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Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

www.fda.gov/dockets/ecomments

Re: Docket No. 2005N-0479: International Drug Scheduling; Convention on Psychotropic Substances

These comments are submitted in response to the December 13th, 2005, *Federal Register* Notice requesting comments on abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of nine drug substances for the Food and Drug Administration to consider in responding to the World Health Organization regarding the abuse liability and diversion of these drugs [Docket No. 2005N-0479], 70 FR 73775.

The Convention on Psychotropic Substances serves an important purpose in controlling the use of substances lacking a medical or scientific purpose at an international level. Concurrently, it is in the interest of the U.S. to maintain the appropriate availability of psychotropic drugs with a legitimate medical purpose, and foster access to drug products for genuine scientific research. In this context, we comment below on butorphanol, dronabinol, tramadol, zopiclone, and buprenorphine.

Butorphanol is a synthetically derived opioid agonist-antagonist marketed in the U.S. under Schedule IV of the Controlled Substances Act for the management of pain when the use of an opioid analgesic is appropriate, as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during childbirth. While there was limited evidence of misuse and abuse after the introduction of a nasal spray formulation, such events occur less often relative to other controlled substances. National surveys that attempt to gather information about abuse of licit and illicit drugs fail to show any indication of widespread abuse or diversion of butorphanol. Establishing international control for butorphanol would hamper legitimate medical use by reducing its accessibility to patients who require this drug for analgesia and anesthetic use.

Dronabinol (trade name Marinol) is a cannabinoid marketed in the U.S. under Schedule III of the Controlled Substances Act for the treatment of anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Effective July 2, 1999, Marinol was rescheduled from Schedule II to Schedule III. This was based on findings that Marinol has a potential for abuse less than other Schedule I and Schedule II substances, is an FDA-approved product with an accepted medical use in treatment, and meets the physical and psychological dependence criteria for Schedule III, (i.e., abuse may lead to moderate or low physical dependence, or high psychological dependence). Since its rescheduling, there is no

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evidence to contradict these findings. There is no indication that the rescheduling of dronabinol has resulted in increased abuse or diversion in the U.S.

Tramadol is a centrally acting analgesic marketed in the U.S. for the management of moderate to moderately severe pain in adults. Approved as an unscheduled drug, it appropriately remains unscheduled. As evidenced by the results of one of the most extensive monitoring programs ever initiated to monitor for abuse and diversion, abuse of tramadol remains low, even after the introduction of new branded and generic products [Cicero TJ, Inciardi JA, Adams EH, Geller A, Senay EC, Woody GE, Munoz A. Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. Pharmacoepidemiol Drug Saf. 2005 Dec;14(12):851-9.]. Establishing international control over tramadol would be detrimental to legitimate medical use because it would reduce the availability of this drug for patients. In the light of current limitations and fear of the use of COX-2 inhibitors, this drug is especially useful in patients who cannot tolerate other NSAIDs and may already be taking high doses of acetaminophen or have liver damage.

Zopiclone is a short-acting hypnotic controlled as a Schedule IV drug. In the U.S., the S-isomer, eszopiclone, has been marketed for the treatment of insomnia since April 2005 as a Schedule IV drug. While we agree that insomnia is a legitimate medical use, there is some evidence of tolerance and withdrawal symptoms associated with use of the drug, making its current scheduling in the U.S. appropriate. Notably, the results of the 2005 Monitoring the Future survey suggest an increase in prevalence of sedative abuse among 8th, 10th, and 12th graders in the U.S. There is, however, no information whether eszopiclone is playing any role in this increase. Direct-to-consumer advertising of this class of drugs can be expected to increase awareness of the drug among both patients and potential abusers. Taken together, this suggests a need for more careful monitoring for evidence of misuse, abuse, and diversion. In regards to international control, there is no indication that the current control of the drug needs to be changed at this time, but careful monitoring will be useful in informing future considerations.

Buprenorphine is a schedule III opioid ("narcotic"), marketed in the U.S. in two sublingual forms for the treatment of opioid dependence and in the parenteral form for the treatment of pain. Targeted legislation (DATA 2000) established a mechanism for Office Based Opioid Treatment (OBOT), with Schedule III, IV, and V narcotic medications that have been specifically approved by FDA for that indication. Currently the sublingual forms of buprenorphine are the only FDA-approved medications marketed in the U.S. that can be used in the OBOT setting. This much needed treatment is a valuable and viable alternative to traditional Opioid Treatment Program (methadone clinic) settings. Almost 10,000 physicians in the U.S. have been trained, and approximately 7,000 are now certified to provide OBOT treatment. In 2004 it was estimated that 60,000 patients had been treated though OBOT; given there has been a 30% increase in the number of dosage units sold from 2004 to 2005 (CSAT communication, 01/06/05) it is likely that the number of patients who have benefited from this treatment option now approaches or exceeds 100,000. An extensive monitoring program has not indicated any major problems associated with the availability of this product, limited to prescription by specially trained and qualified physicians. Unfortunately, alternative opioid treatment options, such as methadone maintenance treatment programs, remain focused in urban areas, often have long waiting lists for treatment slots, and remain illegal in five states. Thus, transferring buprenorphine from Schedule III of the Convention on Psychotropic Substances (1971), to Schedule I of the Single Convention on Narcotic Drugs (1961), would effectively eliminate this treatment option for

patients, many of whom would otherwise have no access to medical treatment for their opioid dependence. The current scheduling, along with limiting prescribing to certified physicians and the post-marketing monitoring program, provide for treatment of patients in need without overly burdensome access. It is essential that this medication remain available for OBOT treatment.

Respectfully submitted,

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