22 February 2018

English only

Commission on Narcotic Drugs
Sixty-first session
Vienna, 12–16 March 2018
Item 5(a) of the provisional agenda*
Implementation of the international drug control treaties: changes in the scope of control of substances

Extract from the Report of the 39th Expert Committee on Drug Dependence, convened from 6 to 10 November 2017, at WHO headquarters in Geneva**

* E/CN.7/2018/1.
** The present document is reproduced in the form in which it was received.

V.18-00970 (E)

Extract from the Report of the 39th Expert Committee on Drug Dependence

Substances recommended to be placed in Schedule I and IV of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol

Carfentanil

Chemically, carfentanil is Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl) amino]piperidine-4-carboxylate. Carfentanil has no stereoisomers.

Carfentanil has not been previously pre-reviewed or critically reviewed. A notification was received from a Party to the Conventions thus initiating a critical review.

Carfentanil is convertible into sufentanil and alfentanil, two very potent opioid analgesics controlled as Schedule I drugs under the Single Convention on Narcotic Drugs of 1961. It is a μ-opioid receptor agonist, and its pharmacodynamic and clinical effects are similar to fentanyl but it is about 100 times more potent. It binds to opioid receptors, and produces respiratory depression, decreased consciousness, antinociception, and miosis. The substance has been associated with hundreds of deaths and nonfatal intoxications globally, and it has created significant concerns in a number of countries. Due to the extremely small doses that induce lethal effects, it poses a particularly serious threat to public health.

Carfentanil is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that carfentanil (Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

The Committee considered and recognized the impact that international scheduling could have on veterinary access to carfentanil in relation to its therapeutic use in large animals. However, the Committee was particularly concerned regarding the extreme potency of the substance and serious risk to public health. The Committee felt that the therapeutic advantages did not offset the severe threat to human health. As such, and with consideration that substances in Schedule IV afford Parties the opportunity to adopt special measures for drugs with particularly dangerous properties, the Committee recommended that carfentanil (Methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate) be also placed in Schedule IV of the Single Convention on Narcotic Drugs of 1961.

Substances recommended to be placed in Schedule I of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol

Ocfentanil

Chemically, ocfentanil is *N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl) piperidin-4-yl]acetamide. It has no stereoisomers.

Ocfentanil has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to the attention of WHO that ocfentanil is clandestinely manufactured, poses a risk to public health and society, and has no recognized therapeutic use by any party.

Ocfentanil is an opioid that is structurally related to fentanyl that is regulated under Schedule I of the Single Convention on Narcotic Drugs of 1961, and produces opioid effects including analgesia, euphoria, sedation, and potentially serious respiratory depression. Ocfentanil-related deaths have been reported, and it has come under national control in several countries in different regions of the world.

Ocfentanil is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that ocfentanil (*N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

Furanyl fentanyl

Chemically, furanyl fentanyl is *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide. Furanyl fentanyl has no stereoisomers.

Furanyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that furanyl fentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

Furanyl fentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that furanyl fentanyl (*N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

Acryloylfentanyl (Acrylfentanyl)

Chemically, acryloylfentanyl is *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide. It has no stereoisomers.

Acryloylfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that acryloylfentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

Acryloylfentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that acryloylfentanyl (*N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

4-Fluoroisobutyrfentanyl (4-FIBF, pFIBF)

Chemically, 4-fluoroisobutyrfentanyl (4-FIBF, pFIBF) is *N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide.

4-Fluoroisobutyrfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that it is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

4-Fluoroisobutyryfentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that 4-fluoroisobutyryfentanyl (*N*-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl) piperidin-4-yl]propanamide) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

Tetrahydrofuranyl fentanyl (THF-F)

Chemically, tetrahydrofuranyl fentanyl is *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide. Tetrahydrofuranyl fentanyl contains a stereogenic centre allowing for the existence of a pair of enantiomers, (*S*)-tetrahydrofuranyl fentanyl and (*R*)-tetrahydrofuranyl fentanyl. There is no information on the actual enantiomers found on the illicit drug market at the time of the report.

Tetrahydrofuranyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that tetrahydrofuranyl fentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

Tetrahydrofuranyl fentanyl is a compound liable to similar abuse and with similar ill effects to controlled opioids such as fentanyl that are included in Schedule I of the Single Convention on Narcotic Drugs of 1961. It has no recorded therapeutic use, and its use has been associated with fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that tetrahydrofuranyl fentanyl (*N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide) be placed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as consistent with Article 3, paragraph 3 (iii) of that Convention in that the substance is liable to similar abuse and productive of similar ill effects to drugs in Schedule I.

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

AB-CHMINACA

Chemically, AB-CHMINACA is *N*-[(2S)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide. AB-CHMINACA contains a chiral centre, so that two enantiomers exist: (R)- AB-CHMINACA and (S)- AB-CHMINACA. Based on the literature and the most likely precursors to be used in manufacture, an (S)-configuration of the stereocenter should be expected.

AB-CHMINACA has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention

that AB-CHMINACA is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

AB-CHMINACA is a synthetic cannabinoid receptor agonist. It is clandestinely manufactured and sold under a variety of brand names. Its mode of action suggests also the potential for dependence and likelihood of misuse. Effects of AB-CHMINACA are consistent with those of synthetic cannabinoid receptor agonists and include relaxation, euphoria, depersonalization, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, tachycardia, and nausea and vomiting. Its cannabimimetic effects are more potent than those of THC, which is listed in Schedule II in the Convention on Psychotropic Substances of 1971. There is evidence of an increase in number of persons using AB-CHMINACA in many countries that have included fatal and non-fatal cases. This substance causes substantial harm and has no therapeutic usefulness. AB-CHMINACA has similar abuse and similar ill effects as other synthetic cannabinoids receptor agonists already scheduled in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee recommended that AB-CHMINACA (*N*-[(2S)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

5F-ADB / 5F-MDMB-PINACA

Chemically, 5F-ADB (also known as 5F-MDMB-PINACA) is Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate. 5F-ADB contains a chiral centre, so that two enantiomers exist: (*R*)-5F-ADB and (*S*)-5F-ADB.

5F-ADB has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that 5F-ADB is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

5F-ADB is a synthetic cannabinoid receptor agonist. It has cannabimimetic effects that are more potent than those of THC and MDMB-CHMICA, substances which are listed in Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and likelihood of abuse. There is evidence of an increase in number of persons using 5F-ADB in many countries that have included fatal and non-fatal cases. This substance causes substantial harm and has no therapeutic usefulness. The Committee recommended that 5F-ADB, also known as 5F-MDMB-PINACA, (Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

AB-PINACA

Chemically, AB-PINACA is *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1*H*-indazole-3-carboxamide. AB-PINACA has stereoisomers.

AB-PINACA has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that AB-PINACA is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

The Committee considered that the degree of risk to public health and society associated with the abuse of AB-PINACA is substantial. Therapeutic usefulness has not been recorded. It recognized that AB-PINACA has similar abuse and similar ill-effects to other synthetic cannabinoids receptor agonists in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that AB-PINACA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that AB-PINACA (*N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-pentyl-1*H*-indazole-3-

carboxamide) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

UR-144

Chemically, UR-144 is (1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone. It has no stereoisomers.

UR-144 was previously critically reviewed by the 36th ECDD in 2014. The Committee recommended that UR-144 not be placed under international control at that time but be kept under surveillance.

Of particular significance to the Committee was the lack of analytically confirmed cases of non-fatal and fatal intoxications at the time involving solely UR-144. Subsequent data collected from the literature and from different countries indicating that this substance may cause substantial harm and that it has no medical use, warranted an updated critical review.

The Committee considered that the degree of risk to public health and society associated with the abuse of UR-144 is substantial. Therapeutic usefulness has not been recorded. It recognized that UR-144 has similar abuse and similar ill-effects to other synthetic cannabinoids receptor agonists in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that UR-144 is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that UR-144 ((1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

5F-PB-22

Chemically, 5F-PB-22 is Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate. It has no stereoisomers.

5F-PB-22 has not been previously pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that 5F-PB-22 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

The Committee considered that the degree of risk to public health and society associated with the abuse of 5F-PB-22 is substantial. Therapeutic usefulness has not been recorded. It recognized that 5F-PB-22 has similar abuse and similar ill-effects to other synthetic cannabinoids receptor agonists in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that 5F-PB-22 is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that 5F-PB-22 (Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

4-Fluoroamphetamine (4-FA)

The chemical name of 4-FA is 1-(4-Fluorophenyl)propan-2-amine. The presence of a chiral centre gives rise to the enantiomeric pair of (*S*)-4-FA and (*R*)-4-FA, respectively. 4-FA is most likely to be available as the racemic mixture.

4-FA underwent a critical review in 2015. At that time, the committee recommended that 4-FA not be placed under international control due to insufficient evidence regarding dependence, abuse, and risks to public health. However, it was kept under surveillance. Preliminary information collected from various sources indicated that this substance may cause substantial harm and that it has no medical use, thereby warranting an updated critical review.

4-FA is a ring-substituted derivative of amfetamine that is listed in Schedule II of the Convention on Psychotropic Substances of 1971. The clinical features associated with 4-FA intoxications include agitation, tachycardia, hypertension, hyperthermia, cardiovascular toxicity and cerebrovascular complications such as severe headaches and cerebral haemorrhage. Some severe adverse reactions required hospitalizations and others resulted in death.

The Committee considered that the degree of risk to public health and society associated with the abuse of 4-FA is substantial. Therapeutic usefulness has not been recorded. It recognized that 4-FA has similar abuse and similar ill-effects to substances in Schedule II of the Convention on Psychotropic Substances of 1971. The Committee considered that there is sufficient evidence that 4-FA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The Committee recommended that 4-FA (1-(4-Fluorophenyl)propan-2-amine) be placed in Schedule II under the Convention on Psychotropic Substances of 1971.

Substances recommended for critical review

Preparations containing almost exclusively cannabidiol (CBD)

Chemically, cannabidiol is (1'*R*,2'*R*)-5'-Methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol. Cannabidiol (CBD) is normally taken to refer to the naturally occurring (-)- enantiomer.

Cannabidiol has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence (ECDD). The current review was based on the recommendation from the 38th ECDD that pre-review documentation on cannabis-related substances, including cannabidiol, be prepared and evaluated at a subsequent committee meeting.

CBD is not specifically listed in the schedules of the 1961, 1971 or 1988 International Drug Control Conventions. There is no evidence that CBD as a substance is liable to similar abuse and similar ill-effects as substances in the 1961 or 1971 Conventions (including cannabis and dronabinol (THC), respectively). The purpose of the pre-review was to determine whether current information justifies an Expert Committee critical review whereby the Committee finds that information may justify the scheduling or a change in the scheduling of the substance in the 1961 or 1971 Conventions. As CBD is not currently a scheduled substance in its own right (only as a component of cannabis extracts), current information does not justify a change in this scheduling position and does not justify scheduling of the substance.

However, CBD is produced for pharmaceutical purposes as an extract of cannabis, and cannabis extracts and tinctures are included in the Single Convention on Narcotic Drugs of 1961. The pre-review of Cannabis Extracts and Tinctures will be held at the 40th ECDD meeting in May 2018. Therefore it is also recommended that extracts or preparations containing almost exclusively CBD (cannabidiol; (1'*R*,2'*R*)-5'-Methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol) be subject to critical review at that meeting.

Pregabalin

Chemically, pregabalin is (3*S*)-3-(Aminomethyl)-5-methylhexanoic acid. Pregabalin is the (*S*)-(+)-isomer of 3-isobutyl-GABA.

Pregabalin has not been previously pre-reviewed or critically reviewed. A pre-review at the 39th ECDD was proposed based on information received by the WHO Secretariat regarding the misuse of pregabalin.

Pregabalin, a gabapentinoid, is an analogue of gamma amino butyric acid (GABA), but does not act at GABA receptors or synapses or bind to benzodiazepine receptors. While pregabalin has therapeutic uses, the increasing evidence of its misuse and abuse

in many countries is becoming a growing cause for concern. Pregabalin has been shown to have the capacity to produce a state of dependence. On this basis, the Committee recommended that pregabalin ((3*S*)-3-(Aminomethyl)-5-methylhexanoic acid) proceed to a future critical review. The Committee requested that the Secretariat collect further data to support the critical review.

Tramadol

Chemically, tramadol is rac-(1*R*,2*R*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol. Tramadol has two chiral centres and consequently, four different stereoisomers exist: (1*R*,2*R*), (1*S*,2*S*), (1*R*,2*S*), and (1*S*,2*R*).

Pre-reviews of Tramadol have been carried out by the ECDD in 1992, 2000, 2006, and 2014 and a critical review in 2002. The Committee most recently at its 36th meeting in 2014, and based on the evidence available regarding dependence, abuse and risks to public health, recommended that a critical review of tramadol was not warranted at that time. On the basis of information received by the WHO Secretariat regarding the misuse of tramadol, it was recommended that a pre-review of tramadol be carried out at the 39th ECDD in November 2017.

Tramadol is used as a medication for controlling moderate acute and chronic painful conditions, and it is listed in several national essential medicines lists. It produces opioid-like effects predominately through the conversion of tramadol into its active metabolite. There is growing evidence of abuse of tramadol in many countries, accompanied by adverse reactions, and tramadol-associated deaths. The Committee recommended that tramadol ((*rac*-(1*R*,2*R*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol) proceed to a critical review at a subsequent meeting. The Committee requested the Secretariat to collect additional data for the critical review, including engagement with Member States to obtain information on the extent of problems associated with tramadol misuse. Also, the Committee asked for information on the medical use of tramadol including the extent that low income countries, countries facing conflicts and aid and relief agencies use and possibly rely on tramadol for provision of analgesia.

Substance recommended to remain under surveillance

Etizolam (INN)

Chemically, etizolam is 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine. It does not have stereoisomers.

The ECDD reviewed etizolam at the 26th meeting (1989) and the 27th meeting (1990). At the 37th ECDD in 2015, the committee pre-reviewed etizolam and recommended that a critical review of etizolam was warranted for a future meeting. The Committee noted deficiencies in information and suggested several potential sources that could be helpful in the preparation of the critical review, including those from traffic accident reports, seizure data, user forums, and pharmacovigilance data.

Owing to the lack of significantly more information since the pre-review conducted by the 37th ECDD in 2015, and considering the current insufficiency of data regarding dependence, abuse and risks to public health, 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 kept under surveillance. The Committee asked the Secretariat to request more data from Member States that may be affected by the misuse of etizolam, and which could facilitate a future review.