CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021196Orig1s000

PHARMACOLOGY REVIEW(S)

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.

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/s/

Jeri El Hage
4/8/02 04:08:34 PM
PHARMACOLOGIST

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Request for Consultation

Date: 4/18/2002

To: HFD-710/Jin/Kelly

From: Neuropharmacology, HFD-120

IND/NDA No. NDA 21-196

Drug Name sodium oxybate

Trade Name Xyrem

Sponsor Orphan Medical

Indication cataplexy

Type of Document post-NDA submission

Date of Document 4/3/2002

Reason for Request

Orphan Medical has submitted the requested Phase IV carcinogenicty study. Dr. Kathy Haberny is the HFD-120 assigned pharm/tox reviewer. She has requested a stat consult of the carc study results. I believe the submission is in the electronic document room under NDA 21-196.

Thank You,

Anna Marie Homonnay
X4-5535

Signature of Requester	Method of Delivery (Check One) ( ) Mail ( ) Hand
Signature of Receiver	Signature of Deliverer

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