letter, the proposed indication was changed to the treatment of cataplexy in patients with narcolepsy. The letter included a number of requests pertaining to the sponsor's proposed Risk Management System, as well as requests for some additional data analyses, and draft labeling.

The sponsor responded to the Approvable letter with a submission dated 10/5/01. This submission was made after several meetings with Agency staff, in which various areas of disagreement were discussed. The resubmission has been reviewed by Dr. Ranjit Mani, medical officer (reviews dated 3/4/02 and 3/29/02), Dr. Gerald Fetterly, Office of Clinical Pharmacology and Biopharmaceutics (review dated 3/5/02), Dr. Thomas Oliver, chemist (review dated 3/29/02), and Dr. John Feeney, Neurology Team Leader (memo dated 4/3/02). In addition, the various documents associated with the sponsor's proposed Risk Management Program have been reviewed by members of the Controlled Substances Staff, the Office of Drug Safety, DDMAC, and Dr. Judy Racoosin, Safety Team Leader of this division. Finally, it should be noted that the sponsor and we agree that the application will be reviewed under Subpart H.

Drs. Feeney and Mani both recommend that a second Approvable letter be issued. In this memo, I will briefly review the pertinent issues, and offer the division's recommendations for action on this application.

RESPONSES TO ISSUES IN THE APPROVABLE LETTER

A number of issues were raised in the Approvable letter to which the sponsor responded. I will address them by category.

Risk Management Program (RMP)

A number of specific changes in the sponsor's proposed RMP were requested. Dr. Mani has addressed each one; I will describe the major issues discussed.

The sponsor and Agency had previously agreed that physicians would need to assert in writing that they had read the Physician Educational Materials before they could prescribe the medication. In our Approvable letter, we proposed that the physician must assert that the patient for whom they were prescribing Xyrem had narcolepsy with cataplexy (the population for whom we had agreed that the drug would ultimately be indicated).

The sponsor (and its legal counsel) strongly objected to this provision, asserting that restricting prescribing in this way would be an inappropriate infringement on medical practice, and that to do so would run counter to Agency pronouncements over many years that the Agency does not regulate the practice of medicine. Our rationale for proposing this restriction was primarily based on our view that the existing safety database was considerably smaller than we would have wished, the fact that safety (and of course efficacy) had not been established for any population other than that for whom it was to be indicated (indeed, some held the view that the potential serious risks in healthy volunteers might be greater than in patients with narcolepsy), and that there was good reason to believe that, in the absence of an explicit restriction, the drug, once approved, would likely be used for many different medical indications (for example, its use for many indications is described and promoted [not by the sponsor] on the Internet). These factors convinced us, at the time of the Approvable letter, that it would be prudent to require that physicians assert that their patients had the approved indication before it could be released to the patient.

In subsequent discussions with several attorneys in the Office of the Chief Counsel and conversations between the Deputy Center Director and the Chief Counsel himself (conversations with the Chief Counsel did not include members of the division), it became clear that the Chief Counsel (as has been explained to me by Dr. Robert Temple, Director of the Office of Drug Evaluation I) would not support the approval of the application with this proposed restriction, unless we were willing to conclude that the drug could not be used safely without the restriction. That is, if we preferred the restriction, but concluded that the drug could be marketed safely without the restriction, we could not require the sponsor to include the restriction.

Drs. Feeney and Mani imply that the drug cannot be marketed safely without the restriction (they also both have additional reasons for proposing that the application not be approved at this time). I do not believe that the restriction must be a condition of approval.

All other things being equal (see below), I believe that the drug can be marketed safely without the restriction (although I do agree that the restriction is preferable). We have previously determined that the drug, despite the small

safety database, can be used safely in the patients for whom it will be indicated, and this would be, in my view, sufficient to permit marketing of the drug with appropriate labeling. While off-label use is, in my view, imprudent (given the absence of evidence establishing either the safety or effectiveness for any other indication), I cannot conclude, at this time, that its use in these other indications is manifestly unsafe. I share Dr. Mani's concern that the drug, once approved, might be used (and may, in fact, likely be used) in non-narcoleptic, non-cataplectic patients, and that such use might be dangerous, but I believe that it would be inappropriate to withhold approval and availability of the drug for patients for whom we believe it is safe and effective (given the Chief Counsel's opinion) because of fears of adverse consequences in other populations. I believe that additional language in the document that prescribers must sign before the drug can be released can make them aware of the lack of evidence of safety and effectiveness for other indications and serve the purpose of markedly decreasing such off-label use (this is conjecture, of course, as is the conclusion that an explicit restriction will decrease actual off-label use). For these reasons, then, I agree with the sponsor that an explicit restriction need not be imposed, although, again, I do believe that it would be preferable.

The remaining proposals we made in the Approvable letter in reference to the RMP have largely been adopted by the sponsor. We will, however, have a number of comments about the specific wording of various sections of the several documents accompanying the RMP.

Additional safety analyses

In the Approvable letter, we asked for updated safety information on several on-going trials, as well as more complete follow-up on a number of Dr. Scharf's patients and further analyses of the event termed "sleepwalking". In addition, we asked the sponsor to perform a formal study to assess the effects of Xyrem on respiratory function (this last request was supported by our view that Xyrem is a powerful CNS depressant, there were at least 2 reports in the safety database of potential respiratory depression, and such a study is routinely required and performed for standard sedative hypnotics).

The sponsor has responded to these requests. The additional safety updates, including the follow-up for the requested 11 patients of Dr. Scharf who did not enter the Treatment IND and the detailed analyses of the event termed "sleepwalking", revealed no significant untoward events not previously known (although it should be noted that we still do not have a detailed understanding of the exact nature of the events labeled "sleepwalking", and that there is considerable uncertainty as to what this compilation of middle-of-the night behavioral phenomena really are). Nonetheless, the additional data do not provide reason for additional concern.

Our request for a formal study designed to assess the drug's effect on respiratory function was discussed with the sponsor prior to the submission of their response. They told us that they had performed a study primarily designed to assess Xyrem's effect on sleep architecture, but that patients in this study also had had formal assessment of their respiratory function. We agreed that the sponsor could submit this study in an attempt to convince us that the drug caused no important respiratory depression, and they committed to performing a more rigorous study in Phase 4.

The study generated evaluable data in 21 patients with narcolepsy, 4 of whom also had moderate to severe sleep apnea, and 4 of whom had mild sleep apnea (although sleep apnea was an Exclusion Criterion). The study was open-label and uncontrolled, and each patient was assigned to receive the following dose schedule: 4.5 gms/night x 4 weeks, 6 gms/night x 2 weeks, 7.5 gms/night x 2 weeks, and 9 gms/night x 2 weeks. After completion of each dose (and on the first night of treatment with the 4.5 gm dose), a full night's polysomnogram was performed on each patient. Various parameters were measured, including Respiratory Depression Index (RDI), a weighted average of the number of apnea and hypopnea episodes/hour during REM and non-REM sleep, the Apnea Hypopnea Index (AHI), the number of such episodes/hour calculated separately for REM and non-REM sleep, pulse oximetry (from which could be calculated the amount of time spent with O2 saturations below, for example, 90%, as well as other metrics), and other measures (e.g., the total number of central and obstructive apneas).

A total of 18 (86%) of patients was being treated with concomitant stimulants.

Although there was considerable variability in the data, there were slight and intermittent abnormalities in many of the measures of respiratory depression compared to baseline over the course of the study.

For example, there was slight numerical worsening in the RDI over the course of the study compared to baseline, with the maximum abnormalities seen on the polysomnogram performed after the first 4 weeks (i.e., after the 4.5 gm dose). The differences seen after the 6 and 9 gm dose were trivial, with a more abnormal response after the 7.5 gm dose. In general, this pattern occurred for other measures as well. That is, overall changes were relatively minor, with the most abnormal values seen with the 4.5 gm dose; variability was great throughout.

With regard to measures of O2 saturation, there were few even numerical changes in mean measures, with a very small, but stable, increase in the percent of the duration of the night during which O2 saturation was < 90% compared to baseline.

Given that this study was uncontrolled, unblinded, and non-randomized, it might more accurately be seen as a case series of 21 individual patients' experience. In this case, examination of the individual cases is appropriate, whereas this would not be so if the trial had been randomized and controlled (where groups would be the appropriate experimental unit).

When we examine the individual patients, it becomes clear that a few patients are responsible for the numerical trends seen. That is, a few patients experienced considerable worsening of their symptoms over the course of the study. Dr. Feeney has described those patients whose experience he finds particularly disturbing.

In particular, Patient 17301 had an RDI of 32 at baseline (consistent with moderate sleep apnea), which increased to 100 with the 4.5 gm dose in the first half of the night (down to about 80 during the second half of the night). Although the RDI decreased after the 4.5 gm dose during the first half of the night toward the baseline value (although it did not fully return to baseline), the decrease after the 4.5 gm dose during the second half of the night was considerably complete. A somewhat similar pattern of abnormality on the number of central apneas was also seen for this patient.

Further, this patient spent a majority of the night with O2 saturation below 90%, compared to about 120 minutes below 90% saturation at baseline, and the percent of time during which the saturation was below 90% appeared to be dose related, going from about 35% of the first half of the night at 4.5 gms to about 70% of the first half of the night at 9 gms. About 15% of the second half of the night was spent with an 02 saturation below 90% at 4.5 gms, compared to about 60% at the 9 gm dose (the baseline percent was about 25%).

A second patient with an RDI of 36 at baseline was recorded to have an RDI of 100 at the 4.5 gm dose, with a more modest increase compared to baseline at the 6 gm dose. However, after a few days at 7.5 gms, her husband noticed increased apneic episodes and snoring. There was also a significant increase in central apneas at the 4.5 gm dose (259/night) compared to baseline (21/night), with a less significant increase (81/night) at the 6 gm dose. She discontinued the study because of her increased apneic and snoring episodes before she completed the 2 weeks on the 7.5 gm dose. This patient was not noted to have abnormalities compared to baseline in O2 saturation indices at doses less than 7.5 gms (again, she was not tested at the 7.5 gm dose, the dose at which she was reported to have become importantly symptomatic).

A third patient had an RDI of 3 at baseline (an RDI of 5 is essentially the lowest value compatible with a diagnosis of sleep apnea) which rose to 16 at the 7.5 and 9 gm doses.

As Dr. Feeney notes, therefore, 2 of 4 patients with moderate to severe sleep apnea had a considerable worsening of various measures of respiratory function, and a third patient, who had not been diagnosed with sleep apnea, developed over the course of the study an RDI (at the highest doses) compatible with mild-moderate sleep apnea.

Again, the nature of the experience reported permits us to examine individual patient responses. This examination reveals some significant abnormalities, primarily in patients with a diagnosis of moderate to severe sleep apnea. These findings raise a number of questions.

Of course, the findings may be spurious. The uncontrolled, non-randomized nature of the experiment does not allow us to conclude definitively that any results are causally related to treatment. Further, while there are a number of mean changes in the direction of worsening on some parameters, they are not monotonically dose related, with the maximum abnormalities seen in most cases at the 4.5 gm dose.

However, as I have noted, it is reasonable, given the design of the experiment, to examine individual patient responses. When one does this, it is clear that there were at least 2, maybe 3, patients who had, at least at some time (dose) of the study, abnormalities of clinical concern. Again, we cannot definitively link these abnormalities causally to treatment with GHB. In particular, several of these abnormalities do not strictly follow a clear dose response, although some appear to (e.g., time spent with O2 saturation below 90%). Nonetheless, the results in these patients do raise concerns that treatment with GHB may cause worsening of respiratory function in patients with sleep apnea, and perhaps in some patients not diagnosed with sleep apnea. While we do not have evidence that any patient has suffered a serious acute clinical event related to any decrement in respiratory function in this study (or in the rest of the database), it is well known that patients with sleep apnea have an increased risk of serious cardiovascular disease; the magnitude of the risk is presumably related to the severity of the apnea. Further, as Dr. Feeney has noted, it is at least possible that the events labeled "sleepwalking" by the sponsor might actually be confusion related to hypoxia. While there is no question that Dr. Mani's observation that there is great variability in the data (when, for example, mean responses are examined) is correct, I am inclined to share Dr. Feeney's concern that the data suggest that GHB might be associated with a significant decrement in respiratory function in some patients (in particular those with sleep apnea). Again, this conclusion is entirely provisional. That is, these conclusions may be wrong, and a well designed and conducted trial might establish that no such drug effect occurs. Nonetheless, until such a study is performed, we must continue to presume that these events are treatment related.

What, then, should be the consequence of this finding?

It is possible, I suppose, to approve the application without definitive information about the effect of GHB on respiratory function, either in the entire population of patients or in specific sub-groups (e.g., those with sleep apnea). Were we to do this, certainly a description of this study would need to be included in labeling. My view is that such an approach, by itself, would be inadequate. It is, of course, true that all drugs are approved for marketing in the face of incomplete information about many of their effects. However, I believe that it is incumbent upon the sponsor to make all reasonable attempts to fully evaluate important effects of a treatment on critical physiologic functions prior to marketing. I would argue that GHB's effects on respiratory function falls in this category. We are well aware that GHB is a powerful CNS depressant, and we made it clear in our Approvable letter (and in subsequent meetings with the sponsor) that such an evaluation would be required prior to marketing. While we agreed to review the data in Study 20, we did not agree that this study would be adequate. Close examination of the results suggests that GHB may have important deleterious effects on respiration, especially in patients with sleep apnea. Indeed, the FD&C Act requires sponsors to perform "adequate tests by all methods reasonably applicable" to demonstrate that the drug is safe in use as described in labeling. While the interpretation of this clause in any given case is, of course, a matter of judgement, it is not unreasonable, in my view, to require the sponsor to perform such tests.

One could argue that this data would be sufficient to support approval because these effects, if they do exist, did not result in catastrophic outcomes; that is, no one died as a result.

This is true in this study, to be sure, but we cannot presume to know, given the small database, especially at the maximum dose to be prescribed (a total of 74 patients exposed to 9 gms/night for at least 6 months) that GHB-induced respiratory depression cannot cause serious clinical outcomes related to respiratory depression. My own view is that the absence of deaths attributed to this presumed mechanism (this does not address the possibility of increased mortality caused by cardiovascular disease associated with sleep apnea) does not absolve the sponsor from adequately assessing GHB's capacity to effect respiratory function. Further, the experience at the 9 gm dose, in particular, is quite small, as noted. Unless the mortality associated with this dose was exceptionally high, no deaths would be expected to emerge in such a small cohort. Knowledge of the drug's untoward effects, if any, on respiratory function would add critical information necessary for the prescriber to make an informed treatment decision, especially in the face of a small empirical experience.

In my view, we should be able to expect (and, again, I believe the Act requires) a sponsor to make a reasonable effort to evaluate important effects of a drug, even if those effects may not be associated with immediate adverse consequences, like mortality. Specifically, while one could argue that because no deaths occurred in this study, approval could be supported with appropriate labeling, (for

example, by including language that states that the effect on respiratory function has not been adequately assessed, but that the effect may be serious and adverse, and even perhaps contraindicating its use in patients with sleep apnea), I believe that such an approach, generically, is ill advised.

I believe that our obligation is to assess, and describe in labeling, if appropriate, important effects of the drug prior to approval. The absence of observed deaths is not sufficient to justify approval, in my view. We routinely require a standard battery of tests prior to approval, regardless of their outcome. For example, we routinely require that animal carcinogenicity tests be performed. A drug may be approved for marketing even if the results demonstrate that the drug is carcinogenic (depending upon the clinical indication, of course). We could, of course, not require such tests, and simply state in labeling that these tests (or a host of other required tests) have not been performed, but we do not, ordinarily, take this position. We require these tests because we have decided, I believe, that it is important for prescribers to have this information so that they may make an informed decision about whether or not a particular drug is appropriate for a particular patient. We do not ordinarily "assume the worst" for a given drug, and proceed to approve that drug in the absence of the required tests.

Of course, certain factors in this case would seem to support a lesser standard.

First, no drug is currently approved for the treatment of cataplexy, a potentially devastating symptom, and GHB is clearly effective. While independent evidence of a clear effect of GHB on major cataplexy attacks does not exist, GHB is numerically superior to placebo on these attacks. One could argue that these patients should not be deprived of this treatment on the basis of a suspicion of an adverse event. Further, and importantly, GHB will be distributed under what amounts to a registry. Each patient who receives GHB (regardless of indication) will be registered in a central registry, and presumably assessed by their physician no less frequently than every three months. Adverse events will be documented at these visits. In essence, this distribution system resembles a long-term open, uncontrolled extension study of the sort usually performed in Phase 3. This "study" should provide extensive, well-documented safety experience relatively rapidly in thousands of patients. Indeed, we have imposed these highly unusual provisions for detailed safety monitoring in Phase 4 precisely because the pre-marketing database is so small.

In my view, then, the issue is whether or not the suspicions raised by Study 20 are of sufficient concern to require a more detailed assessment of respiratory function prior to marketing, or can they be further assessed formally after marketing. In other words, does the current NDA database, in conjunction with the monitoring provisions of the restricted distribution system, support the safe marketing of GHB, with appropriate labeling?

I believe it does not.

As I stated above, ordinarily, a minimum amount of evidence about a drug's effects on important functions is required prior to approval. In the absence of such evidence, I believe it is typically inappropriate to assume the worst and draft labeling that states as much. In this case, I believe that we do not have adequate data on the effects of GHB on respiratory function, especially in patients with sleep apnea, and I further believe it is our responsibility to require the sponsor to obtain it (again, I believe the Act requires it, in my judgment in this case, and I believe this was the position we took in our Approvable letter) prior to approval of the application. The fact that patients will be monitored closely in Phase 4 is comforting, but it does not, in my view, absolve us or the sponsor of the need to adequately characterize the drug's effects on this critical function. The only potentially supportable position in the absence of adequate data might be to contraindicate the drug in patients with sleep apnea, but I believe even this approach is inadequate, because, if it is true that there is a significant co-morbidity with narcolepsy, such use will undoubtedly occur. If such an approach were to be adopted, in that case I would argue strongly for the inclusion of a statement in the document the prescriber must sign attesting to the fact that the patient does not have sleep apnea (and I probably would also require that patients be tested prior to initiation of treatment to rule out the presence of sleep apnea). In this case, I believe that I would not agree to the drug's approval without such a statement, a position which I assume would be supported by the Chief Counsel.

CMC and Biopharmaceutics Issues

In addition to the issues above, we asked the sponsor to provide additional CMC data, which they have done, and which Dr. Oliver finds acceptable. Further, we asked the sponsor to provide additional data on the effects of GHB on the CYP 450 system, which they have done.

Post-marketing issues

We had asked the sponsor to provide a plan to evaluate the interaction between GHB and drugs that alter gastric pH (GHB is ionized in the GI tract, and we were concerned that these drugs may alter the absorption of GHB); the sponsor has submitted such a plan.

Finally, we asked the sponsor to submit the results of a rat carcinogenicity study in Phase 4. That study is complete, and, according to the sponsor, is negative. It will be submitted soon.

Additional issue

We became aware on 1//24/02 of a potential problem concerning the data generated by a Dr. Martha Hagaman of Nashville, TN. Dr. Hagaman was a

principal investigator in both Orphan-sponsored controlled trials, as well as in several of the long-term uncontrolled safety studies, including the treatment IND.

The sponsor informed us in a letter dated 1/24/02 that the IRB at St. Thomas Hospital had terminated Dr. Hagaman's on-going treatment IND study at that institution in a letter dated 1/21/02. Among the reasons cited by the IRB were:

Further investigation of the issue revealed that the IRB had previously suspended Dr. Hagaman as principal investigator for over a year, re-instating her in May, 2001; we had not been told of this previous suspension by the sponsor, who initially told us that she had not been formally suspended by the IRB. The sponsor did tell us in a submission dated 2/14/02 that she had, in fact, been officially suspended by the IRB.

As a result of the IRB's actions, the Agency performed an inspection of Dr. Hagaman's site (records for the 2 controlled trials and 2 open, uncontrolled trials, including the treatment IND) on 3/11-14/02. Dr. Feeney was present at the inspection for the first several days. Dr. Hagaman was issued a 483 at the end of the inspection, which outlined numerous deficiencies, the most important of which are described below.

The sponsor had employed a CRO to provide oversight for the study, and this CRO on several occasions wrote to Dr. Hagaman informing her that she was engaging in a number of unacceptable practices. Dr. Hagaman appeared not to

respond to these letters, and the sponsor seems not to have intervened at any time.

Dr. Hagaman provided 46 patients to the total NDA database, with 44 enrolled in open, uncontrolled safety studies, including 21 in the treatment IND (she is the second largest contributor to the treatment IND; Dr. Scharf, with 50 patients, is the greatest contributor to the treatment IND). The controlled trials were re-analyzed with Dr. Hagaman's patients (and Dr. Scharf's patients) removed; between-treatment contrasts in both studies continued to yield p-values of <0.05.

Inspection of the efficacy data in Dr. Hagaman's studies suggested that these data were accurately recorded from the patients' diaries.

The results of the inspection, as described on the 483, as well as described by those who conducted the inspection (Dr. Ni Khin, Dr. John Feeney, and Patricia Smith of the Birmingham District Office) suggest that there were serious deficiencies in Dr. Hagaman's conduct of studies. While her conduct was deficient, what is of most concern for our purposes at this time is the reliability of the data. All inspectors agreed that these deficiencies raise serious concerns about the reliability of the data.

The most important issues raised, in my view, concern the fact that adverse events described on some source documents (patient diaries) were not recorded on the CRFs, and therefore not recorded in the NDA. Further, some adverse events recorded in the CRFs were not described in the source documents. Both of these problems could potentially have been prevented if patients had been seen at the protocol specified timepoints by a competent investigator who probed the patients' reports, interpreted the findings, and recorded the events contemporaneously, as called for in the protocol, and which either did not happen, or, if it did happen, was not documented. As a result of these failures, the data as recorded on the CRFs, and submitted to the NDA, are less than reliable.

The questionable reliability of these data is particularly problematic for several reasons.

Dr. Hagaman's patients, though only 21 in the treatment IND, represent, as noted above, the second largest patient contribution provided by any single investigator in the treatment IND. The total dataset is, as has been pointed out frequently, unusually small, especially as regards long term data, and especially at the highest effective dose. The removal of any substantive portion of this data results, obviously, in a data set that is even more marginal. Further, the poor quality of her data, especially in the face of repeated admonitions of the CRO providing oversight, raises serious questions about Orphan Medical's surveillance and on-going monitoring of the trial.

While one previous site (Dr. Schwartz) had been inspected by the Agency, and found to be acceptable, this site provided only short-term, controlled trial data. Dr. Hagaman's site is the only site inspected in which long-term, uncontrolled safety data was gathered. Given the questions raised about the reliability of the safety data reported from this site, given the small safety database, and given the questions raised about the adequacy of the sponsor's oversight and monitoring of the collection of this safety data, it is prudent, in my view, to withhold approval of the application until additional sites that collected safety data can be inspected.

In this regard, it is important to note that the largest single contributor to the treatment IND was Dr. Scharf, who contributed 50 long-term patients to the IND; this represents about 20% of the data in the treatment IND. Given the questions raised about the adequacy of the sponsor's monitoring of the collection of long-term safety, given Dr. Scharf's major contribution to the safety database, and especially given the previous concerns about Dr. Scharf's monitoring and collection of adverse event data under his own IND (which, recall, was entirely rejected from consideration under the IND due to extraordinarily inadequate data collection), in my view it is imperative that Dr. Scharf's treatment IND data be inspected and found to be acceptable before approval can be considered. If Dr. Scharf's data are found to be unacceptable, additional well-monitored long-term safety data would need to be accrued before approval could be granted.

In sum, then, minor revisions will need to be made to various aspects of the sponsor's proposed Risk Management Plan, as well as to a number of the documents related to it. The package is being forwarded with our proposals for all documents related to the RMP, including the Physician and Patient Success Programs, the package insert and Med Guide, and the comments of Dr. Lisa Stockbridge of DDMAC pertaining to the sponsor's proposed initial advertisement. Of much greater concern, however, are two outstanding issues.

First, questions raised about the potential for Xyrem to cause serious respiratory problems (especially in patients with sleep apnea) must be adequately addressed, ideally with a formal, well-designed study of the effects of Xyrem on respiratory function at night. It would be ill advised, in my view, to approve the application before we are confident that Xyrem does not have important deleterious effects on respiration.

Second, the results of the inspection of Dr. Hagaman's site raise serious questions about the reliability of the safety data she contributed, as well as serious questions about the adequacy of the sponsor's monitoring of the study. Given the small database, the removal of even a relatively small number of patients (which we might be tempted to do with her patients) makes the remaining patient experience even more meager. Further, the questions raised about the sponsor's monitoring, coupled with the fact that the largest contributor

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 with sodium oxybate overdose responsive to atropine intravenous administration. No reversal of the central effects of sodium oxybate can be expected from naloxone or flumazenil administration,

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

DOSAGE AND ADMINISTRATION

Preparation and Administration Precautions

Bottles of Xyrem provided with a child resistant cap and dosing cups.

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

See Patient Use Instructions for a complete description.

HOW SUPPLIED

Xyrem® (sodium oxybate) oral solution is supplied in kits containing one bottle of Xyrem, a press-in-bottle-adaptor, a 10 ml oral measuring devise (plastic syringe), a professional insert, and two ml dosing cups with child resistant. 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.

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.

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For questions of a medical nature or to order Xyrem call the Xyrem Patient Success Program at 1-XXX-XXX-XXXX..

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