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

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