



European Monitoring Centre
for Drugs and Drug Addiction

**Risk Assessment Report on a new psychoactive substance:
methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-car-
bonyl]amino]butanoate (MDMB-4en-PINACA) in accordance with
Article 5c of Regulation (EC) No 1920/2006 (as amended)**

ADVANCED RELEASE

Note: In the interests of public health protection the EMCDDA is releasing this report before formal page layout in the EMCDDA house style. The final report will be available on the EMCDDA website in due course.

Statement regarding the United Kingdom

This report covers a reference period from 2017 to November 2020. The United Kingdom left the European Union as of 1 February 2020. However, during the transitional period, the United Kingdom continues to participate in the European Union Early Warning System on new psychoactive substances. Unless stated otherwise, for the purpose of this report, the term 'Member States' shall include the United Kingdom.

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Introduction

New psychoactive substances can cause serious cross-border threats to health. In Europe, Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast) (as amended) (hereafter the 'Regulation') and Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking sets up a three-step legal framework of early warning, risk assessment and control measures that allows the EU to rapidly detect, assess and respond to the public health and social risks caused by new psychoactive substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two steps in this system, namely operating the EU Early Warning System on new psychoactive substances (EWS) in close cooperation with Europol, and conducting risk assessments. The European Commission is responsible for proposing control measures. Thus, the legal framework allows the institutions of the EU and the Member States to act on all new psychoactive substances (NPS) that appear on the European drug market.

In accordance with Article 5a of the Regulation, methyl 3,3-dimethyl-2-([1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino)butanoate (commonly known as MDMB-4en-PINACA) was formally notified as an NPS by the EMCDDA on behalf of Slovenia on 23 August 2018. The notification related to a collected sample (test purchase) of 7.89 g of yellow powder. However, based on information subsequently reported to the EMCDDA by Germany concerning a seizure made by Police, MDMB-4en-PINACA has been available on the European drug market since at least 2017.

Based on the information reported to the Early Warning System, and, in accordance with Article 5a of the Regulation, on 2 September 2020, the EMCDDA assessed the existing information on MDMB-4en-PINACA. The EMCDDA concluded that the assessment gave rise to concerns that MDMB-4en-PINACA may pose health or social risks at EU level, and, consequently, determined that an initial report should be produced in accordance with Article 5b of the Regulation. The initial report was submitted to the Commission and Member States on 14 October 2020. Based on the findings of the initial report, on 28 October 2020, the Commission requested that the EMCDDA carry out a risk assessment on MDMB-4en-PINACA in accordance with Article 5c of the Regulation.

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the Scientific Committee of the EMCDDA on MDMB-4en-PINACA. The report is intended for policymakers and decision-makers in the institutions of the EU.

The report has been prepared and drafted in accordance with the requirements of Article 5c of the Regulation as well as the conceptual framework and the procedure set out in the EMCDDA risk assessment operating guidelines. It is written as a stand-alone document, which presents a summary of the information considered during the detailed assessment of

the scientific and law enforcement information available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on MDMB-4en-PINACA prepared by the EMCDDA (Annex 1), is provided below.

In accordance with Article 5c of the Regulation, the meeting to assess the risks of MDMB-4en-PINACA was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a list of experts approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented or not sufficiently represented in the Scientific Committee, and whose contribution is necessary for the balanced assessment of the risks posed by MDMB-4en-PINACA. A further six experts were observers to the risk assessment: two experts from the Commission, two experts from the EMCDDA, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 7 December 2020. Owing to the on-going response to the coronavirus (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the meeting was conducted by videoconference and hosted by the EMCDDA.

The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, the EMA, the European Centre for Disease Prevention and Control (ECDC), the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA). A list of the Scientific Committee members, observers and other participants attending the risk assessment meeting is annexed to this report (Annex 2).

For the risk assessment, the Scientific Committee considered the following information resources:

- the EMCDDA technical report on methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate (MDMB-4en-PINACA) (Annex 1);
- the EMCDDA initial report on the new psychoactive substance methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA);
- open source information, including scientific articles, official reports, grey literature, Internet drug discussion forums and related websites;
- additional information provided during the course of the risk assessment meeting by the participants;
- EMCDDA operating guidelines for the risk assessment of new psychoactive substances;
- Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast) (as amended); and

- Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking (as amended).

Background

Methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate (MDMB-4en-PINACA) is a synthetic cannabinoid receptor agonist (synthetic cannabinoid) which does not appear to have a history in the scientific literature. However, it is structurally related to compounds of the indazole-3-carboxamide class that feature pendant amino acid esters (methyl *L-tert*-leucinate) previously developed as part of pharmaceutical research.

Synthetic cannabinoids, such as MDMB-4en-PINACA, are functionally similar to Δ^9 -tetrahydrocannabinol (THC), the major psychoactive principle of cannabis. Like THC, they bind to and activate the CB₁ and CB₂ cannabinoid receptors which form part of the endocannabinoid system — a system that helps regulate a large number of physiological functions in the body such as behaviour, mood, pain, appetite, sleep, the immune system, and the cardiovascular system.

Many synthetic cannabinoids were first developed to study the endocannabinoid system as well as to explore their potential as therapeutic agents to treat a number of diseases and their symptoms (such as neurodegenerative diseases, drug dependence, pain disorders, and cancer).

Since around 2006, 'legal high' products containing synthetic cannabinoids have been sold in Europe as 'herbal smoking mixtures' and marketed as 'legal' replacements for cannabis. These products are made by dissolving the synthetic cannabinoids in solvents such as acetone or methanol and then mixing them with, or, spraying them on, plant material such as the herbs *Turnera diffusa* (Damiana) and other herbs such as *Melissa*, *Mentha* and *Thymus* species of the Lamiaceae family. Such products are generally referred to by a variety of names in Europe, including 'Spice' ⁽¹⁾, 'herbal smoking mixtures', 'herbal incense', and 'synthetic cannabis'. They may also be mixed with tobacco. Manufacturers of smoking mixtures frequently change the synthetic cannabinoids in the products, which means that product names are not a reliable source of information regarding the actual substances that are present. More than 210 synthetic cannabinoids have been identified on the European drug market since 2008. They are the largest group of substances that are monitored by the EMCDDA through the EU Early Warning System. In recent years, alongside smoking mixtures, new dosage forms, including e-liquids for vaping using electronic cigarettes, as well as paper (including blotters) impregnated with synthetic cannabinoids, have appeared on the drug market.

⁽¹⁾ 'Spice' was the most common brand name used for these types of products when they first appeared on the European market.

A number of cannabinoids are controlled under the United Nations Convention on Psychotropic Substances, 1971. These include: the major active principle of cannabis, Δ^9 -tetrahydrocannabinol ⁽²⁾ (Schedule I), dronabinol ⁽³⁾ (Schedule II) as well as an increasing number of synthetic cannabinoids, including 5F-MDMB-PINACA (5F-ADB) ⁽⁴⁾ (Schedule II) that is closely related to MDMB-4en-PINACA.

MDMB-4en-PINACA has been available on the drug market in Europe since at least 2017. It is important to highlight that no formal epidemiological studies have been conducted, which limits understanding of the frequency and patterns of use of MDMB-4en-PINACA. Related to this, the presence of MDMB-4en-PINACA on the drug market and its involvement in serious adverse events (such as acute poisonings presenting to hospital emergency rooms and medico-legal death investigations) may be underreported because the substance is not routinely screened for in some forensic and toxicology laboratories in Europe. Therefore, the presence of MDMB-4en-PINACA on the drug market may be undetected in some areas. In addition, in some areas not all laboratories are part of national early warning systems; for this reason, the identification of MDMB-4en-PINACA may go unreported to the Reitox national focal points, and, as a result, to the EMCDDA. Finally, it is also important to note that, in some settings, the on-going COVID-19 pandemic may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving MDMB-4en-PINACA.

Chemical and physical properties and the methods and precursors used for manufacture

Chemical and physical properties

Methyl 3,3-dimethyl-2-([1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino)butanoate (MDMB-4en-PINACA) is a synthetic cannabinoid receptor agonist (synthetic cannabinoid). The MDMB-4en-PINACA code name for the substance is derived from its structural features ⁽⁵⁾: a methyl 3,3-dimethylbutanoate linked group (MDMB), a terminal alkene (4en), thus representing a modified *N*-pentyl tail (P), an indazole core (INA), and a carboxamide linker (CA).

MDMB-4en-PINACA is structurally related to 5F-MDMB-PINACA (5F-ADB) ⁽⁴⁾, placed under international control in 2018 (Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances). MDMB-4en-PINACA is also structurally related to 4F-MDMB-BINACA ⁽⁶⁾, and 5F-MDMB-PICA (5F-MDMB-2201) ⁽⁷⁾. The latter two substances were placed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances in 2020. MDMB-4en-PINACA is also related structurally to MDMB-PINACA, its saturated counterpart, which is not controlled internationally.

⁽²⁾ Including some of its named isomers and their stereochemical variants.

⁽³⁾ And its stereochemical variants.

⁽⁴⁾ 5F-MDMB-PINACA (5F-ADB): methyl 2-([1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino)-3,3-dimethylbutanoate.

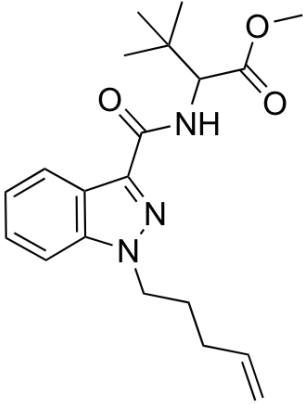
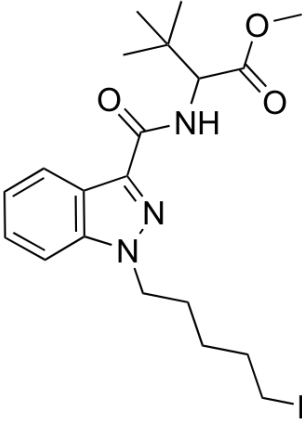
⁽⁵⁾ Different naming systems exist and are used for applying short/code names to synthetic cannabinoids.
<http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>.

⁽⁶⁾ 4F-MDMB-BINACA: methyl 2-([1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl]amino)-3,3-dimethylbutanoate.

⁽⁷⁾ 5F-MDMB-PICA (5F-MDMB-2201): methyl 2-([1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino)-3,3-dimethylbutanoate.

The chemical structures, molecular formulae and molecular weights of MDMB-4en-PINACA and 5F-MDMB-PINACA (5F-ADB) are provided in Figure 1.

Figure 1. Chemical structures and molecular information of MDMB-4en-PINACA and 5F-MDMB-PINACA

MDMB-4en-PINACA	5F-MDMB-PINACA (5F-ADB)
	
Molecular formula: C ₂₀ H ₂₇ N ₃ O ₃	Molecular formula: C ₂₀ H ₂₈ FN ₃ O ₃
Molecular weight: 357.45	Molecular weight: 377.45
Monoisotopic mass: 357.2052	Monoisotopic mass: 377.2115

In its pure form MDMB-4en-PINACA has been described as neat solid but also as a colourless oil. It is soluble in organic solvents such as chloroform and expected to be only partially soluble in water.

MDMB-4en-PINACA contains a stereogenic centre and therefore two possible enantiomers may exist, (*S*)-MDMB-4en-PINACA and (*R*)-MDMB-4en-PINACA. No information is available on whether the MDMB-4en-PINACA detected in the European drug market corresponds to the (*R*)- or (*S*)- enantiomer, or a mixture of both, which may in part reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Based on the literature and the precursors that are most likely to be used, an (*S*)-configuration of the stereocentre could be expected.

Information provided from seizures and collected samples reported to the EMCDDA have noted that MDMB-4en-PINACA is typically found in herbal/plant material (including as commercially-branded 'legal high' products) and as a powder. Other forms, such as pieces of paper impregnated with the substance (including blotters), liquids and e-liquids have also been reported.

The analytical identification of MDMB-4en-PINACA in physical and biological samples is possible using standard analytical techniques. These include chromatographic and mass spectrometric methods.

Analytical reference material is important for correct identification and for facilitating the quantification of MDMB-4en-PINACA in physical and biological samples. Such material is commercially available in form of the (S)-enantiomer.

Methods and precursors used for manufacture

There is no information on the actual manufacturing methods or chemical precursors used to synthesise the MDMB-4en-PINACA that has been identified on the drug market in Europe. Information from seizures made by customs suggests that at least some MDMB-4en-PINACA on the market in Europe has been supplied from China. Although the synthetic routes reported in the scientific literature involve several steps, they are straightforward and make use of common manufacturing equipment. The starting materials for either synthetic route are readily available. The multi-step production of MDMB-4en-PINACA requires basic knowledge of and experience in synthetic organic chemistry.

Commercially available domestic or industrial chemicals which could be used for synthesis of MDMB-4en-PINACA may be potentially toxic. Use of such products as reagents or solvents may result in serious toxic effects if the resultant contaminated product is consumed. The herbal plant material which is used as a basis for smoking mixtures may also contain toxicologically relevant substances (such as pesticides that could potentially be present in the plant material).

Pharmaceutical forms

Information on the pharmaceutical forms available for MDMB-4en-PINACA is limited. There are three main types of products containing synthetic cannabinoids that are available on the drug market: smoking mixtures, where the cannabinoid is mixed with herbal plant material or tobacco that is then smoked (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint')) or inhaled using a vaporiser; e-liquids, where a solution of the cannabinoid is prepared by mixing it with a solvent, which is then inhaled ('vaped') using an e-cigarette; in addition, synthetic cannabinoids are also impregnated on to paper which can then be smoked or vaped. The latter is a commonly used approach to smuggle synthetic cannabinoids into prison in some countries. To a lesser extent, people who are using these substances may also prepare their own products using powdered synthetic cannabinoids purchased from a vendor or dealer.

Products containing synthetic cannabinoids such as MDMB-4en-PINACA rarely state the correct ingredients and concentrations. Given the illicit nature of the trade in MDMB-4en-PINACA, the composition of products containing MDMB-4en-PINACA is likely to vary over time and place, as well as based on the specific location in the drug supply chain from which the product was obtained (e.g. from the manufacturer, wholesaler, retailer or at street-level illicit market). In Europe, MDMB-4en-PINACA has been seized by law enforcement in the form of powders, smoking mixtures, pieces of paper impregnated with the substance (including blotters), liquids and e-liquids. Information on the concentration of MDMB-4en-PINACA present in seized powders (chemical purity) has not been reported. In at least some

of the seizures other synthetic cannabinoids were present. Information on the enantiomeric composition of seized and collected samples has not been reported.

Pharmacological and toxicological properties

Pharmacological properties

There is limited information on the pharmacological properties of MDMB-4en-PINACA. Current available information from *in vitro* studies suggests that MDMB-4en-PINACA binds to and activates the cannabinoids type 1 (CB₁) receptor as a full agonist with high potency. No information is available on binding and activation of the CB₂ receptor. *In vivo* studies in mice suggest that MDMB-4en-PINACA shares similar properties compared to other synthetic cannabinoids. Cannabimimetic (i.e. Δ⁹-THC-like) ⁽⁸⁾ effects commonly reported for such substances include hypolocomotion, antinociception, hypothermia, and catalepsy. Together, this suggests that MDMB-4en-PINACA may produce effects in humans similar to other cannabinoid receptor agonists, such as THC and other synthetic cannabinoids.

Data on the pharmacokinetics of MDMB-4en-PINACA are limited to the identification of metabolites and investigations on intrinsic metabolic stability. So far, a number of metabolites have been identified in humans, which included the ester hydrolysis transformation product ⁽¹⁴⁾ that was found to result in a 233-fold drop in potency regarding CB₁ receptor activation. It is not known whether MDMB-4en-PINACA or its metabolites affect other pharmacological targets, such as receptors, enzymes or transport processes.

Toxicological properties

No information is available on the toxicological properties (including pre-clinical safety data) of MDMB-4en-PINACA. Ingestion of highly potent full CB₁ receptor agonists have been associated with acute toxicity in humans; this suggests that the acute toxicity of MDMB-4en-PINACA may be much greater than THC and similar to that observed for related synthetic cannabinoids under international control. The involvement of other, non-cannabinoid toxicological targets or unexpected drug-drug interactions in the overall pharmacotoxicological effects of MDMB-4en-PINACA cannot be excluded.

There is no known antidote to poisoning caused by synthetic cannabinoids. Treatment in poisoning cases should be symptomatic.

Health risks

No studies are available on the acute and chronic health effects of MDMB-4en-PINACA. The clinical features of poisonings caused by MDMB-4en-PINACA are expected to be similar to those reported from related synthetic cannabinoids resulting in gastrointestinal, neurological,

⁽⁸⁾ THC: Δ⁹-THC; (-)-*trans*-Δ⁹-tetrahydrocannabinol

cardiovascular, renal clinical features. These dose-dependent effects appear to be much more pronounced and severe when compared to cannabis.

Acute toxicity

There is limited information on the acute toxicity of MDMB-4en-PINACA. Based on the available information, the health risks are likely to be similar to those observed with other synthetic cannabinoids. Adverse effects from overdosing MDMB-4en-PINACA might include gastrointestinal (e.g. nausea and vomiting (including hyperemesis)), neurological (e.g. hallucination, seizures, convulsions, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including susceptible individuals) and severe central nervous system depression (such as rapid loss of consciousness/coma), cardiovascular (e.g. tachycardia, hypertension, acute myocardial infarction and sudden cardiac death) and renal (e.g. acute kidney failure) clinical features, and respiratory depression.

In addition, some of the features of poisoning—particularly loss of consciousness, respiratory depression, and behavioural effects—may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury. The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

The reasons for these more pronounced and severe effects, as well as severe and fatal poisoning, are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the synthetic cannabinoids, including MDMB-4en-PINACA, which are sold on the drug market, are typically potent, full agonists compared to THC. This means that even at very small doses they can activate the CB₁ receptor much more potently than THC, which may be responsible for the more pronounced and unexpected pharmacotoxicological effects in humans.

Secondly, in respect to smoking mixtures, the process for mixing the synthetic cannabinoids with the plant material to make the smoking mixture can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of substances to be added, while the mixing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general, as well as in products where the solid particles of synthetic cannabinoids are clumped together, forming highly concentrated pockets within the plant material. In fact, in the latter case, simply tapping a packet containing a smoking mixture can dislodge the substances from the plant material. In addition, paper (such as blotters and cards) impregnated with synthetic cannabinoids can pose a similar high risk of poisoning because the amount of synthetic cannabinoid can be unevenly distributed in different parts of the paper, sometimes forming highly concentrated sections on the paper. These issues are exacerbated as the products are typically smoked

or vaped, allowing the substances to be rapidly absorbed into the bloodstream and to reach the central nervous system and other parts of the body to cause their effects.

Together, these factors, coupled to the typically high potency of synthetic cannabinoids, makes it difficult for users to control the dose that they are exposed to. This can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings suggest that in some cases a small number of puffs from a cigarette (“joint”) have been sufficient to cause severe and fatal poisoning.

Similarly to other synthetic cannabinoids, the use of MDMB-4en-PINACA together with other drugs, especially central nervous system depressants (such as alcohol, opiates/opioids, and sedative-hypnotics) is likely to increase the risk of life-threatening poisoning.

Acute poisonings

Acute poisonings reported by the Member States

A total of 11 acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA were reported to the EMCDDA by the United Kingdom. The cases occurred between January and August 2020. All cases included clinical features of poisoning similar to those reported for other synthetic cannabinoids, such as confusion, tachycardia, respiratory insufficiency, reduced conscious level, seizures, abnormal sweating, agitation, aggression. In all cases other substances were identified, such as synthetic cannabinoids, benzodiazepines, opioids/opiates, pregabalin, THC, cocaine, ketamine and methamphetamine. In ten of the cases, the poisoning was considered life threatening and required hospitalisation of the patients.

Acute poisonings identified from other sources

United States of America

The detection of MDMB-4en-PINACA and/or its ester hydrolysis metabolite in 8 cases from suspected clinical toxicology investigations has been described. No further information about the cases was reported and in seven of these cases other synthetic cannabinoid metabolites could be detected.

Deaths

Deaths reported by the Member States

A total of 12 deaths with confirmed exposure to MDMB-4en-PINACA were reported by Hungary (8), the United Kingdom (3) and Sweden (1). The cases occurred between January 2019 and August 2020. In all cases, other substances were identified, such as synthetic cannabinoids, benzodiazepines, opioids, pregabalin, THC, alcohol, synthetic cathinones, and methylphenidate. A cause of death was reported in all cases:

- in the cases reported by Hungary, the reported causes of death were: cardiac arrest due to substance overdose (4 cases), acute heart failure (3 cases), and asphyxiation

following aspirating vomit (1 case);

- in the cases reported by the United Kingdom, the reported causes of death were: synthetic cannabinoid (MDMB-4en-PINACA) and alcohol toxicity (1 case), synthetic cannabinoid use (1 case) and mixed drug toxicity (1 case);
- in the case reported by Sweden, the cause of death was trauma from a fall where the contribution from drugs present could not be determined.

Deaths identified from other sources

Open source information – United Kingdom

The detection of MDMB-4en-PINACA and its metabolites is described in a case published in the literature. The case relates to a 40-year old female who was found dead and was known to use drugs (including 'Mamba'). The study reports the detection of methadone, pregabalin, mirtazapine, 4F-MDMB-BINACA metabolites, and MDMB-4en-PINACA and metabolites. The cause of death was ruled as mixed drug toxicity.

United States of America

The detection of MDMB-4en-PINACA and/or its ester hydrolysis metabolite⁽¹⁴⁾ in 16 post-mortem samples has been described which included the detection of other substances in most cases, such as synthetic cannabinoids, alcohol, psychostimulants and others. The samples were collected between May 2019 and March 2020 and were from many regions across the United States. Based on information from the death investigations, two death cases happened in prison settings and one case involved homeless individual. The authors stated that the results from toxicology testing paired with case history showed the potential for MDMB-4en-PINACA to cause or contribute to impairment or death.

Physical, mental and behavioural effects

The physical effects of MDMB-4en-PINACA have not been studied. Based on the pharmacological properties of the substance, as well as information from observations from closely related substances, it is likely that the dose-dependent effects of MDMB-4en-PINACA are similar to those commonly reported for other synthetic cannabinoids, including tachycardia, dry mouth, nausea, vomiting, balance deficiencies and ocular effects such as reddened conjunctivae, glassy eyes and delayed or unresponsive pupil light reactions, and impaired motor performance.

The mental and behavioural effects of MDMB-4en-PINACA have not been studied. Based on the pharmacological properties of the substance, the effects of MDMB-4en-PINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids. This may include: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, and paranoia.

Overall, these effects may be much more pronounced and severe when compared to cannabis. In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported.

There are no studies on the effects of MDMB-4en-PINACA on the ability to drive and operate machines. However, synthetic cannabinoids impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to MDMB-4en-PINACA. Hungary reported 4 identifications of MDMB-4en-PINACA in biological samples reported as suspected driving under the influence of drugs (including two traffic accidents).

Chronic toxicity

There is no information on the chronic toxicity of MDMB-4en-PINACA. Similar to other synthetic cannabinoids, chronic use has been associated with greater risks for developing mental health disorder than cannabis, which may include dependence. Acute and chronic use of synthetic cannabinoids has also been associated with cases displaying detrimental cardiovascular health.

Abuse liability and dependence-producing potential

There is limited information on abuse liability and dependence producing potential of MDMB-4en-PINACA. Drug discrimination studies in mice have demonstrated that MDMB-4en-PINACA showed THC-like discriminative stimulus effects, consistent with other synthetic cannabinoids. Given what is currently known about the properties of synthetic cannabinoids in general (and some similarities to THC), it is expected that MDMB-4en-PINACA may have a potential for abuse and dependence. It has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when use is discontinued following a regular use. Withdrawal-like symptoms following cessation of synthetic cannabinoids have been described in the literature. These include: anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis (increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness.

Anecdotal reports from people who used a substance believed to be MDMB-4en-PINACA suggest that tolerance develops quickly when inhaled by 'vaping'. However, the assessment of such reports is problematic not least because users cannot confirm the actual substance or the amount used. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Social risks

There is no specific information on the social risks posed by MDMB-4en-PINACA. There is no information on whether or not criminal groups are involved in the manufacture, trafficking and distribution of MDMB-4en-PINACA within Europe.

It is possible that any such social risks may have some similarities with those associated with the use of cannabis and other synthetic cannabinoids. Such risks include negative impacts on social functioning and criminal activities, such as the involvement of organised crime in the manufacture, trafficking and distribution of the substance.

It is noteworthy that in some settings, synthetic cannabinoids are increasingly used by high-risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these people are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication. They are considered cheap and easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

In prisons, alongside the adverse health effects, the market in and use of synthetic cannabinoids has been linked to an increase in aggression, violence, bullying, and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment.

In addition, the detection of MDMB-4en-PINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

Extent and patterns of use, availability and potential for diffusion

There is limited information on the extent and patterns of use, availability and potential for diffusion of MDMB-4en-PINACA in Europe. No formal epidemiological studies have been conducted, which limits the understanding of the extent and patterns of use of MDMB-4en-PINACA, as well as the potential for diffusion. In relation to this, the presence of MDMB-4en-PINACA on the drug market and its involvement in serious adverse events may be undetected in some areas because the substance is not routinely screened for in some forensic and toxicology laboratories.

MDMB-4en-PINACA has been available on the drug market in Europe since at least 2017, when it was seized for the first time by police in Germany. As of November 2020, MDMB-4en-PINACA has been identified in 21 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom), Norway and Turkey. A total of 770 seizures have been reported, which include approximately 47 kg of powder and 4.7 kg of smoking mixtures. Although MDMB-4en-PINACA was first identified on the drug market in 2017, it is only since 2019 that there has been a large increase in the number of Member States identifying the substance for the first time. In addition, during 2020 there was a large increase in the quantity of MDMB-4en-PINACA seized by customs, with approximately 99% of the total amount of powder (44 kg) seized by customs during the year. MDMB-4en-PINACA has been seized in prisons and other custodial settings in at least 6 Member States and, overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings. The most recent identification of MDMB-4en-PINACA reported to the EMCDDA in November 2020 by

the Netherlands involved the analysis of collected samples of cannabis which was adulterated with MDMB-4en-PINACA.

Based on the available information, it appears that at least some of the MDMB-4en-PINACA on the market in Europe has been supplied from China. It is imported into Europe as bulk powders and then sold and distributed in wholesale and retail amounts within Europe either as a powder for processing into products or finished consumer products. There are three main types of products containing MDMB-4en-PINACA that are available on the drug market: smoking mixtures, where MDMB-4en-PINACA is mixed with herbal plant material or tobacco that is then smoked (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint')) or inhaled, for example using a vaporiser; e-liquids, where a solution of MDMB-4en-PINACA is prepared by mixing it with a solvent, which is then inhaled using an e-cigarette; in addition, MDMB-4en-PINACA is also impregnated on to paper which can then be smoked or vaped. In some countries, the latter is a commonly used approach to smuggle synthetic cannabinoids into prisons. To a lesser extent, people who are using these substances may prepare their own similar products using MDMB-4en-PINACA purchased from a vendor or dealer.

MDMB-4en-PINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds. In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as homeless people and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication. They are considered to be cheap, and easy to smuggle. Similar to other new psychoactive substances, it also appears that there is interest in MDMB-4en-PINACA by people who self-experiment with a range of substances (so-called psychonauts). Overall, the available information does not suggest widespread use of the substance.

Limited information is available regarding the dose and the dose regimens of MDMB-4en-PINACA. User reports specifically about MDMB-4en-PINACA were not particularly revealing. It is not possible to discern the 'typical' dosages administered as most individuals use pre-made smoking mixtures. Synthetic cannabinoids such as MDMB-4en-PINACA may be active at less than 1 mg. Products containing synthetic cannabinoids such as MDMB-4en-PINACA rarely state the correct ingredients and concentrations. As such, people who use such products will be unaware that they are using MDMB-4en-PINACA nor will they be able to obtain accurate dosage information. MDMB-4en-PINACA can be inhaled by smoking and by vaporising e-liquid solutions ('vaping'), for example by using electronic cigarettes. To a lesser extent, other routes of administration for synthetic cannabinoids have been reported; these include sub-lingual, oral and rectal.

The high potency of the synthetic cannabinoids, coupled to the unintentionally high doses that users are potentially exposed to, is responsible for outbreaks of mass poisonings involving smoking mixtures. Such outbreaks have ranged in size from four or five to over 800 victims, including deaths. While many of the outbreaks that have been reported so far are

from the United States, they have also occurred in Russia and Europe. Mass poisonings can rapidly overwhelm emergency responders and other local healthcare systems.

Unknown to users, synthetic cannabinoids have also been sold as cannabis, ecstasy (MDMA) and other illicit drugs. In some cases, this has led to severe poisoning. Opioids have also been identified in smoking mixtures; while the overall number of detections appears to be relatively small, they could pose a risk of severe opioid poisoning, including life-threatening respiratory depression, especially in individuals with no tolerance to opioids. Users of smoking mixtures will be unaware of this risk.

Commercial and industrial uses, the extent of such use and its use for scientific research and developmental purposes

Based on the available information reported to the EMCDDA from the EMA, it appears that MDMB-4en-PINACA is not an active substance in any medicinal product for human use or in any veterinary medicinal product in Europe. However, although unlikely, the use of MDMB-4en-PINACA as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States.

There is currently no information suggesting that MDMB-4en-PINACA is used for legitimate purposes, including commercial and industrial uses, other than a scientific research or forensic application.

According to the recent critical review of MDMB-4en-PINACA published by the World Health Organization, China reported that the substance is 'being used in industrial or other non-medical or non-scientific use'.

Other relevant information

Restrictive measures

International restrictive measures

At international level, MDMB-4en-PINACA is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, nor under the Convention on Psychotropic Substances of 1971. MDMB-4en-PINACA was assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held on 12–16 October 2020.

National restrictive measures

Thirteen Member States (Bulgaria, Czechia, Denmark, Estonia, Greece, Ireland, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) reported that MDMB-4en-PINACA is not subject to restrictive measures at national level.

MDMB-4en-PINACA is subject to restrictive measures in fifteen Member States. Ten Member States (Croatia, Cyprus, Finland, France, Italy, Latvia, Luxembourg, Poland, Sweden, and the United Kingdom) control MDMB-4en-PINACA under drug control legislation. One Member State (Lithuania) controls MDMB-4en-PINACA under medicines legislation. Four Member States (Austria, Belgium, Germany, and Hungary) control MDMB-4en-PINACA under new psychoactive substance legislation. In addition, MDMB-4en-PINACA is controlled under medicines legislation in Norway and under drug control legislation in Turkey.

It is unknown if MDMB-4en-PINACA is controlled in China, where at least some of the substance on the European market has been sourced from.

COVID-19 pandemic

In some settings, the on-going COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving MDMB-4en-PINACA.

Conclusion

MDMB-4en-PINACA (methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate) is an indazole-based synthetic cannabinoid receptor agonist (synthetic cannabinoid). The (*S*)-MDMB-4en-PINACA stereoisomer has been shown to act as a potent, full agonist at the cannabinoid type 1 (CB₁) receptor when investigated under *in vitro* conditions. This suggests that in humans, MDMB-4en-PINACA may produce some similar effects both to THC, which is responsible for the major psychoactive effects of cannabis, and, in particular, closely related synthetic cannabinoids that are under international control, such as 5F-MDMB-PINACA.

MDMB-4en-PINACA is often sold as a 'legal' replacement for cannabis and other synthetic cannabinoids. It is typically administered by smoking a mixture of the substance with herbal plant material or tobacco. These are either from a ready-to-use products sold as commercial 'legal high' products or made by drug dealers; less commonly they are self-prepared. Similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint') but it may also be smoked in a pipe or 'bong'. MDMB-4en-PINACA can also be inhaled using an e-cigarette or other vaporisation devices. In the case of impregnated papers, typically these are either smoked with tobacco or vaped using an e-cigarette.

The high potency of synthetic cannabinoids and the variable content of the substance in products such as smoking mixtures and impregnated papers constitute a high risk of poisoning, which can be life-threatening or even fatal. These factors are responsible for the outbreaks of mass poisonings seen with synthetic cannabinoids. Although no mass poisonings have been reported for MDMB-4en-PINACA, it is used in a context making it liable to the occurrence of mass poisonings. Such outbreaks have the potential to

overwhelm local healthcare systems, which is of particular concern given the on-going COVID-19 pandemic and the additional burden already on healthcare systems. There is no antidote to poisoning caused by synthetic cannabinoids.

MDMB-4en-PINACA has been available in Europe since at least 2017 and has been identified in 21 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom), Norway and Turkey. MDMB-4en-PINACA has been detected in smoking mixtures, powders, paper impregnated with the substance (including blotters), liquids (including e-liquids). Although MDMB-4en-PINACA was first identified on the drug market in 2017, it is only since 2019 that there has been a large increase in the number of Member States identifying the substance for the first time. In addition, during 2020 there was a large increase in the quantity of MDMB-4en-PINACA seized by customs, with approximately 99% of the total amount of powder seized by customs during the year. Of note is that, the recent increase in seizures of consignments of bulk powder of MDMB-4en-PINACA made by European customs agencies appears to coincide with the recent decision to internationally control two closely related synthetic cannabinoids commonly found on the drug market in Europe, 4F-MDMB-BINACA and 5F-MDMB-PICA. As such, it is possible that MDMB-4en-PINACA will be a replacement for these substances.

As with other synthetic cannabinoids, the available data suggests that MDMB-4en-PINACA is used by people who use cannabis, by those who are regularly subjected to drug testing procedures, and by 'psychonauts'. It may also be used by high-risk drug users and other vulnerable groups (such as prisoners and people experiencing homelessness) as synthetic cannabinoids have gained a reputation for causing profound intoxication, they are cheaper than other drugs, and easy to smuggle. No information is available on the size and demand and the characteristics of these groups of people.

Eleven acute intoxications with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by the United Kingdom. The cases occurred between January and August 2020. While exposure to other substances was reported in most cases, including other synthetic cannabinoids, at least some of the clinical features of the poisonings were consistent with exposure to synthetic cannabinoids. In ten of the cases, the poisoning was considered life threatening and required hospitalisation of the patients.

Twelve deaths with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by Hungary (8 cases), the United Kingdom (3 cases), and Sweden (1 case). The deaths occurred between January 2019 and August 2020. In all cases, other substances were identified. In some of the cases, MDMB-4en-PINACA was reported to be the cause of death or to have contributed to the death.

It is important to note that presence of MDMB-4en-PINACA on the drug market and as the cause of serious adverse events may be undetected because the substance is not routinely screened for in some laboratories. In addition, the on-going COVID-19 pandemic may have

reduced the capacity of early warning systems to detect and report events involving MDMB-4en-PINACA.

There is no information available on the chronic health effects of MDMB-4en-PINACA, including abuse liability and dependence producing potential in humans. The chronic health risks might share some similarities to those seen with other synthetic cannabinoids. This may include dependence animal studies suggest that MDMB-4en-PINACA may show some similarity to the dependence producing potential of THC.

There is no information on whether or not criminal groups are involved in the manufacture, trafficking and distribution of MDMB-4en-PINACA within Europe. The available information suggests that at least some of the MDMB-4en-PINACA seized in Europe is manufactured by chemical companies based in China. The impact of the on-going COVID-19 pandemic on the manufacture, trafficking, distribution and use of MDMB-4en-PINACA is also currently unknown. It is possible, that in case of a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including MDMB-4en-PINACA. However, seizures of bulk powders by European national customs agencies during the first wave of the epidemic highlights that it continues to be imported into and distributed within Europe during 2020. It is conceivable that should there be a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups as well as people who use drugs, may use a range of replacement substances, including MDMB-4en-PINACA.

There is no information on the actual chemical precursors or manufacturing methods used to synthesise the MDMB-4en-PINACA that has been identified on the drug market in Europe. Although the synthetic routes reported in the scientific literature involve several steps, depending on precursor availability, they are straightforward and make use of common manufacturing equipment. The starting materials for either synthetic route are readily available. The multi-step production of MDMB-4en-PINACA requires a basic knowledge of and experience in synthetic organic chemistry.

There is no specific information available on the potential social risks posed by MDMB-4en-PINACA. The social risks might share some similarities with those posed cannabis and other synthetic cannabinoids. As highlighted, synthetic cannabinoids are increasingly used by high-risk drug users and vulnerable groups, such as prisoners and people experiencing homelessness, which has exacerbated existing health and social problems as well as creating new issues. For example, in prisons, alongside the adverse health effects, the market in and use of synthetic cannabinoids has been linked to an increase in aggression, violence, bullying, and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment. As such, it is a concern given the reports of seizures of MDMB-4en-PINACA in prisons and other custodial settings in at least six Member States and, that overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings. In addition, the detection of MDMB-4en-PINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

There is currently limited information on the extent or patterns of use of MDMB-4en-PINACA in Europe, nevertheless, information from law enforcement seizures that occurred in 2020 suggest that its availability and potential for diffusion within the Union may be significant. Based on the available information, the consumption of MDMB-4en-PINACA appears to have the potential to cause harms to health associated with its acute toxicity and abuse liability or dependence-producing potential. This harm to health is considered life-threatening because it may cause death. There is also a potential for severe physical and mental impairment. In addition, although limited, information suggests potential social harms related to consumption of MDMB-4en-PINACA including from use in prisons. Overall, these effects appear to be comparable to those of other closely related synthetic cannabinoids that are under international control, such as 5F-MDMB-PINACA.

It appears that MDMB-4en-PINACA is not an active substance in any medicinal product for human use or in any veterinary medicinal product in Europe. However, although unlikely, the use of MDMB-4en-PINACA as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States. There is currently no information suggesting that MDMB-4en-PINACA is used for legitimate purposes other than research or forensic applications in Europe.

MDMB-4en-PINACA is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. In October 2020, MDMB-4en-PINACA was critically reviewed by the Expert Committee on Drug Dependence of the World Health Organization. At the time of the present risk assessment meeting a written recommendation had not been published.

Ten Member States (Croatia, Cyprus, Finland, France, Italy, Latvia, Luxembourg, Poland, Sweden, and the United Kingdom) and Turkey control MDMB-4en-PINACA under drug control legislation. Five Member States (Austria, Belgium, Germany, Hungary, and Lithuania) and Norway control MDMB-4en-PINACA under other legislation. It is unknown if MDMB-4en-PINACA is controlled in China, where at least some of the substance on the European market has been sourced from.

The Committee notes that while the available information on MDMB-4en-PINACA indicates that it is a potent synthetic cannabinoid *in vitro*, overall there is limited information available on its pharmacology, toxicology, abuse liability and dependence-producing potential. Additional information may emerge with later studies but ideally would have been available in this assessment. The Committee notes that, to strengthen early warning, preparedness and response activities within the EU, such studies should be undertaken systematically prior to risk assessment.

As for any NPS, many of the questions related to MDMB-4en-PINACA that are posed by the lack of data on the risks to individual health, risks to public health and social risks could be answered through further research. Areas where additional information would be important include studies on epidemiology (frequency and patterns of use, including studies that examine the groups of people who use MDMB-4en-PINACA and risk behaviours); the

market; chemical profiling; extended pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between MDMB-4en-PINACA and other substances; the abuse liability and dependence-producing potential; and the public health and potential social risks associated with its use.

The Committee notes that a decision to control MDMB-4en-PINACA has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks arising from the use of MDMB-4en-PINACA. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, pharmacologically analogous substances that may replace MDMB-4en-PINACA are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation.

Finally, the Committee notes that it is important to continue to collect accurate information on MDMB-4en-PINACA and to disseminate it to people who use the substance, as well as to practitioners, policymakers and decision-makers.