

WHO Expert Committee on Drug Dependence

Forty-second report



World Health
Organization

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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization



**World Health
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WHO Expert Committee on Drug Dependence: forty-second report

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WHO Expert Committee on Drug Dependence

Geneva, Switzerland, 21–25 October 2019

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Abbreviations and acronyms

CND	Commission on Narcotic Drugs
ECDD	Expert Committee on Drug Dependence
INCB	International Narcotics Control Board
UNODC	United Nations Office on Drugs and Crime

Introduction

The forty-second meeting of the WHO Expert Committee on Drug Dependence (ECDD) was held on 21–25 October 2019 at WHO headquarters in Geneva, Switzerland.

Open session

Before the start of the meeting, an open session was held so that the Expert Committee could hear presentations and question representatives of interested parties about data that had been provided about the substances under review.

The session was opened by Dr Mariângela Simão, Assistant Director-General, and chaired by Dr Gilles Forte, Coordinator of the Access to Medicines, Vaccines and Pharmaceuticals Division, WHO.

Dr Simão noted that the open session was an opportunity to share views and experiences on the benefits and risks of the substances under review. She described WHO's major challenges in tackling the world drug problem, while preventing and managing the harm of drug use and ensuring access to controlled medicines for those who need them. She described key areas of WHO work in this area, including the ECDD's review of several new psychoactive substances and the recommendations made to the Commission on Narcotic Drugs that they be placed under international control.

Dr Simão also described the first ECDD review of cannabis and cannabis-related substances since those substances were placed under international control in the 1961 and 1971 drug conventions. WHO recommended a change in the international control of cannabis and its components to ensure a more rational system that would prevent drug-related harm while ensuring that cannabis-derived pharmaceutical preparations are available for medical and scientific use. In March 2019, the Commission on Narcotic Drugs (CND) decided to defer a vote on the recommendations to allow Member States more time to discuss the consequences of any change in scheduling cannabis for national and international control.

Dr Simão discussed WHO's concern about inadequate access to opioid analgesics for pain relief and palliative care, particularly in low-income countries. She welcomed the support of Member States, civil society groups, the private sector and other non-State actors for ECDD evidence-based decision-making and acknowledged close collaboration and dialogue with the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB).

Dr Dilkushi Poovendran, Access to Medicines, Vaccines and Pharmaceuticals cluster, described the role and mandate of the ECDD with respect to the international drug control conventions. WHO has the mandate to assess the risks of abuse, dependence and harm to health of psychoactive substances and make recommendations to the CND about the appropriate level of international control. When relevant, the ECDD also considers whether a substance has a medical or scientific application. This mandate is reinforced by several resolutions of the United Nations General Assembly and the CND.

WHO fulfils its mandate through the ECDD in accordance with WHO guidance on the review of psychoactive substances for international control. These processes and procedures were developed by the World Health Assembly, and revisions were approved by the WHO Executive Board in 2010.

Closed session

Welcoming remarks

Dr Simão welcomed all participants on behalf of the WHO Director-General and thanked the ECDD members for the time and effort they had dedicated to reviewing the substances on the agenda. She reiterated WHO's mandate under the 1961 Single Convention on Narcotic Drugs (1) and the 1971 Convention on Psychotropic Substances (2), which is to assess psychoactive substances with potential for abuse and dependence and that harm health and, when relevant, to assess therapeutic use of these substances. She recalled that evidence-based assessment of psychoactive substances as mandated by the international drug control conventions is central to the work of the ECDD. She reminded participants that they were acting in their personal capacities and not as representatives of their governments.

Statement of confidentiality

Dr Claudia Nannini of the WHO Office of the Legal Counsel recalled that the Expert Committee is convened in accordance with WHO's Regulations for expert advisory panels (3) and the Guidance on the WHO review of psychoactive substances for international control (4). In accordance with that document, the functions of the ECDD are to review the information available to it on the substances being considered for international control and for exemptions, and to advise the Director-General on such control. Dr Nannini also reminded participants of the confidentiality of the ECDD's deliberations.

Declarations of interest

Competing interests in health care may result in conflicts of interest, in biased generation or assessment of evidence and in misinformed health care policies. WHO has a stringent policy on avoiding conflicts of interest, particularly in the preparation of official guidance documents that affect health care. As a declaration of conflicts of interest is insufficient to neutralize potentially harmful effects, the Organization has mechanisms for accurate identification of relevant conflicts of interest and approaches to managing any conflicts (such as exclusion of members, recusal from participation in meeting sessions, restricting participation), thus ensuring the validity, transparency and credibility of the Expert Committee's decisions.

Before the opening of the meeting, in accordance with WHO policy, all members of the Expert Committee and all temporary advisers attending the meeting were asked to submit written disclosures of potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence in relation to the subject matter of the meeting. The WHO ECDD Secretariat received several disclosures and sought the advice of the Office of Compliance, Risk Management and Ethics in addressing them.

The Secretariat of the 42nd meeting of the ECDD considered that the disclosed interests were not in conflict with any of the issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee or temporary advisers were deemed relevant to the work of the group.

Election of chairperson, co-chairperson and rapporteur

The members of the Expert Committee elected Professor Jason White as Chair, Dr Afarin Rahimi-Movaghar as Co-chair and Dr Pamela Kaduri as Rapporteur. The Chair welcomed all participants, and the agenda proposed by the Secretariat was approved.

1. Update on priorities from international agencies

1.1 United Nations Office on Drugs and Crime

Dr Conor Crean made a statement on behalf of the UNODC and updated work on the scope of control of substances under the international drug control conventions. Scheduling of substances under the three conventions continues to be a cornerstone of the rule-based system of ensuring access to substances for medical and scientific use, while preventing their abuse. The International Drug Control Conventions provide measures for controlling the illicit trafficking, diversion and use of the substances in its Tables and for illicit manufacture of some of the substances under international control. UNODC's role in scheduling has been to facilitate understanding in Member States of the procedures and the technical reasons for the recommendations of the treaty bodies. This is vital to ensure effective implementation of scheduling decisions in countries. In this regard, UNODC continues to find value in engaging in the risk assessments of WHO with regard to the 1961 and 1971 Conventions and of the INCB with regard to the 1988 Convention, with the support of their respective scientific advisory groups or expert panels when possible.

Since 2015, the CND has decided to schedule 48 substances under various schedules in the 1961 and 1971 Conventions and two precursors of fentanyl and its analogues and three precursors of amphetamine-type stimulants under the 1988 Convention. In terms of normative work to support Member States in implementing recent scheduling decisions, UNODC has continued its programme of preparing and disseminating best practice guidelines and manuals. These include revisions of its recommended laboratory methods for analysing synthetic cathinones and synthetic cannabinoids in seized materials and a supplement to the Multilingual Dictionaries of Narcotic Drugs and Psychotropic Substances under International Control. The UNODC national forensic laboratory proficiency-testing programme, and the International Collaborative Exercises, supported 282 laboratories in 89 countries in 2018 and provided almost 2700 units of chemical reference materials, including for recently scheduled new psychoactive substances, to forensic institutions in 51 countries in the first half of 2019.

The UNODC Early Warning Advisory is monitoring 950 new psychoactive substances reported in 120 countries and territories and is providing evidence for identification of the most harmful, persistent and prevalent new psychoactive substances through its toxicology portal, developed in collaboration with the International Association of Forensic Toxicologists. The first of the biannual reports on the threat of new psychoactive substance was published in March 2019. This and other reports will continue to inform prioritization of substances for action by the treaty bodies. The reports should also ensure early identification

and anticipation of threats, timely reduction of associated risks and appropriate support to Member States and the international community in implementing appropriate strategies to reduce supply and prevent use.

The biannual Global SMART Update series raises awareness about changes in synthetic drug markets, through volume 21, “Understanding the global opioid crisis” (March 2019) and volume 22, “The Amphetamine-Type Stimulant (ATS) market – 10 years after the 2009 plan of action” (October 2019) and also “Synthetic drugs in East and South-East Asia – trends and patterns of amphetamine-type stimulants and new psychoactive substances” (March 2019).

In June 2018, UNODC issued an integrated strategy to support countries in addressing the synthetic opioid crisis, which affects mainly North America with fentanyl and its analogues, and parts of Africa, Asia and the Middle East with tramadol. The strategic response brings together UNODC expertise and programmes for a timely, organization-wide response based on a set of complementary activities and resources and coordinated inter-agency collaboration. In collaboration with WHO and INCB, the UNODC launched the United Nations Toolkit on Synthetic Drugs in March 2019, which provides guidance on options for responding to the opioid crisis, such as legislative and administrative measures, reducing the supply for non-medical uses while ensuring access for medical and scientific purposes, reducing the supply of precursors used in illicit manufacture of synthetic drugs and increasing national forensic capacity. A module on postal security, developed in collaboration with the Universal Postal Union, was launched in 2019 at an intersessional meeting of the CND. The module is designed for experts, practitioners, policy- and decision-makers in the fields of health, forensics and research as an interactive, user-friendly tool for Member States. UNODC will continue to work with national, regional and international partners on further modules to assist Member States in assuring a comprehensive response to the synthetic drugs problem.

1.2 International Narcotics Control Board (INCB)

Mr Bernard Leroy, Board Member, INCB, described the role and functions of INCB within the United Nations drug control system. INCB holds a dual mandate, to limit the manufacture, international trade and use of narcotic drugs and psychotropic substances to medical and scientific purposes and to ensure their availability for these purposes. The INCB comprises 13 members elected by the United Nations Economic and Social Council for 5 years, with the possibility of re-election. Ten members are nominated by governments, and three are nominated by WHO. Members have medical and pharmacological experience and serve in their personal capacity and not as government representatives. INCB's work covers narcotic drugs, psychotropic substances and precursor chemicals.

Mr Leroy presented key points from INCB's annual report for 2018, which marked 50 years of promoting consistent application of the international drug control treaties. The report addressed medical and non-medical use of cannabis, technical and financial assistance to Afghanistan, the global disparity in the availability of narcotic drugs and a global assessment of psychotropic substances. He recalled that international drug control does not limit the availability of substances for legitimate medical and scientific use. He cited the example of phenobarbital, which had been reported as important by over 160 countries in 2018. National authorities should conduct training and raise the awareness of health care professionals and address problems in finding financial resources to ensure the availability of controlled substances for medical and scientific purposes.

In a survey of 130 government authorities, INCB found global disparity in the availability of controlled medicines. Mr Leroy described WHO's collaboration with INCB in the INCB learning project.

1.3 WHO

Dr Gilles Forte reported WHO's work on the public health dimension of the world drug problem. Several World Health Assembly resolutions and decisions address the problem, including WHA70 (2017), which requests WHO to improve coordination and collaboration with UNODC and INCB in fulfilling their mandates and to report to the World Health Assembly and the CND on its work on treaty mandates.

WHO is mandated by the international drug control conventions to assess psychoactive substances according to the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. WHO fulfils these mandates by assessing the risks of abuse, dependence and harm of substances and considers the importance of a substance's therapeutic use, when relevant. The ECDD makes recommendations to the CND on whether substances should be placed under international control or whether their level of control should be changed. Through this mechanism, WHO has reviewed and scheduled many synthetic drugs.

WHO maintains its Surveillance and Health Alert system for new psychoactive substances and other substances for which there is insufficient evidence for scheduling. The surveillance system ensures that evidence is monitored, so that a substance is reviewed for scheduling when there is sufficient evidence. Alerts are then issued to Member States on the potential dangers associated with particularly harmful substances. The first phase of the system is an online platform for Member States to report data annually and ad hoc.

WHO continues to improve access to controlled medicines. It is revising its guidelines for balanced national policies on access to controlled medicines and on the management of pain in children. WHO has released guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents and contributed to a United Nations interagency toolkit that includes legal and health models that reflect WHO's work in this area. WHO has contributed to intergovernmental expert meetings on opioids with UNODC and INCB and continues to provide technical support to countries.

Ms Annette Verster presented an update on WHO's public health approach to HIV infection, viral hepatitis and drug use, including work with people who inject drugs. Uptake of treatment for hepatitis C remains low, and strategies are required to improve assessment and treatment of these blood-borne viruses.

WHO issues norms and standards on harm reduction to end the AIDS epidemic and combat hepatitis, with partners such as UNODC, UNAIDS, civil society and academia. WHO also provides technical support and advocacy on harm reduction and supports inclusion of harm reduction interventions in universal health coverage strategies. WHO has prepared a package of interventions with collaborators that was endorsed politically in 2009 and in 2018 in a United Nations Common Position. Its technical guidance is continuously updated after reviews of evidence, and new updates were issued in 2019.

The United Nations Common Position promotes rebalancing of drug policies towards public health, calls for more investment in harm reduction interventions and for universal health coverage for people who use drugs, promotes decriminalization of drug use and possession, reduces stigmatization and discrimination, involves civil society organizations, improves data and improves access to controlled medicines. The United Nations Joint Common Position will result in broader international cooperation in advancing balanced, integrated health, human rights and criminal justice responses to drug supply and demand.

1.4 Follow-up of recommendations made by the ECDD at its 41st meeting

Dr Forte presented the follow-up of recommendations made by the ECDD at its 41st meeting, when WHO reviewed several new psychoactive substances and recommended that they be scheduled within the international drug control conventions. WHO also recommended that the scheduling of cannabis and cannabis-related substances be changed to recognize their medical use in pharmaceutical preparations.

New psychoactive substances

As recommended by the ECDD at its 41st meeting, in March 2019, the CND decided that the following substances be added to Schedule I of the Single Convention on Narcotic Drugs (1961):

- Parafluorobutyrylfentanyl
- Ortho-fluorofentanyl
- Methoxyacetyl fentanyl
- Cyclopropylfentanyl

As recommended by the ECDD at its 41st meeting, in March 2019, the CND decided that the following substances be added to Schedule II of the Convention on Psychotropic Substances (1971):

- ADB-FUBINACA
- FUB-AMB (MMB-FUBINACA, AMB-FUBINACA)
- CUMYL-4CN-BINACA
- ADB-CHMINACA (MAB-CHMINACA)
- N-Ethylnorpentylone (ephylone)

Cannabis and cannabis-related substances

WHO communicated the ECDD recommendations on cannabis and cannabis-related substances to the CND in January 2019 for further dissemination to Member States. The 62nd CND voted to postpone the vote that should have taken place in March 2019 and requested that information sessions be held so that Member States could pose questions about the recommendations to WHO. WHO attended information sessions at the 4th and 5th CND intersessional meetings in June and September 2019 respectively. A vote on the recommendations will be considered by the 63rd CND in March 2020.

2. Review of substances

At its 126th session in January 2010, the WHO Executive Board approved the publication *Guidance on the WHO review of psychoactive substances for international control* (4). In accordance with this document, WHO reviews psychoactive substances in two steps. The first step is a pre-review, which is a preliminary review by the Expert Committee to determine whether a fully documented critical review of the substance is required. A pre-review is initiated when a proposal has been submitted to the Expert Committee with supporting information by the WHO Secretariat, Member States, any member of the Expert Committee or representatives of other organizations invited to participate in the Expert Committee meeting. In the second step, if a preceding meeting of the Committee found that a critical review of a substance was warranted, the Secretariat prepares the required material for a more thorough review to take place at a future meeting of the Committee. Following consideration of a pre-review, however, the Committee may decide to conduct a critical review during the same meeting.

According to the *Guidance on the WHO review of psychoactive substances for international control* (4) a critical review is initiated by the Expert Committee in any of the following cases:

1. there has been notification from a Party to the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances concerning the scheduling of a substance;
2. there has been an explicit request from CND to review a substance;
3. a pre-review of a substance has resulted in an Expert Committee recommendation for critical review; or
4. information has been brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party.

2.1 Synthetic cannabinoids

2.1.1 APINACA (AKB-48)

Substance identification

APINACA (N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide), also known as AKB-48, is a synthetic cannabinoid. It has been found as a white powder, in solution or sprayed on plant material.

WHO review history

APINACA (AKB-48) was reviewed at the 36th meeting of WHO Expert Committee on Drug Dependence and has been under surveillance by WHO since that time. The present critical review updates the previous review.

Similarity to known substances and effects on the central nervous system

APINACA binds as a full agonist to CB1 and CB2 cannabinoid receptors. It shares similar molecular mechanisms and functional properties with other synthetic cannabinoid receptor agonists that are currently controlled under the Convention on Psychotropic Substances of 1971.

In preclinical studies in mice, APINACA produced neurological signs, including convulsions, hyperreflexia, myoclonus and aggression.

No information was available in either controlled studies or case reports on the effects of APINACA on the human central nervous system.

Dependence potential

No controlled experimental studies on the dependence potential of APINACA in either human subjects or laboratory animals are available. In view of its action on the central nervous system as a full CB1 agonist, APINACA would be expected to produce dependence in a manner similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination tests in animals predictive of subjective effects in humans, APINACA shows typical cannabinoid-like effects and would therefore be likely to be abused. APINACA also stimulates dopamine release in the nucleus accumbens in mice, suggesting that its abuse potential is similar to that of other psychoactive cannabinoids.

Use of APINACA has been reported from five regions and 20 countries since 2015. It has been identified in seized materials and has been detected in the blood of impaired drivers. Data on seized material, however, indicates that use of APINACA has decreased in a number of countries.

Therapeutic usefulness

APINACA is not known to have any therapeutic use.

Recommendation

APINACA (N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide; also known as AKB-48) is a synthetic cannabinoid receptor agonist. While it may

potentially have effects that are similar to those of other synthetic cannabinoids, information on its effects in humans is currently lacking. The magnitude of the public health problem associated with use of APINACA may not be great as the use of this substance has declined.

- **Recommendation:** The Committee recommended that APINACA (N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide) be kept under surveillance.

2.1.2 AB-FUBINACA

Substance identification

AB-FUBINACA (1-amino-3-methyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide) is a synthetic cannabinoid. It has been found sprayed on plant material for smoking.

WHO review history

AB-FUBINACA has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that AB-FUBINACA was manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

AB-FUBINACA is a synthetic cannabinoid with a profile of centrally mediated effects similar to those of other synthetic cannabinoids. It is a potent full agonist at CB1 receptors and binds to CB2 receptors. It is a structural analogue of ADB-FUBINACA, which is currently controlled under the Convention on Psychotropic Substances of 1971.

In preclinical studies in mice, AB-FUBINACA produced pharmacological effects characteristic of psychoactive cannabinoids, including suppression of locomotor activity, antinociception, hypothermia and catalepsy. These effects were reversed by a CB1 antagonist. AB-FUBINACA also impaired coordination and balance and produced neurological signs such as convulsions, hyperreflexia, myoclonus, sensorimotor alterations and spontaneous aggressiveness.

Little information is available on its effects on the human central nervous system. In a case report in which AB-FUBINACA was used with ADB-FUBINACA, the clinical features of intoxication included confusion, agitation, somnolence, hypertension and tachycardia, similar to those with other synthetic cannabinoid receptor agonists.

Dependence potential

No controlled experimental studies of the dependence potential of AB-FUBINACA in humans or animals were available. In view of its action as a full CB1 agonist in the central nervous system, however, AB-FUBINACA would be expected to produce dependence in a manner similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

In tests of drug discrimination in animals predictive of subjective effects in humans, AB-FUBINACA had typical cannabinoid-like effects and would therefore be likely to be abused.

Many cases of intoxication with AB-FUBINACA have been reported. At least one death has been reported in which AB-FUBINACA was the only synthetic cannabinoid detected.

AB-FUBINACA has been seized in a number of countries in various regions.

Therapeutic usefulness

AB-FUBINACA is not known to have any therapeutic use.

Recommendation

AB-FUBINACA is a synthetic cannabinoid receptor agonist with a mode of action that suggests the likelihood of dependence and abuse and similar ill-effects to other synthetic cannabinoids. Its use has been associated with a wide range of severe adverse effects, including death. The effects are similar to those of other synthetic cannabinoids that have the same mechanism of action as AB-FUBINACA and which are in Schedule II of the Convention on Psychotropic Substances of 1971. AB-FUBINACA has no therapeutic use.

- **Recommendation:** The Committee recommended that AB-FUBINACA (1-amino-3-methyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.1.3 5F-AMB-PINACA

Substance identification

5F-AMB-PINACA (methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl}amino)-3-methylbutanoate, is a synthetic cannabinoid. It is likely to be sprayed on plant material for smoking.

WHO review history

5F-AMB-PINACA has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that 5F-AMB-PINACA is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

5F-AMB-PINACA binds to CB₁ and CB₂ receptors with full agonist activity at the CB₁ receptor. It has molecular mechanisms and functional properties similar to those of other synthetic cannabinoid receptor agonists that are currently controlled under the Convention on Psychotropic Substances of 1971.

In preclinical studies in mice, 5F-AMB-PINACA induced convulsions.

In a single report of intoxication in humans, in which 5F-AMB-PINACA was confirmed analytically to be the only drug present, the clinical features were consistent with those of other synthetic cannabinoids. The features included bloodshot eyes, cognitive impairment, slowed movement, slurred speech, anxiety and poor coordination. Memory impairment has also been reported after use of the drug.

Dependence potential

No controlled experimental studies on the dependence potential of 5F-AMB-PINACA in animal or human models were available. In view of its action on the central nervous system as a full CB₁ agonist, however, it would be expected to produce dependence in a manner similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination tests in animals predictive of subjective effects in humans, 5F-AMB-PINACA showed typical cannabinoid-like effects and would therefore be likely to be abused.

At least three deaths have been associated with use of 5F-AMB-PINACA, confirmed by analysis of blood. 5F-AMB-PINACA has been identified as a causal factor in a number of motor vehicle accidents, some of which resulted in fatalities.

It has been detected in over 30 countries in different regions and is currently controlled in several countries.

Therapeutic usefulness

5F-AMB-PINACA is not known to have any therapeutic use.

Recommendation

5F-AMB-PINACA is a synthetic cannabinoid receptor agonist with a mode of action that suggests the likelihood of abuse and dependence potential similar to that of other synthetic cannabinoids. Its use has been associated with severe adverse effects, including death. These effects are similar to those produced by synthetic cannabinoids that are placed in Schedule II of the Convention on Psychotropic Substances of 1971. 5F-AMB-PINACA has no therapeutic use.

- **Recommendation:** The Committee recommended that 5F-AMB-PINACA (methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl}amino)-3-methylbutanoate be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.1.4 5F-MDMB-PICA

Substance identification

5F-MDMB-PICA (methyl (2S)-2-{{[1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino}-3,3-dimethylbutanoate) is a synthetic cannabinoid also known as 5F-MDMB-2201. It has been detected in plant material intended for smoking and as a powder.

WHO review history

5F-MDMB-PICA has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that 5F-MDMB-PICA is manufactured clandestinely, poses a risk to public health and society and is of no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

5F-MDMB-PICA is a full agonist at CB₁ and CB₂ cannabinoid receptors. It is an analogue of 5F-MDMB-PINACA, which is listed in Schedule II of the Convention on Psychotropic Substances of 1971.

Adverse effects in humans have included impaired mental status, agitated delirium and seizures; these effects are also produced by other synthetic cannabinoids.

Dependence potential

No controlled experimental studies of the dependence potential of 5F-MDMB-PICA have been published. In view of its action on the central nervous system as a CB₁ receptor agonist, however, it is expected to produce dependence in a manner similar to other synthetic cannabinoids.

No information was available on the abuse potential of 5F-MDMB-PICA in animal or human models.

5F-MDMB-PICA has been identified in seized and collected material and has been detected in attempted smuggling into prisons. In some countries, it is one of the most frequently detected synthetic cannabinoids.

Cases of apparent mass overdose reported in one country were associated with use of 5F-MDMB-PICA with other synthetic cannabinoids and fentanyl. 5F-MDMB-PICA use has been linked to at least one death.

Therapeutic usefulness

5F-MDMB-PICA is not known to have any therapeutic uses.

Recommendation

5F-MDMB-PICA is a synthetic cannabinoid receptor agonist that is administered by smoking plant material sprayed with the substance or inhaling vapour after heating. Its pharmacological mechanism of action suggests the likelihood of dependence and abuse and ill effects similar to those of other synthetic cannabinoids. Its use has been associated with substantial harm. Its effects are similar to those of other synthetic cannabinoids that are placed in Schedule II of the Convention on Psychotropic Substances of 1971. 5F-MDMB-PICA has no therapeutic use.

- **Recommendation:** The Committee recommended that 5F-MDMB-PICA methyl (2S)-2-[[1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.1.5 4F-MDMB-BINACA

Substance identification

4F-MDMB-BINACA (methyl (2S)-2-[[1-(4-fluorobutyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate) is a synthetic cannabinoid also known as 4F-MDMB-BUTINACA. It has been detected in powdered form, in liquids used for vaping and as a constituent of plant mixtures used for smoking.

WHO review history

4F-MDMB-BINACA has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that 4F-MDMB-BINACA is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

4F-MDMB-BINACA is an agonist at CB₁ receptors. It is an analogue of 5F-ADB (5F-MDMB-PINACA), which is listed in Schedule II of the Convention on Psychotropic Substances of 1971. In humans, 4F-MDMB-BINACA produces central nervous system effects that include paranoia, agitation, confusion and insomnia. Euphoria, irregular heartbeat, chest pain and vomiting have also been described.

Dependence potential

No controlled experimental studies of the dependence potential of 4F-MDMB-BINACA in humans or animals were available. In view of its action on the central nervous system as a full CB₁ agonist, however, 4F-MDMB-BINACA would be expected to produce dependence in a manner similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

There are no data on the abuse potential of 4F-MDMB-BINACA in animal or human models.

Seized and collected specimens of 4F-MDMB-BINACA have been reported in numerous countries in various regions. In some countries, 4F-MDMB-BINACA has been detected in cases of attempted smuggling into prisons.

4F-MDMB-BINACA has been detected in biological specimens from drug-related fatalities and from cases of impaired driving. It was frequently found with other psychoactive substances.

Therapeutic usefulness

4F-MDMB-BINACA is not known to have any therapeutic uses.

Recommendation

4F-MDMB-BINACA is a synthetic cannabinoid receptor agonist that is administered by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the likelihood of dependence and abuse and similar ill effects to other synthetic cannabinoids. Its use has been associated with a wide range of severe adverse effects, including death. These effects are similar to those produced by other synthetic cannabinoids that are placed in Schedule II of the Convention on Psychotropic Substances of 1971. 4F-MDMB-BINACA has no therapeutic use.

- **Recommendation:** The Committee recommended that 4F-MDMB-BINACA (methyl (2S)-2-[[1-(4-fluorobutyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.2 Synthetic stimulants

2.2.1 4-Chloromethcathinone

Substance identification

4-CMC (4-chloromethcathinone; 1-(4-chlorophenyl)-2-methylamino)propan-1-one) is a synthetic cathinone also known as clephedrone. It is found in powder or crystalline form.

WHO review history

4-CMC has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that 4-CMC is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

4-CMC increases extracellular neurotransmitter levels, most notably dopamine, noradrenaline and serotonin. Its molecular mechanisms and functional properties are similar to those of other psychostimulants that are listed in Schedule II of the Convention on Psychotropic Substances of 1971.

In humans, the reported effects of 4-CMC include increased concentration, increased self-confidence and increased sociability. Adverse effects associated with the use of 4-CMC include hypertension, chest pain, tachycardia, agitation, fear, aggression, psychoses, hallucinations and sleeplessness. These adverse effects are similar to those of other psychostimulants such as amphetamine and 3,4-methylenedioxy-methamphetamine (MDMA), as well as other cathinones.

Dependence potential

No controlled experimental studies of the dependence potential of 4-CMC in animals or humans were available. In view of its action in the central nervous system, however, 4-CMC would be expected to produce a state of dependence similar to that of amphetamine and other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

4-CMC caused time- and dose-dependent increase in locomotor activity in mice. In drug discrimination assays in animals predictive of subjective effects in humans, its effects were similar to those of MDMA, cocaine and methamphetamine. 4-CMC also showed rewarding effects in a brain stimulation model that is predictive of abuse potential.

4-CMC has been analytically confirmed in biological fluids from cases of non-fatal and fatal intoxication. In most of these cases, other substances were also reported.

This compound has been detected in seized materials and in biological samples in countries in various regions, including in cases of impaired driving. It has also been identified in used syringes. Seized materials containing both 4-CMC and MDMA have also been identified. One non-fatal case of intoxication with 4-CMC alone was reported.

Therapeutic usefulness

4-CMC is not known to have any therapeutic use.

Recommendation

4-CMC (4-chloromethcathinone) is a synthetic cathinone with effects similar to those of other synthetic cathinones listed as Schedule II substances in the Convention on Psychotropic Substances of 1971. Its mode of action and effects are consistent with those of other cathinones, indicating that it has the potential for dependence and the likelihood of abuse. There is evidence of use of 4-CMC in a number of countries in various regions, and its use has resulted in fatal and non-fatal intoxications. The substance causes substantial harm and has no therapeutic use.

- **Recommendation:** The Committee recommended that 4-CMC (1-(4-chlorophenyl)-2-methylamino)propan-1-one) be added to Schedule II of the 1971 Convention on Psychotropic Substances.

2.2.2 N-Ethylhexedrone

Substance identification

N-Ethylhexedrone (2-(ethylamino)-1-phenylhexan-1-one) is a synthetic cathinone also known as NEH and hexen. Although originally synthesized and described as a potential anorexigenic agent, N-ethylhexedrone has appeared as a new psychoactive substance on global markets only since 2016.

WHO review history

N-Ethylhexedrone has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that *N*-ethylhexedrone is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

Similar to other psychostimulants, such as other synthetic cathinones, *N*-ethylhexedrone increases extracellular concentrations of the neurotransmitters dopamine and noradrenaline. *N*-Ethylhexedrone is structurally similar to pentedrone, which is listed in Schedule II of the Convention on Psychotropic Substances of 1971.

Human users of *N*-ethylhexedrone describe psychostimulant effects such as euphoria, empathy, an enhanced sense of well-being, increased talkativeness, sociability, insomnia, increased creativity, increased libido, increased concentration and sensory enhancement. Also, like other psychostimulants, rebound effects such as fatigue, depressive states, anxiety, irritability and insomnia are reported to occur after the initial effects of the drug.

Observation of hospital admissions due to intoxication and users' reports indicate that the adverse effects of *N*-ethylhexedrone include hypertension, tremors, convulsions, chest pains, tachycardia, dysrhythmia, limb numbness and elevated temperature. These effects are similar to those of other psychostimulants.

Dependence potential

No controlled experimental studies of the dependence potential of *N*-ethylhexedrone have been reported in animals or humans. In view of its action on the central nervous system, however, *N*-ethylhexedrone would be expected to produce a state of dependence similar to amphetamine and other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination tests in animals that are predictive of subjective effects in humans, *N*-ethylhexedrone had methamphetamine- and cocaine-like effects that suggest similar abuse liability.

N-Ethylhexedrone has been detected in biological fluids collected from several cases of non-fatal intoxication as well as one fatality. In some of these cases, *N*-ethylhexedrone was the only drug detected.

A number of countries in various regions have reported use or detection of the compound in seized materials, including in used syringes.

Therapeutic usefulness

N-Ethylhexedrone is not known to have any therapeutic use.

Recommendation

N-Ethylhexedrone (2-(ethylamino)-1-phenylhexan-1-one) is a synthetic cathinone with effects similar to those of other synthetic cathinones that are listed as Schedule II substances in the Convention on Psychotropic Substances of 1971. Its mode of action and effects are consistent with those of other cathinones, indicating that it has the potential for dependence and likelihood of abuse. There is evidence that use of *N*-ethylhexedrone in a number of countries in various regions has resulted in cases of fatal and non-fatal intoxication. The substance causes substantial harm and has no therapeutic use.

- **Recommendation:** The Committee recommended that *N*-ethylhexedrone(2-(ethylamino)-1-phenylhexan-1-one) be added to Schedule II of the 1971 Convention on Psychotropic Substances.

2.2.3 Alpha-PHP

Substance identification

Alpha-PHP (alpha-pyrrolidinohexanophone; 1-phenyl-2-(pyrrolidine-1-yl)hexan-1-one) is a synthetic cathinone that was developed and patented in 1967 but never marketed. In its pure form, alpha-PHP is usually a crystalline solid or powder.

WHO review history

Alpha-PHP has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that alpha-PHP is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

Alpha-PHP enhances the activity of the neurotransmitter dopamine by blocking re-uptake. It has a similar but lesser effect on the neurotransmitter noradrenaline. It shares similar molecular mechanisms and functional properties with other psychostimulants that are currently controlled under the Convention on Psychotropic Substances of 1971.

In humans, alpha-PHP causes central nervous system stimulation similar to other psychostimulants, with effects such as tremor, sweating, psychosis, paranoia, hallucinations, agitation, anxiety, hypertension, tachycardia, seizures

and unconsciousness. Other reported adverse effects include depressed mood, irritability, headache, insomnia and nausea. Consistent with the effects of other psychostimulants, alpha-PHP is an anorexic, has reinforcing properties and induces craving. Because of its extended half-life, long-lasting psychotic symptoms have been reported. Users report a range of effects that are consistent with the stimulant activity of the drug.

Dependence potential

No controlled experimental studies of the dependence potential of alpha-PHP in humans or animal models have been reported. Its mechanism of action, particularly the effect on dopamine, suggests, however, that it is highly likely to produce a state of dependence similar to amphetamine and other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination tests in animals, alpha-PHP was readily self-administered, with greater reinforcing effects than some other cathinones, suggesting that it has high abuse liability. In drug discrimination assays in animals predictive of subjective effects in humans, alpha-PHP showed effects similar to those of cocaine and methamphetamine.

Alpha-PHP has been identified on the illicit drug market, and hundreds of seizures have been reported.

In reports of fatal and non-fatal intoxications, alpha-PHP has been detected in biological fluids, sometimes as the only drug present or as the drug that made the most significant contribution to the person's condition.

Therapeutic usefulness

alpha-PHP is not known to have any therapeutic use.

Recommendation

Alpha-PHP (1-phenyl-2-(pyrrolidine-1-yl)hexan-1-one; also known as alpha-pyrrolidinohexanophenone), is a synthetic cathinone with effects similar to those of other synthetic cathinones and of other psychostimulants such as amphetamine, that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. Through its mechanism of action and effects, alpha-PHP can stimulate the central nervous system and produce a state of dependence. There is evidence that its abuse constitutes a public health and social problem. It has no therapeutic use.

- **Recommendation:** The Committee recommended that alpha-PHP (1-phenyl-2-(pyrrolidine -1-yl) hexan-1-one) be added to Schedule II of the 1971 Convention on Psychotropic Substances.

2.3 Hallucinogen

2.3.1 DOC (2,5-Dimethoxy-4-chloroamphetamine)

Substance identification

DOC (1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine) is a synthetic hallucinogen also known as 2,5-dimethoxy-4-chloroamphetamine. It is commonly found in the form of impregnated blotting paper as well as a powder, liquid and tablets.

WHO review history

DOC has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that DOC is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

DOC is a hallucinogen with actions on the central nervous system mediated predominantly through receptors of the neurotransmitter serotonin. DOC is an analogue of 2,5-dimethoxy-4-bromoamphetamine (DOB) and 2,5-dimethoxy-4-methylamphetamine (DOM), hallucinogenic amphetamine derivatives that are listed in Schedule I of the Convention on Psychotropic Substances of 1971. Its actions on the nervous system and effects in animals and humans are comparable to those of the hallucinogenic amphetamines DOB, DOM and 2,5-dimethoxy-4-iodoamphetamine (DOI). DOC also has actions and effects similar to those of the hallucinogens lysergic acid diethylamide (LSD), psilocybin, mescaline and N,N-dimethyltryptamine. The effects in humans included tonic-clonic seizures, agitation, hyperthermia, aggression and visual hallucinations.

DOC has a long duration of action and the hallucinatory effects have been reported to last 12–24 h.

Dependence potential

No controlled experimental studies of the dependence potential of DOC in humans or animals have been reported. Like other serotonergic hallucinogens such as LSD and psilocybin, however, use of DOC is unlikely to result in dependence.

Actual abuse and/or evidence of likelihood of abuse

In animals, DOC had rewarding effects and depressed locomotor activity. In drug discrimination assays in animals predictive of subjective effects in

humans, DOC had effects similar to those of the hallucinogens LSD and N,N-dimethyltryptamine (DMT), but much less similar to those of the stimulants MDMA and methamphetamine.

No studies of the likelihood of abuse of DOC in humans were identified. A number of countries in different regions have reported seizure and collection of specimens of DOC.

DOC is sold on the Internet, commonly misrepresented as LSD. DOC has been detected in cases of intoxication, often with other substances. At least one death has been attributed to use of DOC.

Therapeutic usefulness

DOC is not known to have any therapeutic use.

Recommendation

DOC (1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine)) is a hallucinogenic amphetamine derivative with effects similar to those of other hallucinogenic amphetamines such as DOM and DOB, which are controlled in Schedule I of the 1971 Convention on Psychotropic Substances. Its mode of action and effects indicate the likelihood of abuse. DOC has been associated with a number of non-fatal cases of intoxication and at least one fatal case. It has no therapeutic use, and its use constitutes an especially serious risk to public health.

- **Recommendation:** The Committee recommended that DOC (1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine)) be added to Schedule I of the 1971 Convention on Psychotropic Substances.

2.4 Fentanyl analogues

2.4.1 Crotonylfentanyl

Substance identification

Crotonylfentanyl (E-N-(1-phenylethylpiperidin-4-yl)-N-phenylbut-2-enamide) is a synthetic analogue of the opioid fentanyl and a structural isomer of cyclopropylfentanyl, both of which are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. It is found in powder and tablet forms.

WHO review history

Crotonylfentanyl has not been reviewed previously. A critical review was proposed on the basis of information brought to WHO's attention that crotonylfentanyl is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

Crotonylfentanyl is a μ -opioid receptor agonist that is more potent than oxycodone and morphine but less potent than fentanyl. In view of its mechanism of action, it would be expected to produce the typical range of opioid effects, including analgesia, respiratory depression and sedation. In animals, it produces antinociceptive effects, which are blocked by the opioid antagonist naltrexone, and changes in locomotor activity.

Consistent with its μ -opioid agonist effect, the effects of crotonylfentanyl were reversed by an opioid antagonist in a clinical case of intoxication.

Dependence potential

No controlled experiments of the dependence potential of crotonylfentanyl were available. In view of its mechanism of action, however, crotonylfentanyl would be expected to produce dependence similar to other opioid drugs.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination assays in animals predictive of subjective effects in humans, crotonylfentanyl fully substituted for oxycodone and would therefore be likely to be abused.

In humans, the abuse potential of crotonylfentanyl has not been evaluated; however, the drug has been found in seized materials either alone or in combination with cyclopropylfentanyl.

Therapeutic usefulness

Crotonylfentanyl is not known to have any therapeutic use.

Recommendation

The available evidence indicates that crotonylfentanyl has opioid actions and effects that are similar to those of other opioid agonists such as cyclopropylfentanyl and fentanyl, which are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Crotonylfentanyl has no known therapeutic use and could cause substantial harm.

- **Recommendation:** The Committee recommended that crotonylfentanyl (*E-N*-(1-phenylethylpiperidin-4-yl)-*N*-phenylbut-2-enamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.4.2 Valerylfentanyl

Substance identification

Valerylfentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpentanamide) is a synthetic analogue of the opioid fentanyl that is also known as pentanoylfentanyl, pentanyl fentanyl and phenylvaleramide. It has been found in powder and tablet forms.

WHO review history

Valerylfentanyl has not been reviewed previously. A direct critical review was proposed on the basis of information brought to WHO's attention that valerylfentanyl is manufactured clandestinely, poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

Valerylfentanyl is a μ -opioid receptor agonist that is less potent than fentanyl. In view of this mechanism of action, it would be expected to produce the typical range of opioid effects, including analgesia, respiratory depression and sedation.

In a drug discrimination assay in animals predictive of subjective effects in humans, valerylfentanyl produced oxycodone-like effects. It also produces typical opioid effects, such as antinociception, suppresses opioid withdrawal and would therefore be likely to be abused. Both the antinociceptive and discriminative effects were blocked by an opioid antagonist.

Dependence potential

Studies demonstrating the ability of valerylfentanyl to suppress withdrawal in morphine-dependent monkeys suggest that it can produce physical dependence similar to other opioids. No controlled experimental studies pertinent to the dependence potential of valerylfentanyl in humans have been reported.

Actual abuse and/or evidence of likelihood of abuse

In drug discrimination tests in animals predictive of subjective effects in humans, valerylfentanyl produced oxycodone-like effects and would therefore be likely to be abused.

Seized materials containing valerylfentanyl have been reported in a few countries in several regions. Use of valerylfentanyl has been associated with several documented deaths. Cases of driving under the influence of valerylfentanyl have also been documented.

Therapeutic usefulness

Valeryl-fentanyl is not known to have any therapeutic use.

Recommendation

The available evidence indicates that valeryl-fentanyl has opioid actions and effects very similar to those of other opioid agonists such as oxycodone and morphine, which are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Valeryl-fentanyl has no known therapeutic use and could produce substantial harm, including death.

- **Recommendation:** The Committee recommended that valeryl-fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpentanamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.5 Benzodiazepines

2.5.1 Flualprazolam

Substance identification

Flualprazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) is a triazolo-benzodiazepine. Flualprazolam has been detected in seized samples of tablets and, more rarely, powder, blotters and liquid. It was the subject of a patent but has never been marketed as a pharmaceutical.

WHO review history

Flualprazolam has not been reviewed previously. A direct critical review was proposed on the basis of information brought to WHO's attention that flualprazolam poses a risk to public health and society and has no therapeutic use recognized by any Party.

Similarity to known substances and effects on the central nervous system

Flualprazolam is an agonist at the benzodiazepine site of the gamma-aminobutyric acid (GABAA) receptor. Its pharmacological effects are similar to those of other benzodiazepines, such as alprazolam, which is currently controlled under the Convention on Psychotropic Substances of 1971.

User reports have indicated that flualprazolam depresses central nervous system function, with effects such as sedation, loss of memory and disinhibition, similar to other benzodiazepines.

Dependence potential

No studies on the dependence potential of flualprazolam in humans or animals were available. In view of its mechanism of action, however, flualprazolam would be expected to produce dependence similar to other benzodiazepines, particularly the closely related alprazolam.

Actual abuse and/or evidence of likelihood of abuse

No studies on the abuse potential of flualprazolam in humans or animals were available. Flualprazolam has a fast onset of action, which would suggest that it would have a high abuse liability, similar to that of alprazolam.

Users reported that flualprazolam reduces anxiety and causes sedation, suggesting that it has significant abuse potential.

A number of countries in various regions have reported detection of flualprazolam in fatal and non-fatal intoxications and in cases of impaired driving. Over 25 deaths occurred after confirmed exposure to flualprazolam.

Therapeutic usefulness

Flualprazolam is not known to have any therapeutic uses.

Recommendation

Flualprazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) is a benzodiazepine that is chemically similar to the benzodiazepines alprazolam and triazolam, which are listed under Schedule IV of the 1971 Convention on Psychotropic Substances. In common with other benzodiazepines, flualprazolam can produce a state of dependence as well as central nervous system depression. There is sufficient evidence that it is being abused and therefore constitutes a public health and social problem. It has no therapeutic use.

- **Recommendation:** The Committee recommended that flualprazolam be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

2.5.2 Etizolam

Substance identification

Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) is a thienodiazepine derivative. It is used as a pharmaceutical for treatment of anxiety in some countries, but is also produced as an unapproved drug in tablet and powder forms.

WHO review history

The ECDD reviewed etizolam at its 26th meeting, in 1989, and at its 27th meeting, in 1990. At its 37th meeting, in 2015, the Committee pre-reviewed etizolam and recommended that a critical review be conducted at a future meeting. A critical review of etizolam was prepared for the 39th meeting, in 2017. At that meeting, the Committee noted that there were insufficient data on dependence, abuse and risks to public health posed and therefore recommended that it be kept under surveillance. A critical review was initiated at the 42nd meeting, as new information had been presented to the Committee on dependence, abuse and risks to public health.

Similarity to known substances and effects on the central nervous system

Etizolam is an agonist at the benzodiazepine site of the GABAA receptor. Its pharmacological effects are similar to those of other benzodiazepines such as diazepam, which is currently controlled under the Convention on Psychotropic Substances of 1971.

In animal models, etizolam induced effects characteristic of benzodiazepines, such as muscle relaxation, anticonvulsive effects and sedation.

Central nervous system depression has also been described in humans. The effects, which include drowsiness, sedation, muscle relaxation, ataxia, slurred speech and loss of consciousness, are reversed by the benzodiazepine receptor antagonist flumazenil.

Dependence potential

The dependence potential of etizolam in humans has been described in case reports and on drug information forums. Non-medical use is associated with the development of tolerance as well as craving and withdrawal on cessation of use. The withdrawal symptoms described in a case report were characteristic of benzodiazepine withdrawal and included palpitations, impaired sleep, agitation and tremors.

Actual abuse and/or evidence of likelihood of abuse

In the animal drug discrimination model, etizolam showed pentobarbital-like effects, suggesting that it may have subjective drug effects similar to those of sedative hypnotics.

Non-medical use of etizolam has been documented in a number of countries. It has been detected in impaired drivers and in biological samples from cases of fatal drug overdose, often in combination with other substances. In one country, it was reported to contribute to up to 46% of all drug-related deaths.

Therapeutic usefulness

Etizolam was patented in the 1970s and has been marketed since the early 1980s. It is not on the WHO Model List of Essential Medicines or the WHO Model List of Essential Medicines for Children, but it is sold commercially as a medicine in a few countries. Etizolam is also sold by several companies for research purposes. It has been used for the treatment of anxiety disorders and other psychiatric conditions.

Recommendation

Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3*a*][1,4]diazepine) is a thienodiazepine derivative 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. It has therapeutic indications and has marketing authorization in a few countries. There is sufficient evidence of its abuse so as to constitute a public health and social problem.

- **Recommendation:** The Committee recommended that etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3*a*][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

2.6 Pre-reviews

2.6.1 Preparations of acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine listed in Schedule III of the 1961 Single Convention on Narcotic Drugs.

Substance identification

The Committee examined information on preparations of the following drugs listed in Schedule III of the 1961 Single Convention on Narcotic Drugs: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine, norcodeine and pholcodine, when compounded with one or more other ingredients containing not more than 100 mg of the drug per dosage unit and with a concentration of not more than 2.5% in undivided preparations. Generally, these preparations are administered as medicines orally as tablets, syrups, extended-release syrups and sublingual drops.

WHO review history

These preparations have not been reviewed previously. A pre-review was proposed on the basis of concern communicated to the WHO Secretariat about preparations of codeine pursuant to Schedule III of the 1961 Single Convention on Narcotic Drugs. The Committee also noted significant problems of abuse and dependence on these codeine preparations in several countries.

As many of the substances listed in the first entry of Schedule III of the 1961 Single Convention are chemically and pharmacologically similar to codeine, these eight preparations were considered together.

Similarity to known substances and effects on the central nervous system

The active ingredients in these preparations are opioids that are controlled under Schedule II of the 1961 Single Convention on Narcotic Drugs. These opioids can cause dependence, respiratory depression and other central nervous system effects. In severe cases of overdose, apnoea, circulatory collapse, cardiac arrest and death may occur.

Dependence potential

There is evidence of dependence on preparations of codeine and dihydrocodeine listed in Schedule III of the 1961 Single Convention on Narcotic Drugs. There is less evidence of dependence on the other preparations.

Actual abuse and/or evidence of likelihood of abuse

There is evidence of abuse of codeine preparations as defined in Schedule III of the 1961 Single Convention on Narcotic Drugs and also of some of the other preparations. All the listed preparations have abuse potential because of their opioid activity, although the strength of the effect differs by substance and preparation.

Some studies have addressed the abuse liability of some of these substances. For example, ethylmorphine has some potential for abuse that may be linked to its metabolism to morphine. The abuse potential of pholcodine is reported to be low, whereas acetyldihydrocodeine, nicocodine and nicodicodine have some abuse liability.

Therapeutic usefulness

These preparations have been marketed and used as antitussive medicines and analgesics for mild to moderate pain, although some are no longer commonly used. In many countries, these preparations are available without a medical prescription.

Recommendation

In view of the evidence on dependence, abuse and risks to public health, the Committee recommended that a critical review of the following preparations included in Schedule III of the 1961 Convention be carried out at a future meeting: acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicodine, nicodicodine, norcodeine and pholcodine when formulated with one or more other ingredients containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations.

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SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The Public Health Dimension of the World Drug Problem: How WHO works to prevent drug misuse, reduce harm and improve safe access to medicines.

Geneva: World Health Organization; 2019 (WHO/MVP/EMP/2019.02). Licence: CC BY-NC-SA 3.0 IGO (12 pages)

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)

WHO Technical Report Series, No. 1021, 2019, ISBN 978-92-4-121030-0 (681 pages)

WHO Expert Committee on Drug Dependence

Forty-first report

WHO Technical Report Series, No. 1018, 2019, ISBN 978-92-4-121027-0 (68 pages)

WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents

Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

WHO Expert Committee on Drug Dependence

Fortieth report

WHO Technical Report Series, No. 1013, 2018, ISBN 978-92-4-121022-5 (60 pages)

WHO Expert Committee on Drug Dependence

Thirty-ninth report

WHO Technical Report Series, No. 1009, 2018, ISBN 978-92-4-121018-8 (48 pages)

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children)

WHO Technical Report Series, No. 1006, 2017, ISBN 978 92 4 121015 7 (604 pages)

WHO Expert Committee on Drug Dependence

Thirty-eighth report

WHO Technical Report Series, No. 1005, 2017, ISBN 978 92 4 1210140 (44 pages)

WHO Expert Committee on Drug Dependence





Thirty-seventh report

WHO Technical Report Series, No. 998, 2016, ISBN 978 92 4 120998 4 (34 pages)

WHO Expert Committee on Drug Dependence

Thirty-sixth report

WHO Technical Report Series, No. 991, 2015, ISBN 978 92 4 120991 5 (62 pages)



The report summarizes the findings of the forty-second meeting. The report also contains updates from international bodies concerned with controlled substances. The ECDD will advise the Director-General of WHO to schedule or to amend the scheduling status of a substance. The Director-General will, as appropriate, communicate the recommendations to the Secretary-General of the United Nations, who will in turn communicate the advice to the Commission on Narcotic Drugs. The report summarizes the findings of the forty-second meeting. The report also contains updates from international bodies concerned with controlled substances.

