Dated: February 10, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2021–N–0165]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Isotonitazene; MDMB-4en-PINACA; CUMYL-PEGACLONE; Flubromazolam; Clonazolam; Diclazepam; 3-Methoxyphencyclidine; Diphenidine; Request for Comments

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 United States' position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, in April 2021. This notice is issued under the Controlled Substances Act (CSA).

DATES: Submit either electronic or written comments by March 22, 2021.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2021–N–0165 for ''International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Isotonitazene; MDMB-4en-PINACA; CUMYL-PEGACLONE; Flubromazolam; Clonazolam; Diclazepam; 3-Methoxyphencyclidine; Diphenidine; Request for Comments.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Center for Drug Evaluation and Research, Controlled Substance Staff, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5150, Silver Spring, MD 20993–0002, 301–796–3156, *james.hunter@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (1971 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 1971 Convention that the 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 (Secretary of 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 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 seven substances to be considered for control under the 1971 Convention. This notification reflects the recommendation from the 43rd WHO Expert Committee for Drug Dependence (ECDD), which met in October 2020. In the **Federal Register** of August 4, 2020 (85 FR 47217), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II. Section 201(d)(2)(B) of the CSA 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 persons to submit information and comments on the proposed scheduling action.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs (1961 Convention). The Secretary of State has received a notification from the Secretary-General regarding one substance to be considered for control under this convention. The CSA does not require HHS to publish a summary of such information in the **Federal Register**. Nevertheless, to provide interested and affected persons an opportunity to submit comments regarding the WHO recommendations for drugs under the 1961 Convention, the notification regarding these substances 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 position of the United States 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 regarding control of substances under the 1961 Convention.

II. United Nations Notification

The formal notification from the United Nations that identifies the drug substances and explains the basis for the scheduling recommendations is reproduced as follows (non-relevant text removed):

Reference:
NAR/CL.1/2020
WHO/ECDD43; 1961C–Art.3, 1971C–Art.2
CU 2021/7(A)/DTA/SGB

The Secretariat of the United Nations presents its compliments to the Permanent Mission of the United States of America and has the honour to inform the Government that in a letter dated 30 November 2020, the Director-General of the World Health Organization (WHO), pursuant to article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (1961 Convention), and article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances of 1971 (1971 Convention), notified the Secretary-General of the following recommendations of the forty-third Meeting of the WHO's Expert Committee on Drug Dependence (ECDD):

Substance recommended to be added to Schedule I of the 1961 Convention:

—Isotonitazene
chemical name: N,N-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine

Substances recommended to be added to Schedule II of the 1971 Convention:

—CUMYL-PEGACLONE
chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido[4,3-b]indol-1-one
—MDMB-4en-PINACA
chemical name: methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate
—3-Methoxyphencyclidine
chemical name: 1-(1-(3-methoxyphenyl)cyclohexyl)piperidine
—Diphenidine
chemical name: 1-(1,2-diphenylethyl)piperidine

Substances recommended to be added to Schedule IV of the 1971 Convention:

—Clonazolam
chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine
—Diclazepam
chemical name: 7-chloro-5-(2-chlorophenyl)-1- methyl-1,3-dihydro-2*H*-benzo[e][1,4]diazepin2-one
—Flubromazolam
chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine

In accordance with the provisions of article 3, paragraph 2 of the 1961 Convention and article 2, paragraph 2 of the 1971 Convention, the Secretary-General hereby transmits the notification as annex I to the present note. In connection with the notification, WHO also submitted an extract of the report of the forty-third meeting of the WHO Expert Committee on Drug Dependence, which provides a summary of the assessment and recommendations made by the Expert Committee on Drug Dependence (attached as annex II).

Also in accordance with the same provisions, the notification from WHO will be brought to the attention of the sixty-fourth session of the Commission on Narcotic Drugs (12–16 April 2021) in a pre-session document that will be made available in the six official languages of the United Nations on the website of the 64th session of the CND:

https://www.unodc.org/unodc/en/commissions/CND/session/64_Session_2021/session-64-of-the-commission-on-narcotic-drugs.html

In order to assist the Commission in reaching a decision, it would be appreciated if the Government could communicate any comments it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1961 Convention, namely:

—Isotonitazene

as well as any economic, social, legal, administrative or other factors that it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1971 Convention, namely:

—CUMYL-PEGACLONE
—MDMB-4en-PINACA
—3-Methoxyphencyclidine
—Diphenidine
—Clonazolam
—Diclazepam
—Flubromazolam

The Secretariat of the United Nations avails itself of this opportunity to renew to the Permanent Mission of the United States of America to the United Nations (Vienna) the assurances of its highest consideration.

12 January 2012

Annex I

Letter addressed to the Secretary-General of the United Nations From the Director-General of the World Health Organization, dated 30 November 2020

''The Forty-third meeting of the WHO Expert Committee on Drug Dependence was convened in a virtual format from 12 to 16 October 2020 and was coordinated from the WHO headquarters in Geneva. The objective of this meeting was to carry out an in-depth evaluation of the abuse and dependence-producing capacity of psychoactive substances in order to make recommendations on appropriate international scheduling measures.

The Forty-third WHO ECDD Meeting critically reviewed eleven psychoactive substances, including one synthetic opioid, one hallucinogen, one synthetic stimulant, two synthetic cannabinoid receptor agonists, three dissociative-type drugs, and three benzodiazepines. These substances had not previously been formally reviewed by WHO and are currently not under international control. Information was brought to WHO's attention that these substances are clandestinely manufactured, of especially serious risk to public health and society, and of no recognised therapeutic use by any Party. Therefore, a critical review to consider international scheduling measures was undertaken for each substance.

With reference to Article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol, and Article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances (1971), WHO is pleased to submit recommendations of the Forty-second Meeting of ECDD as follows:

To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):

—Isotonitazene
chemical name: N,N-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine

To be added to Schedule II of the Convention on Psychotropic Substances (1971):

—CUMYL-PEGACLONE
chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one
—MDMB-4en-PINACA
chemical name: methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate
—3-methoxyphencyclidine
chemical name: 1-(1-(3-methoxyphenyl)cyclohexyl)piperidine
—Diphenidine
chemical name: 1-(1,2-diphenylethyl)piperidine

To be added to Schedule IV of the Convention on Psychotropic Substances (1971):

—Clonazolam
chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine
—Diclazepam
chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one
—Flubromazolam
chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine

The assessments and findings on which these recommendations are based are set out in detail in the forty-third meeting report of the WHO Expert Committee on Drug Dependence. An extract of this report, providing a summary of the assessment and recommendations made by the ECDD, is contained in Annex 1 to this letter.

I am very pleased with the ongoing collaboration between WHO, the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB) and in particular, how this collaboration has benefited the work of the WHO Expert Committee on Drug Dependence and more generally, the implementation of the operational recommendations of the United Nations General Assembly Special Session 2016.

Annex II

Summary Assessment and Recommendations of the 43rd Expert Committee on Drug Dependence, 12–16 October 2020

To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):

Isotonitazene

Substance identification

Isotonitazene (Chemical name: *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) belongs to the 2-benzylbenzimidazole group of compounds, which includes the closely related opioids etonitazene, metonitazene, and clonitazene. It is found in yellow, brown, or off-white powder forms.

WHO Review History

Isotonitazene has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Isotonitazene is a chemical analogue of etonitazene and clonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Isotonitazene is a potent opioid analgesic with a rapid onset of action. Preclinical studies have demonstrated that isotonitazene is more potent than fentanyl and hydromorphone, and substantially more potent than morphine. There is limited research on the effects of this compound on the central nervous system, but given its demonstrated potency at the μ-opioid receptor, it would be expected to produce analgesia, respiratory depression and sedation.

Dependence Potential

No controlled animal or human studies have assessed the dependence potential of isotonitazene. As a potent μ-opioid agonist, it would be expected to produce dependence. An unverified online report described dependent use and withdrawal symptoms, including flu-like symptoms and anxiety.

Actual Abuse and/or Evidence of Likelihood of Abuse

There are no controlled studies of the abuse potential of isotonitazene, but as a potent μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability.

Due to its relatively recent appearance on the illicit drug market, there is limited information on the prevalence of use of isotonitazene or its associated harms. Seizures have been reported in multiple countries and regions. It is noted to be used via a range of routes including sublingually, vaping and intravenously.

The number of deaths involving isotonitazene has increased in a short time span. Deaths commonly occur in combination with other opioids or benzodiazepines. Isotonitazene deaths share common features with heroin deaths, including evidence of injection, and signs consistent with opioid overdose such as pulmonary and/or cerebral oedema. Deaths are likely to be underreported due to its recent and rapid appearance.

Recommendation

Isotonitazene (Chemical name: N,N-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) has a mechanism of action such that it is liable to similar abuse and productive of similar ill effects as other opioids which are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects including deaths. It has no known therapeutic use and is likely to cause substantial harm.

Therapeutic Usefulness

Isotonitazene is not known to have any therapeutic use.

To be added to Schedule II of the Convention on Psychotropic Substances (1971):

CUMYL-PEGACLONE

Substance Identification

CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one) is a synthetic cannabinoid. It has been found in seized material formulated for smoking and vaping.

WHO Review History

CUMYL-PEGACLONE has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

CUMYL-PEGACLONE is a synthetic cannabinoid with a mechanism of action similar to that of other synthetic cannabinoids. It is a potent full agonist at CB1 receptors.

There are no controlled studies of its effects, but there are online user reports describing euphoria, dissociation, red eyes, dry mouth and appetite stimulation. These effects are consistent with known cannabinoid agonist effects.

Dependence Potential

There are no controlled animal or human studies that address the dependence potential of CUMYL-PEGACLONE. However, CUMYL-PEGACLONE has been shown to be a full and potent agonist at the CB1 receptor and therefore would be expected to produce dependence consistent with other CB1 receptor agonists.

Actual Abuse and/or Evidence of Likelihood of Abuse

There are no controlled animal or human studies that address the abuse potential of CUMYL-PEGACLONE.

A number of countries across several regions have reported that CUMYL-PEGACLONE is being used for its psychoactive properties.

There are reports of adverse effects such as seizures and of fatalities involving CUMYL-PEGACLONE. While other drugs were present, CUMYL-PEGACLONE was deemed to be a causal or contributory factor in a number of these deaths.

Therapeutic Usefulness

CUMYL-PEGACLONE is not known to have any therapeutic use.

Recommendation

CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one) is a synthetic cannabinoid receptor agonist with a mode of action that suggests a likelihood of dependence and abuse, and similar ill-effects to other synthetic cannabinoids. Its use has been associated with severe adverse effects and fatalities. The effects of CUMYL-PEGACLONE are similar to those of other synthetic cannabinoids that are controlled under Schedule II of the

Convention on Psychotropic Substances of 1971. CUMYL-PEGACLONE has no therapeutic use, and its use constitutes a substantial risk to public health.

• The committee recommended that CUMYL-PEGACLONE (Chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one), be added to Schedule II of the Convention on Psychotropic Substances of 1971.

MDMB-4en-PINACA

Substance Identification

MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) is a synthetic cannabinoid. It has been identified in seized material formulated for smoking, and found as white to yellow/brown powder.

WHO Review History

MDMB-4en-PINACA has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

MDMB-4en-PINACA is a synthetic cannabinoid that binds to CB1 cannabinoid receptors as a full and potent agonist. It is structurally similar to 5F-MDMB-PINACA (5F-ADB) which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. A report from an unpublished animal study indicates that MDMB-4en-PINACA can produce the characteristic effects of CB1 cannabinoid agonists such as hypothermia and lethargy. Reports from online user forums describe cannabis-like euphoria at moderate levels of intake, with dissociation described at higher doses. Both sedation and stimulation have been reported, in addition to memory loss, confusion and agitation.

Dependence Potential

No animal or human studies were identified that described the dependence potential of MDMB-4en-PINACA. As a full CB1 agonist, it would be expected to produce dependence similar to other CB1 receptor agonists.

Actual Abuse and/or Evidence of Likelihood of Abuse

No animal or human studies have been conducted to provide an indication of the likelihood of abuse of MDMB-4en-PINACA, though CB1 receptor agonists have known abuse potential. A number of countries across different regions have reported MDMB-4en-PINACA use. Its use has been associated with cases of impaired driving and death.

Therapeutic Usefulness

MDMB-4en-PINACA is not known to have any therapeutic use.

Recommendation

MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) is a potent synthetic cannabinoid receptor agonist with a similar mechanism of action, and similar effects to a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Use of MDMB-4en-PINACA has been associated with severe adverse effects, including fatal intoxications, and cases of impaired driving. MDMB-4en-PINACA has no therapeutic use.

• The Committee recommended that MDMB-4en-PINACA (Chemical name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

3-methoxyphencyclidine (3-MeO-PCP)

Substance Identification

3-methoxyphencyclidine (3-MeO-PCP), (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) is an arylcyclohexylamine and 3-methoxy derivative of phencyclidine (PCP) which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. It appears as powder and tablets.

WHO Review History

3-methoxyphencyclidine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

3-methoxyphencyclidine is an N-methyl-D-aspartate (NMDA) receptor antagonist with a similar mechanism of action and effects to phencyclidine. These effects include an altered mental state characterized by confusion, disorientation and out of body experiences as well as hallucinations and other psychotic symptoms.

Dependence Potential

No human or animal studies have examined the dependence potential of 3-methoxyphencyclidine.

Actual Abuse and/or Evidence of Likelihood of Abuse

As an NMDA receptor antagonist, 3-methoxyphencyclidine would be expected to produce similar effects, and have abuse potential similar to that of phencyclidine.

Adverse effects include cardiovascular effects (such as hypertension and tachycardia) and cognitive effects including psychosis, confusion and agitation. There may be a greater risk of psychosis in those with a history of, or vulnerability to psychotic illness. Cases of severe and fatal intoxication are reported from several countries and regions.

Seizures have been reported in a number of countries from several different regions.

Therapeutic Usefulness

3-methoxyphencyclidine is not known to have any therapeutic use.

Recommendation

3-methoxyphencyclidine (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl] piperidine) is an analogue of, and has similar effects to phencyclidine (PCP), which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests a likelihood of abuse. There is evidence of use of this substance in a number of countries across different regions. 3-methoxyphencyclidine causes substantial harm, including severe adverse events such as hallucinations, other psychotic symptoms, and fatal intoxications. It has no therapeutic use.

• The Committee recommended that 3-methoxyphencyclidine (Chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Diphenidine

Substance Identification

Diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) is a dissociative and hallucinogenic substance of the 1,2-diarylethylamine class. It appears as powder and tablets.

WHO Review History

Diphenidine has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Diphenidine is known to produce hallucinogenic and dissociative effects through its action as an N-methyl-D-aspartate (NMDA) receptor antagonist. This mechanism of action as well as its effects are similar to those of phencyclidine (PCP) which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

Dependence Potential

No animal or human studies have determined the dependence potential for diphenidine.

Actual Abuse and/or Evidence of Likelihood of Abuse

As an NMDA receptor antagonist, diphenidine would be expected to have abuse potential similar to that of phencyclidine. In addition, diphenidine causes dopamine release, in a manner similar to, but to a lesser degree, than cocaine. This effect may also contribute to its abuse potential.

Cases of intoxication requiring hospitalization are reported. Adverse effects include cardiovascular effects (such as tachycardia and hypertension) and central nervous system effects including hallucinations, depersonalization, delusions, paranoia, dissociation, confusion, nystagmus and muscle rigidity. These effects have resulted in cases of acute intoxication leading to emergency department admissions. A small number of fatal intoxications involving diphenidine have been documented. All deaths involved multiple drug toxicity, though cardiovascular and hallucinogenic symptoms described in the cases are consistent with the effects of diphenidine.

Seizures have been reported in a number of countries from several different regions.

Therapeutic Usefulness

Diphenidine is not known to have any therapeutic use.

Recommendation

The available evidence indicates that diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) has a mechanism of action and effects that are similar to those of phencyclidine (PCP), which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests a likelihood of abuse. There is evidence of significant harm due to diphenidine, including psychosis and cardiovascular effects, which represents a substantial risk to public health. Diphenidine has no therapeutic use.

- The Committee recommended that diphenidine (Chemical name: 1-(1,2-diphenylethyl)piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Substances recommended to be scheduled in Schedule IV of the Convention on Psychotropic Substances (1971):

Clonazolam

Substance Identification

Clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) is 1-4 triazolobenzodiazepine similar to clonazepam, triazolam and alprazolam. It is sold in powder, blotter, liquid and tablet form.

WHO Review History

Clonazolam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Clonazolam enhances the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through binding at the benzodiazepine site of the GABA-A receptor. This mechanism of action, as well as its effects (sedation, muscle relaxation, slurred speech and loss of motor control, amnesia) are similar to those of the benzodiazepines (such as diazepam, triazolam and alprazolam) which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

In cases of clonazolam poisoning, the effects have been reversed with the benzodiazepine antagonist flumazenil, confirming that its action is mediated via the benzodiazepine receptor in the GABA-A receptor complex.

Dependence Potential

No controlled animal or human studies have examined the dependence potential of clonazolam, though based on its pharmacological effects, and similarity to other benzodiazepines, it would be expected to have potential to produce dependence.

The development of tolerance to the effects of clonazolam following repeated use and the onset of withdrawal symptoms after cessation of use have been reported on online forums.

Actual Abuse and/or Evidence of Likelihood of Abuse

No human or animal studies have examined abuse liability. Online forums describe its recreational use and consistently report its strong anxiolytic effects.

A number of published reports describe the management of cases of intoxication involving clonazolam in emergency departments or intensive care. Clonazolam use has been analytically confirmed in cases of impaired driving, in combination with other substances. Clonazolam has the potential to increase the effects of other drugs, including opioids, and on its own can cause severe central nervous system depression, including somnolence, confusion, sedation and unconsciousness.

There are reports of its identification in multiple countries representing all regions, indicating that its use may be increasing. Clonazolam is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic Usefulness

Clonazolam is not known to have any therapeutic use, is not listed on the WHO Model List of Essential Medicines, and has never been marketed as a medicinal product.

Recommendation

Clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) is a 1-4 triazolobenzodiazepine that has actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. Like other benzodiazepines, clonazolam can produce a state of dependence and central nervous system depression. There have been a number of reports of abuse, impaired driving and non-fatal intoxications. There is sufficient evidence of its abuse so as to constitute a public health problem, and it has no known therapeutic use.

- The Committee recommended that clonazolam (Chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

Diclazepam

Substance Identification

Diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) is a 2-chloro derivative of the benzodiazepine diazepam. It appears as a white powder, and is commonly sold as tablets, pellets and liquid.

WHO Review History

Diclazepam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health, and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Diclazepam is an agonist at the benzodiazepine site of the GABA-A receptor, acting to increase the effect of the inhibitory neurotransmitter gamma amino butyric acid (GABA). Diclazepam has similar effects to the benzodiazepine diazepam, which is currently controlled under the Convention on Psychotropic Substances of 1971. It is metabolized to the benzodiazepines delorazepam, lorazepam and lormetazepam. These metabolites are active and are also pharmaceuticals that are included in Schedule IV of the Convention on Psychotropic Substances of 1971.

Diclazepam has been demonstrated to cause sedation and muscle relaxation in animals. Central nervous systems depressant effects are also described in humans.

Dependence Potential

No controlled animal or human studies have examined the dependence potential of diclazepam.

Online user reports describe cross-tolerance with other benzodiazepines and use to self-manage benzodiazepine withdrawal. This evidence, along with its mechanism of action, suggests that diclazepam has the capacity to produce dependence similar to other benzodiazepines.

Actual Abuse and/or Evidence of Likelihood of Abuse

No controlled animal or human studies have examined the abuse liability of diclazepam. However, based on its mechanism of action and effects, it would be expected to have abuse liability similar to other benzodiazepines.

Diclazepam has the potential to increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and interactions when combined with other drugs. Fatal intoxications with diclazepam have been reported.

Seizures of diclazepam have been reported from multiple countries across different regions. Diclazepam is increasingly sold as falsified benzodiazepines, commonly as diazepam.

Diclazepam has been implicated in cases of impaired driving, including cases where diclazepam was identified as the main contributor to impairment. It also has been involved in cases of drug-facilitated sexual assault.

Therapeutic Usefulness

Diclazepam is not known to have any therapeutic use, is not listed on the WHO Model List of Essential Medicines and has never been marketed as a medicinal product.

Recommendation

Diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) is a 2-chloro analogue of the benzodiazepine diazepam that has actions and effects very similar to those of benzodiazepines listed under Schedule IV of the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other

benzodiazepines. There have been reports of abuse, impaired driving and fatal and nonfatal intoxications. There is sufficient evidence of its abuse so as to constitute a significant risk to public health, and it has no known therapeutic use.

• The Committee recommended that diclazepam (Chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin2-one) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

Flubromazolam

Substance Identification

Flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) is a 1-4 triazolobenzodiazepine. Flubromazolam is a white powder, often sold as a liquid or as tablets.

WHO Review History

Flubromazolam has never been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is clandestinely manufactured, poses a risk to public health and has no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Flubromazolam is a highly potent benzodiazepine with long lasting depressant effects on the central nervous system. Flubromazolam enhances the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) through binding at the benzodiazepine site of the GABA-A receptor. This mechanism of action, as well as its effects, are similar to those of the benzodiazepines triazolam and alprazolam which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

A single pharmacokinetic study showed that a 0.5 mg flubromazolam dose induced strong sedative effects that lasted more than 10 hours, and caused partial amnesia for more than 24 hours. The effects of flubromazolam have been effectively reversed by the benzodiazepine antagonist flumazenil.

Reports from online user forums describe benzodiazepine-like effects including anxiolytic, euphoric and sedative effects.

Dependence Potential

No controlled animal or human studies describe the dependence potential of flubromazolam, although multiple reports from online sources describe severe withdrawal symptoms, such as muscle aches, sleeping disorders, severe anxiety and panic attacks, dissociative symptoms, perceptual distortions, cramping, chills, vomiting and risk of seizures. There are also descriptions of loss of control over use, and rapid onset of tolerance. The latter suggests that taking increased doses and developing physical dependence is likely.

Actual Abuse and/or Evidence of Likelihood of Abuse

No controlled animal or human studies have assessed the abuse potential of flubromazolam. Impaired driving with flubromazolam as the sole intoxicant is reported. Non-fatal intoxications requiring hospital admission, and fatal intoxications due to flubromazolam use are documented. In these cases, central nervous system depression and severe sedation were clinical features of presentation. Flubromazolam has the potential to increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and interactions when combined with other drugs.

Nonmedical use and seizures of flubromazolam have been documented in multiple countries across different regions. It is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic Usefulness

Flubromazolam is not known to have any therapeutic uses, is not listed on the WHO Model List of Essential Medicines and has never been marketed as a medicinal product.

Recommendation

Flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) is a 1-4 triazolobenzodiazepine that has actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other benzodiazepines. There have been increasing reports of abuse, impaired driving and fatal and non-fatal intoxications. There is sufficient evidence of its abuse to constitute a significant risk to public health, and it has no known therapeutic use.

The Committee recommended that flubromazolam (Chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

III. Discussion

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

Isotonitazene (chemical name: *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine) is a potent synthetic opioid that is abused similar to other synthetic opioids. Its use has resulted in adverse health effects, including positively identified in 49 death investigation cases in the United States between August 2019 and April 2020. Law enforcement data indicate that isotonitazene has appeared in the United States' illicit drug market.

According to the National Forensic Laboratory Information System (NFLIS) database, there have been 53 encounters of isotonitazene in the United States (as of June 2020). There are no commercial or approved medical uses for isotonitazene. On August 20, 2020, the Drug Enforcement Administration issued an order to temporarily control isotonitazene as a Schedule I substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if isotonitazene is placed in Schedule I of the 1961 Convention.

CUMYL-PEGACLONE is a synthetic cannabinoid that has been sold online and used to mimic the biological effects of tetrahydrocannabinol (THC), the main psychoactive constituent in marijuana. Research and clinical reports have demonstrated that synthetic cannabinoids are applied onto plant material so that the material may be smoked as users attempt to obtain a euphoric and psychoactive ''high''. Synthetic cannabinoids have been marketed under the guise of ''herbal incense'', and promoted by drug traffickers as legal alternatives to marijuana. In vitro studies demonstrate that CUMYL-PEGALCONE binds to and activates the cannabinoid one receptor. CUMYL-PEGALCONE has not been encountered within the United States according to the NFLIS database (as of January 14, 2021). There are no commercial or approved medical uses for CUMYL-PEGALCONE and it is not a controlled substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if CUMYL-PEGALCONE is controlled under Schedule II of the 1971 Convention.

MDMB-4en-PINACA is a synthetic cannabinoid that has been sold online and used to mimic the biological effects of THC, the main psychoactive constituent in marijuana. Research and clinical reports have demonstrated that synthetic cannabinoids are applied onto plant material so that the material may be smoked as users attempt to obtain a euphoric and psychoactive ''high''. Synthetic cannabinoids have been marketed under the guise of ''herbal incense'', and promoted by drug traffickers as legal alternatives to marijuana. According to the NFLIS database, MDMB-4en-PINACA was first encountered in the United States in January 2019. There have been 3,331 encounters of MDMB-4en-PINACA in the United States (as of January 14, 2021). MDMB-4en-PINACA has also been encountered mixed with opioids including heroin and fentanyl, with some incidents resulting in violent

behaviors, tachycardia, and hypertension. There are no commercial or approved medical uses for MDMB-4en-PINACA and it is not a controlled substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if MDMB-4en-PINACA is controlled under Schedule II of the 1971 Convention.

3-Methoxyphencyclidine; chemical name: 1-(1-(3-methoxyphenyl) cyclohexyl)piperidine) is a novel N-methyl-D-aspartate (NMDA) receptor antagonist with structural and biochemical similarities to phencyclcycidine (PCP) and other arylcyclohexylamines. 3-Methoxyphencyclidine is classified as an arylcyclohexylamine and produces dissociative anesthetic and hallucinogenic effects. Use of this substance is associated with intoxication and published case reports of both fatal and non-fatal overdose. 3-Methoxyphencyclidine is encountered by law enforcement in drug seizure reports. 3-Methoxyphencyclidine is an analogue of the Schedule II hallucinogen PCP. There is no approved medical use for 3-Methoxyphencyclidine in the United States and is not a controlled substance under the CSA. If intended for human consumption, 3-Methoxyphencyclidine may be treated as a ''controlled substance analogue'' under the CSA pursuant to 21 U.S.C. 802(32)(A) and 813. As such, additional permanent controls will be necessary to fulfill U.S. obligations if 3-Methoxyphencyclidine is controlled under Schedule II of the 1971 Convention.

Diphenidine (chemical name: 1-(1,2-diphenylethyl) piperidine) is a non-competitive NMDA receptor antagonist classified as a diarylethylamine and produces dissociative anesthetic and hallucinogenic effects. It was originally synthesized in the 1920s but reports of abuse started in the last decade. Use of this substance is associated with intoxication and published case reports of both fatal and non-fatal overdose outside of the United States. Diphenidine is encountered by law enforcement in drug seizure reports. Diphenidine is not approved for medical use in the United States and is not a controlled substance under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if diphenidine is controlled under Schedule II of the 1971 Convention.

Flubromazolam, clonazolam, and diclazepam belong to a class of substances known as benzodiazepines. Benzodiazepines produce central nervous system depression and are commonly used to treat insomnia, anxiety, and seizure disorders. Flubromazolam is a triazole analogue of the designer benzodiazepine, flubromazepam. Flubromazolam can be purchased on the internet and is used as a recreational substance in the United States. Flubromazolam has been identified in an increasing number of law enforcement seizures and has been associated with an increasing number of drug overdose deaths. According to the NFLIS database, in 2020 there were 1,446 clonazolam encounters (as of December 2020). It is abused by a broad range of groups including youths, young adults, and older adults. Clonazolam has been involved in an increasing number of drug seizure events as well as drug overdose deaths, alone and in combination with alcohol. As such, the NFLIS database reported 249 encounters in 2020 (as of December 2020). Diclazepam is a designer benzodiazepine sold on the internet and most often found as a liquid solution, but it may be sold as a powder, tablet, blotter paper, or pellet. In 2020, the NFLIS database reported 113 encounters of diclazepam (as of December 2020). In 2018, flubromazolam, clonazolam, and dicalazepam were all identified by law enforcement in driving under the influence of drugs cases in the United States. Flubromazolam, clonazolam, and diclazepam are not approved for medical use in the United States and are not controlled substances under the CSA. As such, additional permanent controls will be necessary to fulfill U.S. obligations if flubromazolam, clonazolam, and dicalazepam are controlled under Schedule IV of the 1971 Convention.

FDA, on behalf of the Secretary of HHS, invites interested persons to submit comments on the notifications from the United Nations concerning these 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, under section 201(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 for control of substances under the 1971 Convention at the CND meeting in April 2021.

Comments regarding the WHO recommendations for control of isotonitazene under the 1961 Single Convention will also be forwarded to the relevant Agencies for consideration in developing the U.S. position regarding narcotic substances at the CND meeting.

Dated: February 12, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended, notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended, and the Determination of the Director, Strategic Business Initiatives Unit, Office of the Chief Operating Officer, CDC, pursuant to Public Law 92–463. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Disease, Disability, and Injury Prevention and Control Special Emphasis Panel (SEP)—SIP21–008, Examining Approaches to Improve Care and Management of People with Lupus.

Date: May 13, 2021.

Time: 11:00 a.m.–6:00 p.m., EDT.

Place: Teleconference.

Agenda: To review and evaluate grant applications.

FOR FURTHER INFORMATION CONTACT: Jaya Raman, Ph.D., Scientific Review Officer, National Center for Chronic Disease Prevention and Health Promotion, CDC, 4770 Buford Highway, Mailstop S107–8, Atlanta, Georgia 30341, Telephone (770) 488–6511, *JRaman@cdc.gov.*

The Director, Strategic Business Initiatives Unit, Office of the Chief Operating Officer, Centers for Disease Control and Prevention, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities, for both the Centers for Disease Control and