Findings of Scientific Misconduct

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: Notice is hereby given that the Office of Research Integrity (ORI) has made final findings of scientific misconduct in the following case:

David F. Eierman, Ph.D., University of North Carolina at Chapel Hill: The Division of Research Investigations (DRI) of the Office of Research Integrity (ORI) reviewed an investigation conducted by the University of North Carolina at Chapel Hill into possible scientific misconduct on the part of Dr. Eierman while a research assistant at the University of North Carolina. Based in part on Dr. Eierman's admission, the University concluded that he committed scientific misconduct by falsifying or fabricating data in biomedical research supported by two Public Health Service grants. The ORI accepted the University's conclusions and found that Dr. Eierman engaged in scientific misconduct.

Dr. Eierman has fully cooperated with the University of North Carolina and ORI in this matter and has signed a Voluntary Exclusion Agreement under which he has agreed to be excluded from support under Federal grants, contracts, and cooperative agreements for a three-year period beginning December 12, 1994, and ending December 11, 1997, and from service on PHS advisory committees, boards, or peer review groups for the same period. ORI notes that Dr. Eierman's cooperation in resolving this matter indicates that he has accepted responsibility for his actions, and this is regarded as a positive factor that was taken into consideration in negotiating the Voluntary Exclusion Agreement. The fabricated and falsified data were reported in two manuscripts that were never published and in Figure 3 of ''β_1 and β_2 Integrin Subunit Regulation of the Monocyte Inflammatory Response,'' Cellular and Cytokine Networks in Tissue Immunity (M. Meltzer, and A. Mantovani, Eds.). (1991). New York: Wiley-Liss.

FOR FURTHER INFORMATION CONTACT: Director. Division of Research Investigations, Office of Research Integrity, 301–443–5330.

Lyle W. Bivens, Ph.D.

Director, Office of Research Integrity.

[FR Doc. 95–1466 Filed 1–19–95; 8:45 am]

BILLING CODE 4160–17–P–M

Findings of Scientific Misconduct

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: Notice is hereby given that the Office of Research Integrity (ORI) has made final findings of scientific misconduct in the following case:

Celia Ryan, R.N., University of Pittsburgh: The Division of Research Investigations (DRI) of the Office of Research Integrity (ORI) reviewed an investigation conducted by the University of Pittsburgh into possible scientific misconduct on the part of Ms. Ryan while an employee of the University. ORI concurred with the factual findings as set forth in the University of Pittsburgh report, and finds that Ms. Ryan committed scientific misconduct by falsifying and fabricating interview data in a research project, ''Assessment of the Variation and Outcomes of Pneumonia,'' supported by a grant from the Agency for Health Care Policy and Research, HS 06468. Ms. Ryan accepted the misconduct finding and agreed to a Voluntary Exclusion and Settlement Agreement under which Ms. Ryan will not apply for, nor permit her name to be used on any application for Federal grant or contract funds, will not receive nor be supported by such funds, and will not serve on PHS advisory committees, boards, or peer review groups for a three-year period beginning January 11, 1995.

FOR FURTHER INFORMATION CONTACT: Director, Division of Research Investigations, Office of Research Integrity, 301–443–5330.

Lyle W. Bivens,

Director, Office of Research Integrity.

[FR Doc. 95–1549 Filed 1–19–95; 8:45 am]

BILLING CODE 4160–17–P

Food and Drug Administration

[Docket No. 94N–0173]

International Drug Scheduling; Convention on Psychotropic Substances; World Health Organization Scheduling Recommendations for Seven Drug Substances

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 and to request an informal public meeting concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, pursuant to international treaties, on certain drug substances. The comments received in response to this notice and/or public meeting 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, on March 14–23, 1995. This notice is issued pursuant to the Controlled Substances Act (CSA).

DATES: Written comments by February 9, 1995; written requests for a public meeting and the reasons for such a request by January 30, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857; written requests for a public meeting and the reasons for such a request to Nicholas P. Reuter (address below).

FOR FURTHER INFORMATION CONTACT: Nicholas P. Reuter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the Convention). Section 201(d)(2)(B) of the CSA (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the 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 (HHS).

The Secretary of HHS must then publish a summary of such information in the **Federal Register** and provide opportunity for interested persons to submit comments. The Secretary of HHS shall then evaluate the proposal and furnish a recommendation to the Secretary of State which shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed below in this document, the Secretary of State has received a notification from the Secretary-General of the United Nations. This notification reflects the recommendations from the 29th WHO Expert Committee for Drug Dependence (ECDD), which met in September 1994. WHO recommends that the substances aminorex, brotizolam, and mesocarb be added to Schedule IV of the Convention. In addition, WHO recommends that etryptamine and methcathinone be

added to Schedule I of the Convention and that zipeprol be added to Schedule II. WHO also recommends that flunitrazepam, presently controlled in Schedule IV of the Convention, be transferred to Schedule III.

A notice published in the **Federal Register** of June 20, 1994 (59 FR 31639), announced the WHO review of these seven substances and provided an opportunity for interested parties to submit information to be forwarded to WHO. Information submitted in response to that notice was forwarded to WHO and was considered during the 29th meeting of the WHO Expert Committee on Drug Dependence in September, 1994.

The full text of the notification from the Secretary-General of the United Nations is provided below in Section II of this notice. Section 201(d)(2)(B) of the CSA (21 U.S.C. 811(d)(2)(B)) requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the **Federal Register** to provide the opportunity for interested parties to submit information and comments on the proposed scheduling action.

II. United Nations Notification

Reference:

NAR/CL.10/1994
UNDCP 421/12(1) 1971 CPS
WHO 29th ECDD
CU 94/231

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of America and has the honour to inform the Government that, pursuant to article 2, paragraphs 1, 4 and 6, of the Convention on Psychotropic Substances of 1971, he has received a notification dated 11 November 1994, from the Director-General of the World Health Organization (WHO), concerning recommendations for international control of the following seven substances: aminorex, brotizolam, etryptamine, flunitrazapam, mesocarb, methcathinone and zipeprol.

In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General hereby transmits the text of that notification as an annex to the present note.

As will be seen from the notification and the attached assessments and recommendations, WHO recommends that aminorex, brotizolam and mesocarb be included in Schedule IV of the 1971 Convention; that etryptamine and methcathinone be included in Schedule I; and that zipeprol be included in Schedule II. WHO also recommends that flunitrazepam be transferred from Schedule IV to Schedule III of the Convention.

Pursuant to article 2, paragraph 2, of the Convention, the notification from WHO will be brought to the attention of the Commission on Narcotic Drugs at its thirty-eighth session (14–23 March 1995). Any action or decision taken by the Commission with respect to the notification, pursuant to article 2, paragraph 5 or 6, or the Convention, will be notified to States Parties in due course.

Article 2, paragraph 5, reads:

''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.''

Article 2, paragraph 6 reads:

''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 in that paragraph, may decide to transfer the substance from one Schedule to another or to delete it from the Schedules.''

The Secretary-General would appreciate it if the Government would submit data on seizures of any of these substances or on the existence of clandestine laboratories manufacturing them. Such data would assist the Commission in its consideration of possible international control of some or all of the substances under review.

In order to further 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 question of the possible scheduling or rescheduling of these seven substances could be communicated by 15 January 1995 to the United Nations International Drug Control Programme, c/o Secretariat of the Commission on Narcotic Drugs, P.O. Box 500, A–1400 Vienna, Austria (telefax 239397).

7 December 1994

ANNEX

Note dated 11 November 1994 addressed to the Secretary-General by the Director-General of the World Health Organization

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to transmit, in accordance with article 2, paragraph 1, 4 and 6 of the Convention on Psychotropic Substances, 1971, assessments and recommendations of the World Health Organization, as set forth in the annex hereto, concerning proposed international control in respect of aminorex, brotizolam, etryptamine, flunitrazepam, mesocarb, methcathinone, and zipeprol.

The Director-General of the World Health Organization avails himself of this opportunity to renew to the Secretary-General of the United Nations the assurance of his highest consideration.

Aminorex

1. Substance identification

Aminorex (INN; CAS 2207–50–3), chemically 2-amino-5-phenyl-2-oxazoline, is also known as aminoxaphen and aminozafen, and formerly as Apiquel and Monocil (aminorex fumarate). Aminorex has one asymmetric carbon atom in the molecule, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and affects on the central nervous system

Aminorex is chemically similar to 4-methylaminorex, which is included in Schedule I of the Convention on Psychotropic Substances, 1971. Aminorex produces effects that are characteristic of central nervous system stimulants such as amfetamine, and was used clinically for its anorectic effects. Aminorex produces adverse effects similar to those produced by central nervous system stimulants. In addition, when used as an anorectic, aminorex was considered to have been responsible for the occurrence of a significant incidence of pulmonary hypertension. This led to its withdrawal from the market in 1968.

3. Dependence potential

In drug discrimination studies, aminorex generalized to amfetamine and cocaine. Animal self-administration studies indicate that aminorex has some reinforcing effects. These animal studies suggest that aminorex has a moderate dependence potential.

4. Actual abuse and/or evidence of likelihood of abuse

Police and forensic reports indicate that aminorex is illicitly distributed in the United States of America as well as to a limited degree in Germany. These cases document the distribution of aminorex as amfetamine or metamfetamine on the street, suggesting that the population using the drug mainly comprises stimulant abusers. In spite of the limited level of actual abuse, aminorex is assessed to have a moderate abuse liability, taking into account the relative simplicity of its manufacturing in clandestine laboratories.

5. Therapeutic usefulness

Because of serious adverse effects, aminorex is assessed to have very little, if any, therapeutic usefulness.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of aminorex is assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that aminorex be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Brotizolam

1. Substance identification

Brotizolam (INN; CAS 57801–81–7), chemically 2-bromo-4-(o-chloropenyl)-9-

methyl-6*H*-thianol[3,2-f]-s-triazolol[4,3-a][1,4]diazepine, is also known as Ladormin, Lendorm, Lendormin, Lindormin, Noctilan, Dormex, and Sintonal.
2. Similarity to already known substances and affects on the central nervous system

Brotizolam produces pharmacological effects typical of the class of benzodiazepines. It binds with high affinity to benzodiazepine receptors. A number of studies have demonstrated the therapeutic effects of brotizolam as a short-acting hypnotic with a mean elimination half-life of 4–5 hours.
3. Dependence potential

Animal studies have shown that brotizolam has barbiturate type subjective effects. It produces alcohol-barbiturate type mild-to-severe withdrawal syndromes, and has some reinforcing effects. The few clinical studies available demonstrate the occurrence of rebound insomnia upon withdrawal of the drug. These findings collectively indicate that brotizolam has a moderate dependence potential similar to other benzodiazepine hypnotics.
4. Actual abuse and/or evidence of likelihood of abuse

In spite of its pharmacological similarity to other benzodiazepine hynotics, and its marketing in 18 countries, actual abuse of brotizolam has been reported only in Germany and Hong Kong. In Germany, although there has been some abuse and illicit activity involving brotizolam, this was not considered serious enough to subject the drug to the distribution control measures which are applicable to controlled drugs. In Hong Kong, following its introduction to the local market in 1988, the abuse of brotizolam increased rapidly among young people, leading to the application of stricter regulatory control measures in 1990. The company withdrew the product from the market in 1992.

Based on the experiences of Germany and Hong Kong with brotizolam, it is assessed that brotizolam has an appreciable abuse liability. The problem may be more acute in situations where prescription requirements for dispensing are not effectively implemented or are not applicable.
5. Therapeutic usefulness

Brotizolam is marketed as a hypnotic in 18 countries and may be considered to have a moderate to great therapeutic usefulness.
6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of brotizolam is assessed to be significant, in cases where prescription requirements are not effectively implemented or required, a situation which exists in many developing countries. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that brotizolam be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Etryptamine

1. Substance identification

Etryptamine (INN; CAS 2235–90–7), chemically 3-(2-aminobutyl)indole, is also known as α-ethyltryptamine and Monase. Etryptamine has a single chiral centre, so that two stereoisomeric forms and one racemate are possible.
2. Similarity to already known substances and affects on the central nervous system

Chemically, etryptamine is similar to hallucinogenic tryptamines, some of which are already in Schedule I of the 1971 Convention. Animal studies indicate that etryptamine produces effects similar to those produced by 3,4,-methylenedioxymetamfetamine (MDMA), but its hallucinogenic effects are more pronounced than its stimulant effects. Like amfetamine, etryptamine increases locomotor activity in rodents. In a study using the behaviour pattern monitoring method, etryptamine significantly decreased investigatory behaviour, which is typical of hallucinogens and MDMA-like substances. The stimulant effects of etryptamine are slower in onset and more prolonged in duration than those of amfetamine. In addition, etryptamine inhibits monoamine oxidase.

In the early 1960s, etryptamine acetate was placed on the United States market as an anti-depressant. Soon after its release on the market, it was reported that etryptamine was associated with a high incidence of agranulocytosis, a potentially fatal condition. More recently, there were isolated reports of etryptamine being associated with the deaths of drug abusers in Germany, Spain, and the United States of America.
3. Dependence potential

Animal drug discrimination studies indicate that etryptamine has subjective effects resembling MDMA. Self-administration studies indicate that etryptamine has a moderate dependence potential, which is lower than that of cocaine.
4. Actual abuse and/or evidence of likelihood of abuse

Information available from various sources indicates that there has been some abuse of etryptamine in Germany, Spain and the United States of America. Etryptamine is estimated to have a high abuse liability.
5. Therapeutic usefulness

In view of its association with serious adverse reactions such as agranulocytosis, the therapeutic usefulness of etryptamine is assessed to be very limited, if any.
6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of etryptamine is assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that etryptamine be included in Schedule I of the Convention on Psychotropic Substances, 1971.

Flunitrazepam

1. Substance identification

Flunitrazepam (INN; CAS 1622–62–4), chemically 5-(o-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one, is also known as Absint, Darkene, Fluninoc, Flunipam, Fluinita, Flunitrazepan-ratiopharm, Hypnodrom, Hipnosedon, Inervon, Narcozep, Parnox, Primun, Rohipnol, Rohypnol and Valsers.
2. Similarity to already known substances and affects on the central nervous system

Flunitrazepam has typical benzodiazepine effects, with a greater sedative-hypnotic potency than diazepam or chlordiazepoxide. Flunitrazepam binds with high affinity to central benzodiazepine receptors. Flunitrazepam is rapidly absorbed after oral administration. The elimination half-life of flunitrazepam following a single oral dose ranges between 9 and 25 hours in humans. Accumulation occurs with chronic administration.
3. Dependence potential

Drug discrimination, drug withdrawal and self-administration studies indicate that flunitrazepam has a dependence potential similar to other benzodiazepines. Rebound insomnia, which is considered a form of withdrawal from sedative-hypnotics, may be contributing to the tendency of continuing the medication. These data do not suggest any substantive difference between flunitrazepam and other benzodiazepine hypnotics.

However, drug preference studies in opiod users have shown that flunitrazepam and diazepam stand out from other benzodiazepines in terms of producing a strong positive reinforcing effect in these subjects.

Based on the above, flunitrazepam is estimated to have a moderate abuse potential which may be higher than other benzodiazepines. The rapid onset and longer duration of action, coupled with the strong sedative-hypnotic effects, may be contributing to its higher abuse potential.
4. Actual abuse and/or evidence of likelihood of abuse

Information available indicates that the non-medical use or abuse of flunitrazepam is widespread among drug abusers, particularly opioid and cocaine abusers. Flunitrazepam is reported to be the most widely abused benzodiazepine by opioid abusers in many large cities in Europe, Asia and Oceania. Flunitrazepam abuse is reported even in the United States of America where the drug is not marketed for therapeutic use.

Reported reasons for the abuse of flunitrazepam include potentiation of opioid effects, substitution for the opioid when it is difficult to obtain, and self-medication for opioid withdrawal. Oral intake is the most common route of administration of flunitrazepam but some abusers take the drug by intravenous injection or by smoking. Health problems associated with the abuse of flunitrazepam include deaths directly or indirectly related with the drug use, drug dependence, withdrawal syndrome, paranoia, amnesia and other psychiatric disorders.

Information on the extent of association of 37 benzodiazepines with illicit activities during the period 1984–1989, available to the 27th meeting of the WHO Expert Committee on Drug Dependence in 1980, clearly indicated a higher incidence of association with illicit activities of both diazepam and flunitrazepam in comparison with other benzodiazepines. At that time, however, the data were not evaluated in relation to drug availability. After and adjustment for the amounts manufactured and for potency, flunitrazepam further stands out in both seizures and the number of illicit cases involving the drug, whereas diazepam is no longer outstanding.

Information on drug involvement in illicit activities after 1980, received from governments in response to the WHO questionnaire in 1994, is limited, and does not allow a comparison among a large number of benzodiazepines. However, the recent report from Interpol and the increasing trend in the United States of America, despite the lack of licit medical supplies in that country, together with several recent reports showing flunitrazepam as being the main non-opioid drug abused by opioid abusers in major European cities, further substantiate its high abuse liability.

5. Therapeutic usefulness

Flunitrazepam is useful for the treatment of insomnia. It is also indicated as a pre-anaesthetic medication to assist in the induction and maintenance of anaesthesia. Flunitrazepam has a therapeutic usefulness similar to other benzodiazepine hypnotics, within the range from moderate to great.

6. Recommendation

Flunitrazepam has a greater likelihood of abuse than other benzodiazepines. Although there is some element of self-medication for opioid withdrawal, the abuse of flunitrazepam by opioid abusers complicates the clinical picture, leading to multiple drug dependence. Its abuse is prevalent also among youths and cocaine abusers. In addition to its oral and intravenous use, abuse by ''snorting'' has recently been reported. As yet, no other benzodiazepine has been reported as being abused by three different routes of administration: oral, nasal and intravenous. Flunitrazepam abuse has been associated with dependence and other behavioural problems. Illicit activities involving flunitrazepam are increasing even in the United States of America, where it is available illegally despite the lack of marketing for therapeutic use.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and paying particular regard to the above characteristics, the degree of seriousness of the public health and social problems associated with the abuse of flunitrazepam is assessed to have become substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that flunitrazepam be rescheduled into Schedule III of the Convention on Psychotropic Substances, 1971.

Mesocarb

1. Substance identification

Mesocarb (INN; CAS 34262–84–5), is chemically 3-(α-methlylphenethyl)-*N*-(phenylcarbamoyl)syndone imine, is also known as Pharbamocarb, Sidnocarb and Sydnocarb. Mesocarb has one asymmetric carbon atom in the molecule, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and effects on the central nervous system

Chemically, mesocarb is a sydnone imine having an amfetamine-like moiety in its molecule. Of the two optical isomers of mesocarb, only the levorotatory isomer exerts a stimulant effect on the central nervous system. This effect is significantly weaker than that of dexamfetamine. Mesocarb produces locomotor stimulation, anorectic activity, enhancement of conditioned reflexes, and shortening of the period of action of hypnotic agents. In addition, there are several pharmacological studies on mesocarb used in combination with other substances in animals, such as mesocarb-acetylsalicylic acid combination. Mesocarb has been reported to increase work capacity and improve cardiovascular function while maintaining normal oxygen consumption. Adverse reactions are similar to those of other CNS stimulants. Several studies in humans have shown that mesocarb increases resistance to environmental stress such as cold temperature, low gravity, and low oxygen levels in the air.

3. Dependence potential

Animal studies indicate that mesocarb has discriminative stimulus effects similar to CNS stimulants such as dexamfetamine and cocaine, as well as some reinforcing effects in monkeys, suggesting a low to moderate dependence potential.

4. Actual abuse and/or evidence of likelihood of abuse

There is some evidence to indicate that mesocab is abused in sports, and its use has been banned by the International Olympic Committee.

Though reportedly discontinued, information from the International Narcotics Control Board indicated that large quantities of a pharmaceutical preparation containing mesocarb and acetylsalicylic acid were illegally exported to western Africa. Although epidemiological data are not available, it is believed that most, if not all, of the exported combination products was abused. On the basis of available information, mesocarb is assessed to have an appreciable abuse liability.

5. Therapeutic usefulness

Mesocarb is used in several countries, mainly in eastern Europe, as a stimulant to counteract acute intoxication by depressants; for the treatment of hyperactivity and nocturnal enureses in children; and as an ''energizer'' to enhance resistance to environmental stress. The therapeutic usefulness of mesocarb is estimated to be within the range between little and moderate.

6. Recommendation

Although no epidemiological data are available on health problems associated with the actual abuse of mesocarb, mesocarb is abused in sports, and illicit activities involving mesocarb have been reported. Based on this and the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of mesocarb is assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that mesocarb be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Methcathinone

1. Substance identification

Methcathinone (CAS 5650–44–2) chemically 2-(methylamino)-1-phenylpropan-1-one, is also know as ephedrone and metylcathinone. It has one chiral centre, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and affects on the central nervous system

Methcathinone is the *N*-methyl derivative of cathinone, and is closely related to metamfetamine. Animal studies have shown that methcathinone produces CNS stimulant effects similar to those produces by amfetamine, metamfetamine, cathinone and cocaine. Of the two optical isomers, the levorotatory form is more active.

3. Dependence potential

Drug discrimination and self-administration studies in animal indicate that methcathinone has a dependence potential similar to central nervous system stimulants such as amfetamine and cocaine. Case reports and a study conducted in the United States of America on methcathinone abusers also suggest that methcathinone has a high dependence potential similar to that of metamfetamine.

4. Actual abuse and/or evidence of likelihood of abuse

Significant abuse of methcathinone has been reported in Estonia, Latvia, the Russian Federation, and in some countries of the Commonwealth of Independent States as well as in the United States of America. Methcathinone is readily manufactured from ephedrine by oxidation. Methcathinone is assessed to have a high abuse liability.

5. Therapeutic usefulness

Methcathinone has not been marketed for therapeutic purposes. Its therapeutic usefulness is assessed to be very limited, if any.

6. Recommendation

Studies from the United States of America and the Russian Federation have confirmed that methcathinone abuse results in adverse health effects similar to those associated with the abuse of metamfetamine, including fatal cases of acute intoxication. Illicit activities involving methcathinone, including clandestine manufacturing, are also reported widely.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and paying particular regard to the above characteristics, the degree of

seriousness of the public health and social problems associated with the abuse of methcathinone is assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that methcathinone be included in Schedule I of the Convention on Psychotropic Substances, 1971.

Zipeprol

1. Substance identification

Zipeprol (INN; CAS 34758–83–3), chemically o-(α-methoxybenzyl—4-(β-methoxyphenethyl)-1-piperazineethanol, is also know as Antituxil-Z, Carm-3024, Chilvax, Delaviral, Dovavixin, Jactus, Eritos, Mirsol, Ogyline, Rospilene, Respirase, Respirax, Sanotus, Sentus, Silentos, Sousibim, Talasa, Tusigen, Tussiflex and Zitoxil. Zipeprol has three asymmetric carbon atoms in the molecule, so that eight stereoisomeric forms are possible.

2. Similarity to already known substances and affects on the central nervous system

In laboratory animals, zipeprol has been shown to have an antitussive activity weaker than codeine and comparable to dextromethorphan. Its pharmacological properties are different from those of opioid antitussives, such as codeine, in that zipeprol has anti-cholinergic activities. It also does not produce respiratory depression, bile duct constriction or constipation, which are often associated with narcotic antitussives.

Unlike opioids, zipeprol is essentially devoid of analgesic activity, but at higher doses, zipeprol acts like a weak opioid agonist. Zipeprol showed a bi-phasic effect in competing for binding sites in rat brain homogenates.

3. Dependence potential

In rats, lower doses of zipeprol amplify some opioid withdrawal manifestations whereas at higher doses it suppresses several morphine withdrawal symptoms. In the monkey, zipeprol suppresses morphine abstinence. Zipeprol is assessed to have a moderate dependence potential.

4. Actual abuse and/or evidence of likelihood of abuse

There have been a number of reports on the abuse of zipeprol from Brazil, Chile, Italy, Mexico, the Republic of Korea, Switzerland, and the former Yugoslavia. These reports suggest that its sedative, hallucinatory and euphorigenic effects, and its ability to suppress some signs of opioid withdrawal at high doses, may be the reasons for its abuse. Over-the-counter distribution of zipeprol preparations may have contributed to its widespread abuse in some places. Taking this into account, zipeprol is assessed to have a moderate abuse liability.

Adverse health consequences of zipeprol abuse include seizures, hallucinations, confusion and amnesia. Dose escalation is not uncommon and fatal cases from intoxication were reported from several countries. The tablet form has been used for intravenous administration.

5. Therapeutic usefulness

A number of clinical studies have demonstrated the therapeutic efficacy of zipeprol in the treatment of cough. The therapeutic usefulness of zipeprol is assessed to be within the range between little to moderate.

6. Recommendation

Although zipeprol is a weak opioid agonist at high doses, its toxicity, hallucinogenic and other psychotropic effects constitute a significant element in its abuse. It is therefore appropriate to consider its control under the Convention on Psychotropic Substances, 1971.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of zipeprol is assessed to be substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that zipeprol be included in Schedule II of the Convention on Psychotropic Substances, 1971.

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 include:

(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.

Methcathinone, etryptamine and aminorex, are controlled under the CSA in Schedule I. The proposed international drug scheduling actions, if adopted by CND, will result in no greater degree of control of these substances than are currently applied domestically. Flunitrazepam is controlled domestically in Schedule IV of the CSA; additional controls may be necessary if the United Nations moves this substance to Schedule III of the Convention. Brotizolam, mesocarb, and zipeprol are neither controlled domestically nor currently marketed for medical use in the United States. In order to comply with obligations under the Convention, these three substances would have to be controlled under the CSA if the United Nations endorses the WHO recommendations.

FDA, on behalf of the Secretary of HHS, invites interested persons to submit comments on the United Nations notifications concerning these seven drug substances. FDA, in cooperation with the National Institute on Drug Abuse, will consider the comments on behalf of HHS in evaluating the WHO scheduling recommendations. Then, pursuant to section 811(d)(2)(B) of the CSA, HHS will recommend to the Secretary of State what position the United States should take when voting on the recommendations at the CND meeting in March 1995.

IV. Submission of Comments and Opportunity for Public Meeting

Interested persons may, on or before February 9, 1995, submit to the Dockets Management Branch (address above) written comments regarding this notice. FDA does not presently plan to hold a public meeting. If any person believes that, in addition to its written comments, a public meeting would contribute to the development of the U.S. position on any of these two substances, a request for a public meeting and the reasons for such a request should be sent to Nicholas P. Reuter (address above) on or before January 30, 1995. The short time period for the submission of comments and requests for a public meeting is needed to assure that HHS may, in a timely fashion, carry out the required action and be responsive to the United Nations. 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 Dockets Management Branch (address above) between 9 a.m and 4 p.m., Monday through Friday.

Dated: January 17, 1995.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

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BILLING CODE 4160–01–F

Advisory Committees; Notice of Meetings

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces forthcoming meetings of public advisory committees of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meetings and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

FDA has established an Advisory Committee Information Hotline (the hotline) using a voice-mail telephone system. The hotline provides the public with access to the most current information on FDA advisory committee meetings. The advisory committee hotline, which will disseminate current information and information updates, can be accessed by dialing 1–800–741–8138 or 301–443–0572. Each advisory committee is assigned a 5-digit number. This 5-digit number will appear in each individual notice of meeting. The