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10 January 2005

DIVISION OF DOCKETS MANAGEMENT (HFA-305)
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE ROOM 1061
ROCKVILLE, MD 20852

Re: Docket No. 2005N-0479

We are responding to the Food and Drug Administration's recent Federal Register notice (the "Notice") requesting comments concerning abuse potential, actual abuse, medical usefulness and impact of potential scheduling changes on the availability for medical use of several chemicals including gamma-hydroxybutyric acid (GHB). 70 *Federal Register* 73,775 (Dec. 13, 2005). The Notice requests information relevant to a United States' response to the WHO Questionnaire for Collection of Information for Review of Dependence-Producing Psychoactive Substances (the "WHO Questionnaire"). We are specifically providing comments relevant to Section 3 of the WHO Questionnaire, which relates to GHB.

As an initial matter, we believe that the 30-day comment period is inadequate for preparation of a comprehensive response to the Notice and request that the deadline for comments be extended by at least 30 days. This comment period duration significantly limits the information available to us that can be provided before the January 12, 2006 deadline, and thus our response must be incomplete.

VIOLATION OF WHO GUIDELINES

It appears that, in calling for a critical review of GHB, WHO has violated its own rules as set forth in the *Guidelines for the WHO review of dependence-producing psychoactive substances for international control* (the "Guidelines"). There was a critical review of GHB in 1998 (and the substance was scheduled by action of the Commission on Narcotic Drugs (the "CND") in 2000. There are four conditions, one of which must be met, in order for a critical review to be called:

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Critical Review

Critical review is conducted by the Expert Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from CND to review a substance; (3) pre-review of a substance has resulted in a recommendation for critical review as indicated in paragraph 13 above; (4) information is brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Member State. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subjected to a pre-review.

The only articulation of a justification for the GHB critical review of which we are aware is in a letter from Dr. Vladimir Lepakhin of WHO; that letter states, concerning GHB, that "… for gamma-hydroxybutyric acid, information has been brought to WHO's attention which justifies the issue to be put on the agenda." It is possible that the critical review was called without full consideration of the distinction that WHO's rules make between a pre-review and a critical review. "Information" is not a reason that meets the standard of WHO's own rules. Within its own prescribed processes, WHO may of course use information from virtually any source as a basis for a pre-review of a substance; the Guidelines expressly provide for that. *See* paragraph 13 of the Guidelines.

It is apparent that none of the conditions for a critical review has been met. There has been no notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance. An examination of the minutes of the meetings of the CND since 2000 reveals that no request has been made by that agency for a review of GHB.[1] There has been no pre-review. And the fourth condition would not apply: GHB has a recognized therapeutic use.

The Guidelines document prescribes the rules by which WHO is to proceed with Expert Committee on Drug Dependence ("ECDD") meetings. Those rules were given to WHO by the Executive Board of the World Health Assembly, WHO's governing body. The Guidelines were established to provide order in the vital process of medical and scientific review that has been delegated to WHO. Abandonment of the principles established in the Guidelines will introduce chaos into the process, and that will have a deleterious effect upon the reliability of the work of WHO's expert committee and consequently, the public health. FDA, acting for the U.S. government, has published the subject Federal Register

[1] Is it possible that WHO has confused a communication from the International Narcotics Control Board with a communication from the CND? A communication from the CND would warrant a critical review, a communication from the INCB would not, under the Guidelines.

notice to advance the process initiated by WHO. Should our government be a participant in a process that violates the Guidelines?

We do not believe that conditions that would incite a re-evaluation of the scheduling of GHB exist. Even if WHO believes that a re-evaluation is necessary, they have not followed the appropriate procedures to ensure a reasoned scientific and medical review of GHB based on all relevant data. While we recognize the US interests in responding to the WHO Questionnaire, we strongly urge the Agency to pursue every possible avenue to require WHO to defer this proposed reevaluation until the proper procedures are followed to allow for a thorough and complete re-evaluation so as not to encourage a process that will, by dint of lack of time to prepare, be incomplete and potentially lead to false conclusions.

RESPONSE TO WHO QUESTIONNAIRE

For ease of review we have reproduced the format for the requested information below with our comments in italics. Due to the time available to us to respond to this questionnaire, the answers that follow represent the information that could be assembled in the limited time frame provided and are not fully complete.

3. GAMMA-HYDROXYBUTYRIC ACID (GHB)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product?

(***Yes***/No) *Yes. GHB is currently listed as a medical product in the USA, Canada and the EU. The original NDA for Xyrem® (sodium oxybate) oral solution was approved by the FDA on 17 July 2002 for the treatment of cataplexy in patients with narcolepsy. The product is designated as an orphan product in these regions. Sodium oxybate is the non-proprietary name for the sodium salt of gamma-hydroxybutyrate (GHB), which is an endogenous compound that exists as the anion in aqueous media. Sodium oxybate is a neuroactive agent with central nervous system depressant (pharmacologic) properties. Sodium oxybate was initially developed as congener of GABA to cross the blood-brain barrier and was shown in the early 1960's to produce sedation, sleep and unconsciousness in a dose-dependent manner. Narcolepsy fulfills the criteria for classification as an orphan disease, and Xyrem was granted an Orphan Drug Status (Number 94-858) by the FDA for the treatment of narcolepsy. Xyrem was approved for cataplexy in patients with narcolepsy in Canada and the EU in 2005. An additional*

indication for the use of Xyrem in the treatment of excessive daytime sleepiness was also approved in 2005 by the FDA. (See attached labeling.)

If “yes”, since when (year of marketing)?

Year of Marketing: *2002 USA; 2005 EU; expected marketing in 2006 for Canada*

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

Trade Name	Dosage Form	Strength(s)	Indication(s)
Xyrem® (sodium oxybate)	*Oral solution*	*500mg/mL*	*Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy*

1.2 If the answer to 1.1 is “no”, is there other legitimate use of the substance? (Yes/No)

Not applicable

If “yes”, please describe the purpose of use.

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported/Manufactured in the country)

Manufactured in the country for USA, exported from the US for Canada and EU

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (***Yes/***No/No information) Yes, although there are few, limited reports for abuse of the commercially available product Xyrem.

2.2 If "yes", any information on the extent of the abuse?

In the early 1990s, prior to FDA approval of a drug product containing GHB, the FDA warned against the use of GHB particularly, for things such as body building, and restricted its sale. This diminished availability of GHB caused a shift toward GHB analogs such as gamma- butyrolactone (GBL) and 1,4-butanediol (1,4-BD) as precursors and surrogates. Both GBL and 1,4-BD are metabolically converted to GHB. Furthermore, GBL is commonly used as a starting material for chemical conversion to GHB. As such, the clinical presentation and management GBL and 1,4-BD intoxication shares a great deal of common ground with that for GHB. This similarity exists not only for acute intoxication but also for withdrawal in those patients with a history of extended high-dose abuse (Palmer 2004). While it cannot be established with certainty, it is likely that many of the current reports of GHB abuse that are being collected by federal agencies and poison control centers represent GHB analogues.

The incidence of emergency room mentions of GHB and GHB-related analogs has decreased by 33% since 2000 (SAMSA 2003). Similarly, reports of GHB exposures reported to the American Association of Poison Control Centers has decreased from 1,916 (6 deaths) in 2001 to 800 (no deaths) in 2003. In contrast, there were 101,331 exposures to antidepressants resulting in 70,253 hospitalizations and 274 deaths in 2003 (Litovitz 2002, Watson 2004). In addition, a recently-published examination of 146 reported GHB overdoses revealed that only 63% were confirmed to represent actual GHB overdoses. These investigators concluded that GHB overdose may be indistinguishable from other drug overdoses or medical conditions (Couper 2004) and suggest that the incidence of GHB overdose may have been previously over- reported.

There are fewer than 10 reports of abuse of Xyrem since entered the marketplace in 2002.

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

Hospital emergency department reports increased 100-fold from 1992 to 1999 (source:

Substance Abuse Mental Health Services Administration, Drug Abuse Warning Network [DAWN]). Sixty percent of the ED reports involved individuals 25 years and younger. Numerous deaths had been reported over that period of time, typically involving GHB in combination with alcohol and other drugs, including five in the DAWN system in which GHB was the only drug that could be identified. However, the incidence of hospital emergency department reports of events involving GHB and GHB-related analogs has decreased by about 33% since 2000, and reports to the American Association of Poison Control Centers of GHB Exposures have decreased from 1,916 (involving 6 deaths) in 2001 to 800 (without any deaths) in 2003 (Xyrem® Physician Insert November 2005).

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizures, etc.)

There have been no confirmed diversions, clandestine manufacture, smuggling, or seizures of sodium oxybate since its introduction to the market place.

4. IMPACT OF TRANSFER TO SCHEDULE II OR III OF THE CONVENTION ON PSYCHOTROPIC SUBSTANCES, 1971, ON MEDICAL AVAILABILITY

4.1 If gamma-hydroxybutyric acid is transferred from Schedule IV of the Convention on Psychotropic Substances, 1971, do you think that its availability for medical use will be affected? (***Yes***/No) *Yes*

4.2 If “yes”, how do you think the transfer will impact its medical availability?

Narcolepsy is a highly debilitating disease. The deleterious impact of narcolepsy on quality of life is well established (Goswami 1998; Daniels 2001). Before and after diagnosis, narcoleptics experience unrelenting psychosocial stress, with different stresses affecting each decade of life. Adolescents commonly report embarrassment, academic decline and loss of self-worth. Cataplexy leads to social withdrawal and avoidance of emotions with a presentation of a “flat affect” and isolation. Hypnagogic hallucination may lead individuals to question their own sanity and may be mistakenly diagnosed with schizophrenia. Adults face major concerns in the workplace and in interpersonal relationships. Sleepiness and cataplexy have major effects on personal and public safety. Of particular concern is the risk of serious accidents at work or while driving. Severe cataplexy, resulting in immediate and sudden body collapse, can be dangerous and can rarely occur so quickly that there is

not time to prepare. Unless cataplexy can be controlled, many normal activities must be avoided, such as driving privileges, family and home duties, and workplace restrictions.

Xyrem is the only drug approved to treat narcolepsy. The current scheduling and Risk Management Program impose a significant burden upon patients with legitimate medical needs. Xyrem was approved by the FDA under the provisions of the restricted distribution regulations, 21 C.F.R. § 314.520, Subpart H: Approval with restrictions to assure safe use of the product. In conjunction with approval, a Xyrem Risk Management Program (RMP) was implemented to provide:

- *A system for restricted distribution and dispensing through a centralized pharmacy which verifies individual prescriptions as well as physicians' DEA and state licenses*
- *Physician and patient education (print and video materials) about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll-free Helpline*
- *Physician and patient registries*
- *Filling of the initial prescription only after the prescriber and patient have received and read/understood the educational materials*

Approximately 60% of patients prescribed the drug for their debilitating condition never fill their prescription, due mainly to the burdensome process involved. Thus, this vulnerable group of patients with no alternative therapeutic drug options is already highly burdened to protect the rest of the population. There has been a substantial decline in abuse/misuse of GHB since Xyrem was first approved in 2002, indicating a declining interest in this compound by abusers. An increase in scheduling would reduce availability to patients with legitimate medical needs, and the data do not support an increased risk to the general population that requires this action.

Response submitted by:

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