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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N–0493]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for Dronabinol and its Stereoisomers, and Oripavine

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, March 12 to 16, 2007. This notice is issued under the Controlled Substances Act.

DATES: Submit written or electronic comments by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*.

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FOR FURTHER INFORMATION CONTACT: James R. Hunter, Center for Drug Evaluation and Research (HFD–9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–5563, e-mail: *james.hunter@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the 1971 Convention). Section 201(d)(2)(B) of the Controlled Substances Act (the CSA) (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the 1971 Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the 1971 Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (the Secretary of HHS). Section 201(d)(2)(B) requires the Secretary of HHS, after receiving notification proposing scheduling, to publish a summary of such information in the **Federal Register** to provide opportunity for interested persons to submit comments on the proposed scheduling action. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed in the following paragraphs, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding the drug substance dronabinol (INN), including its stereoisomers, to be considered for control under the 1971 Convention. The

notification reflects the recommendations from the 34th WHO Expert Committee for Drug Dependence (ECDD), which met in March 2006. In the **Federal Register** of December 13, 2005 (70 FR 73775), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs (the 1961 Convention). The Secretary of State has received notification from the Secretary-General regarding the drug substance oripavine to be considered for control under the 1961 Convention. The CSA does not require the Secretary of HHS to publish a summary of such information in the **Federal Register**. Nevertheless, in an effort to provide interested and affected persons an opportunity to submit comments on the WHO ECDD recommendations for narcotic drugs, notification on this substance is also included in this **Federal Register** notice. The comments will be shared with other relevant agencies to assist the Secretary of State in formulating the U.S. position on the control of these substances. The HHS recommendations are not binding on the representative of the United States in discussions and negotiations relating to the proposal on control of substances under the 1961 Convention.

The full text of these notifications from the Secretary-General is provided in section II of this document.

II. United Nations Notification

The formal United Nations notification that identifies the drug substances and explains the basis for the recommendations is reproduced below.

Reference: NAR/CL.4/2006

CSS–6/06, CU2006/162

WHO/ECDD 34 (1971C and 1961C)

The Secretary-General of the United Nations presents his compliments [to the Secretary of State] and has the honour to inform the Government that the Acting Director-General of the World Health Organization (WHO), pursuant to article 2, paragraphs 1, 4 and 6, of the Convention on Psychotropic Substances of 1971 (1971 Convention), has notified the Secretary-General that it is of the opinion that dronabinol (INN) and its stereoisomers should be transferred from Schedule II to Schedule III of the 1971 Convention; and pursuant to article 3, paragraphs 1 and 3(iii) of the Single Convention on Narcotic Drugs, 1961, and of that Convention as amended by the 1972 Protocol (1961 Convention), has also notified the Secretary-General that it is of the opinion that oripavine should be included in Schedule I of the 1961 Convention.

In connection with the notification, WHO has also submitted advance excerpts from the report of the Thirty-fourth session of the WHO Expert Committee on Drug Dependence (28–31 March 2006) which reviewed the substances. The excerpts from that report concerning dronabinol (INN) and its stereoisomers, recommended for rescheduling; and oripavine, recommended for scheduling, are hereby transmitted as annex II. The excerpts are currently available in English only, pending receipt of the official translation from the World Health Organization.

In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention; and the provisions of article 3, paragraph 2, of the 1961 Convention, the Secretary-General hereby transmits the text of the notification as annex I to the present note. Also in accordance with the same provisions, the notification from WHO will be brought to the attention of the Commission on Narcotic Drugs, at its next session in March 2007.

Any action or decision taken by the Commission with respect to this notification, pursuant to article 2, paragraphs 5 and 6, of the 1971 Convention, will be

communicated to States Parties in due course. Article 2, paragraphs 5 and 6, reads as follows:

"5. The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.

6. If a notification under paragraph 1 relates to a substance already listed in one of the Schedules, the World Health Organization shall communicate to the Commission its new findings, any new assessment of the substance it may make in accordance with paragraph 4 and any new recommendations on control measures it may find appropriate in the light of that assessment. The Commission, taking into account the communication from the World Health Organization as under paragraph 5 and bearing in mind the factors referred to in that paragraph, may decide to transfer the substance from one Schedule to another or to delete it from the Schedules."

Any action or decision taken by the Commission with respect to this notification, pursuant to article 3, paragraph 3 (iii) of the 1961 Convention, will be communicated to States Parties in due course. Article 3, paragraph 3 (iii) reads as follows:

"If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II."

In order to assist the Commission in reaching a decision, it would be appreciated if any economic, social, legal, administrative or other factors the Government may consider relevant to the possible rescheduling under the 1971 Convention of

dronabinol (INN) and its stereoisomers, as well as to the possible inclusion of oripavine under the 1961 Convention, could be communicated at the latest by 1 December 2006 to the Executive Director of the United Nations Office on Drugs and Crime, c/o Secretary, Commission on Narcotic Drugs, P.O. Box 500, 1400 Vienna, Austria, fax:+43–1–26060–5885, e-mail: *Renate.Weidinger@unodc.org*.

13 October 2006

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Annex II

Recommendation on dronabinol (INN)

Substance identification

Dronabinol (INN) is (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6-*H*-dibenzo[*b*,*d*]pyran-1-ol. It is the (6a*R*,10a*R*)-stereoisomer of delta-9-tetrahydrocannabinol and is also designated (–)-*trans*-delta-9-tetrahydrocannabinol.

Other stereoisomers of delta-9-tetrahydrocannabinol are: (6a*R*,10a*S*)-,(6a*S*,10a*R*)- and (6a*S*,10a*S*)-, also known as (–)-*cis*-,(+)-*cis*-and (+)-*trans*-, respectively. Delta-9-tetrohydrocannabinol has two racemates, (6a*RS*,10a*RS*)- and (6a*RS*,10a*SR*)-,also known as (±)-*trans*- and (±)-*cis*-, respectively.

Originally, all isomers of tetrahydrocannabinol were included in Schedule I of the 1971 Convention. This was later amended to include seven named constitutional isomers and their respective stereochemical variants. The term "constitutional isomers" used above has recently been introduced by the International Union of Pure and Applied Chemistry (IUPAC) to replace the traditionally used term "positional isomers".

The term "stereochemical variants" used in the 1971 Convention and mentioned above is equivalent to the term "stereoisomers", which is at present much more widely used in the chemical and related literature. Both terms cover geometric isomers and optical isomers.

Previous review

Delta-9-tetrahydrocannabinol was included in Schedule I of the 1971 Convention at the time of its adoption. At its twenty-sixth meeting, the Committee recommended that dronabinol be moved to Schedule II, while keeping the other isomers and their stereochemical variants in Schedule I (1). This proposal was rejected at the 11th Special Session of the Commission on Narcotic Drugs, and the Committee reviewed the question again at its twenty-seventh meeting when it recommended that all the stereochemical variants of delta-9-tetrahydrocannabinol be rescheduled to Schedule II (*2*). This recommendation was adopted by the United Nations Commission on Narcotic Drugs at its 34th session (3). At its thirty-second meeting, the Committee pre-reviewed dronabinol and recommended its critical review for consideration of the rescheduling on the grounds that the rate of abuse of dronabinol was extremely low (*4*).

Delta-9-tetrahydrocannabinol was critically reviewed by the Expert Committee on Drug Dependence at its thirty-third meeting in September 2002 (5). On the basis of the available data the Committee considered that dronabinol should be rescheduled to Schedule IV of the 1971 Convention. However, no further procedural steps were taken. Therefore, the existing critical review report was updated, including information from recent scientific publications, to enable the Committee to finalize the process of critical review.

Similarity to known substances and effects on the central nervous system

Dronabinol is the main active principle of cannabis and has similar effects on mood, perception and the cardiovascular system. The cannabis plant contains a "natural mixture" of around 70 different cannabinoids, and also contains flavonoids and terpenes, as well as many other substances. Therefore the pharmacological properties of natural cannabis and dronabinol are not identical.

Dependence potential

Animal studies have demonstrated that, like other drugs of abuse, dronabinol acts as a drug reinforcer. Physical dependence, as shown by withdrawal syndrome following chronic administration, has also been demonstrated. Reinforcing effects and physical dependence have also been described in human studies.

Actual abuse and/or evidence of likelihood of abuse

The abuse of dronabinol is currently rare and there have been very few specific reports of its occurrence. In response to the WHO questionnaires only the United States mentioned instances of abuse of delta-9-tetrahydrocannabinol. At present, the quantity produced by licit manufacture is limited. In the United States, which is the major manufacturing country, the abuse of dronabinol medicinal preparations is reported to be very low and there are no reports of diversion of the pharmaceutical product.

Therapeutic usefulness

Dronabinol preparations have been used in a limited number of countries in the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and in the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). It has also been indicated in the treatment of chronic pain (e.g. in multiple sclerosis, neuropathic disorders and arthritis), neurological disorders and appetite loss in cachexia, and is being evaluated for use in various other clinical situations.

Recommendation

The Committee reconsidered the recommendation of the thirty-third Expert Committee after considering the updated critical review report. The Committee concluded that dronabinol constitutes a substantial risk to public health. However this risk is different from those related to cannabis—controlled under the 1961 Convention. The substance has a moderate therapeutic usefulness and as a result of

continuing clinical research its medical use is likely to increase. Therefore, the Committee recommended that dronabinol (INN) and its stereoisomers should be rescheduled from Schedule II to Schedule III of the 1971 Convention.

To avoid legal and forensic chemical problems that may arise in some countries when placing stereoisomers of the same substance under different control systems, the Committee indicated that the recommendation pertains to all stereoisomeric forms of delta-9-tetrahydrocannabinol as specified above.

References

1. WHO Expert Committee on Drug Dependence. Twenty-sixth report. Geneva, World Health Organization, 1989 (WHO Technical Report Series, No. 787).

2. WHO Expert Committee on Drug Dependence. Twenty-seventh report. Geneva, World Health Organization, 1991 (WHO Technical Report Series, No. 808).

3. Report of the thirty-fourth session (29 April–9 May 1991). Economic and Social Council, Commission on Narcotic Drugs, Official Records, 1991, Supplement No. 4. New York, United Nations, 1991 (E/1991/24, E/Cn.7/1991/26).

4. WHO Expert Committee on Drug Dependence. Thirty-second report. Geneva, World Health Organization, 2001 (WHO Technical Report Series, No. 903).

5. WHO Expert Committee on Drug Dependence. Thirty-third report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 915).

Recommendation on oripavine

Substance identification

Oripavine, 3-O-demethylthebaine, or 6,7,8,14-tetradehydro-4,5-*alpha*-epoxy-6-methoxy-17-methylmorphinan-3-ol is a phenanthrene alkaloid contained in species of the *Papaver* plant. It is a major metabolite of thebaine.

Previous review

Oripavine was pre-reviewed at the thirty-third meeting of the Expert Committee in 2002 (1). The reason for pre-review in 2002 was that oripavine is a substance that

is convertible into thebaine, and because thebaine is in turn convertible into morphine. Thebaine and morphine are both in Schedule I of the 1961 Convention. Owing to uncertainties regarding the scheduling of oripavine based on the additional possibility of applying the 1988 Convention (*2*), the Committee did not finalize this review at its thirty-third meeting, but asked WHO for clarification of issues related to the conversion of precursors into scheduled substances. Subsequent clarification of these issues allowed the Committee to come to a conclusion at its thirty-fourth meeting.

Recommendation

The Committee decided that oripavine is a substance that is easily convertible into thebaine and other substances controlled in Schedule I of the 1961 Convention. Hence, the Committee recommended that oripavine be scheduled, like the substances mentioned, in Schedule I of the 1961 Convention.

References

1. WHO Expert Committee on Drug Dependence. Thirty-third report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 915).

2. United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988. New York, United Nations, 1991.

III. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, CND is not obliged to follow the WHO recommendations. Options available to CND for substances considered for control under the 1971 Convention include the following: (1) Acceptance of the WHO recommendations; (2) acceptance of the recommendations to control, but control the drug substance in a schedule other than that recommended; or (3) reject the recommendations entirely.

Synthetic *delta*-9-tetrahydrocannabinol (*delta*–9–THC), or dronabinol, is the active component of the drug product Marinol, which is marketed in the United States as an antiemetic in the setting of cancer chemotherapy and for treatment of AIDS wasting syndrome. Marinol is currently controlled in Schedule III of the CSA, and the drug substance dronabinol (which is the synthetic equivalent of the natural active component of marijuana, *delta*–9–THC) is controlled in Schedule I of the CSA. The drug substance dronabinol, including its stereoisomers, is controlled internationally in Schedule II of the Psychotropic Convention.

Oripavine is controlled domestically in Schedule II of the CSA because it is a derivative of thebaine, opium, and other opiates. Oripavine is not under international control.

IV. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electric comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. The

abbreviated period for the submission of comments is necessary to allow sufficient time for the Secretary of HHS to carry out the required action and respond to the United Nations.

Dated: 12/6/06

December 6, 2006.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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