



European Monitoring Centre
for Drugs and Drug Addiction

**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)**

In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended)

Contents

Statement regarding the United Kingdom.....	3
Acknowledgements.....	3
1. Introduction.....	4
2. Information collection process.....	5
3. Information required by Article 5b(2) of the Regulation.....	7
3.1. Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance	7
3.2. Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction.....	13
3.3. Pharmacological and toxicological description of the new psychoactive substance	18
3.4. Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance.....	19
3.5. Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product	21
3.6. Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes	21
3.7. Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States	22
3.8. Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances.....	23
3.9. Other relevant information.....	24
4. Analysis and assessment.....	24
5. References	27

Statement regarding the United Kingdom

The reference period for this report includes from 2017 to 2020 (up to the moment of writing). The United Kingdom left the European Union as of 1 February 2020. However, during the transitional period, the UK 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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- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein;
- the European Medicines Agency (EMA);
- the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Commission; and,
- the World Health Organization.

In addition, the EMCDDA would also like to express their thanks and appreciation to the Public Health Agency of Sweden and the National Board of Forensic Medicine, Sweden, for providing information on the pharmacology of MDMB-4en-PINACA used in this initial report.

1. Introduction

Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA) is a synthetic cannabinoid receptor agonist. Similar to other synthetic cannabinoids, it is sold as a 'legal' replacement for cannabis and controlled synthetic cannabinoids. Because of their high potency, synthetic cannabinoids can pose a high risk of severe poisoning, which in some cases can be fatal.

In Europe, MDMB-4en-PINACA is monitored by the EMCDDA as a new psychoactive substance ⁽¹⁾ through the European Union Early Warning System (EWS) in accordance with Article 5a of Regulation (EC) No 1920/2006 (as amended) ^(2,3).

MDMB-4en-PINACA was formally notified as a new psychoactive substance ^(4,5) 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.

Since the formal notification, information on MDMB-4en-PINACA has been exchanged between the EMCDDA and the European Union EWS Network (EMCDDA, Europol, Reitox national focal points, and the Commission); the EMA have been kept duly informed.

On 10 July 2020, the EMCDDA issued a public health advisory to the Network highlighting an increase in the number of identifications of MDMB-4en-PINACA in Europe and the potential risks posed by this.

On 27 July 2020, the EMCDDA informed the EWS Network that based on potential public health risks, the EMCDDA had added MDMB-4en-PINACA to the list of new psychoactive substances under intensive monitoring ⁽⁶⁾ and requested that the Network expedite reporting of any event involving MDMB-4en-PINACA to the EMCDDA until further notice.

Article 5b of Regulation (EC) No 1920/2006 (as amended) requires that *'Where the Centre, the Commission or a majority of the Member States considers that information shared on a new psychoactive substance collected pursuant to Article 5a in one or more Member States*

¹ As defined in point 4 of Article 1 of 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 (OJ L 335, 11.11.2004, p. 8).

² 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) (O J L 376, 27.12.2006, p.1-13).

³ Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances (O J L 305, 21.11.2017, p.1-7).

⁴ EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

⁵ EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 2. Formal notification of a new psychoactive substance. <https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%202-%20Formal%20notification%20of%20a%20new%20psychoactive%20substance.pdf>

⁶ EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 6. Intensive monitoring. <https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%207-%20Substances%20of%20high%20concern.pdf>

gives rise to concerns that the new psychoactive substance may pose health or social risks at Union level, the Centre shall draw up an initial report on the new psychoactive substance'.

The initial report is submitted to the Commission and the Member States. The purpose of the initial report is to provide scientific evidence to the Commission to allow it to make an informed decision regarding whether or not there is a need to request a risk assessment on a new psychoactive substance as set out in Article 5c of Regulation (EC) No 1920/2006 (as amended).

Based on the information reported by the Network, on 2 September 2020, the EMCDDA assessed the existing information ^(7,8) on MDMB-4en-PINACA, based on the following criteria:

- reports of health problems;
- reports of social problems;
- reports of seized material;
- pharmacological and toxicological properties and analogy with better-studied substances; and,
- potential for further spread.

The EMCDDA concluded that the assessment gave rise to concerns that MDMB-4en-PINACA may pose health or social risks at Union level, and, consequently, determined that an initial report should be produced.

2. Information collection process

In accordance with the requirements of Article 5b of the Regulation, on 9 September 2020, the EMCDDA launched a procedure for the collection of additional information on MDMB-4en-PINACA in order to support the production of the initial report.

The EMCDDA collected information through:

- a structured reporting form to the Reitox national focal points in the Member States, Turkey, and Norway (Article 5b(4));
- routine monitoring of open source information;
- a search of open source information conducted specifically for the production of the initial report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and online vendors.

⁷ EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

⁸ This included information reported to the EMCDDA through the Early Warning System, including case reports and aggregated datasets.

In addition, the EMCDDA also submitted requests to:

- The World Health Organization (WHO) in order to determine if MDMB-4en-PINACA is under assessment or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances ('United Nations system').
- The European Medicines Agency (EMA) in order to determine if MDMB-4en-PINACA is used as an active substance in a medicinal product for human or veterinary use at Union or national level (Article 5b(5)). Specifically, the EMA was asked if MDMB-4en-PINACA is an active substance in:
 - a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/EC of the European Parliament and of the Council ⁽⁹⁾, Directive 2001/82/EC of the European Parliament and of the Council ⁽¹⁰⁾ or Regulation (EC) No 726/2004 of the European Parliament and of the Council ⁽¹¹⁾;
 - b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;
 - c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;
 - d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;
 - e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council ⁽¹²⁾.
- Europol in order to provide information on the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of MDMB-4en-PINACA, and in any use of MDMB-4en-PINACA (Article 5b(6)).
- The European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) in

⁹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

¹⁰ Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

¹¹ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

¹² Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

order to provide the information and data at their disposal on MDMB-4en-PINACA (Article 5b(7)).

The information collection process was concluded on 7 October 2020. The EMCDDA received responses from all 28 Member States, Turkey, and Norway. In addition, the EMCDDA received responses from WHO, EMA, Europol, ECHA, ECDC, and EFSA.

3. Information required by Article 5b(2) of the Regulation

The order and titles of subsections 3.1 to 3.9, below, are as they appear in Article 5b(2) of Regulation (EC) No 1920/2006 (as amended); sections 3.1 to 3.4 are cross-referenced with the headings of Article 5b(2a) to Article 5b(2d) of the Regulation.

3.1. Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance

Detections of MDMB-4en-PINACA may be under-reported since the substance may not be routinely screened for in forensic and toxicology laboratories. Therefore, the presence of MDMB-4en-PINACA on the European drug market may be undetected in some areas, including in law enforcement seizures as well as in biological samples related to serious adverse events. It is also important to note, that, due to differences in reporting practices across Europe, identifications of MDMB-4en-PINACA may be unreported to the Reitox national focal points and as a consequence to the EMCDDA.

3.1.1. Information from seizures, collected and biological samples

As of 8 October 2020, MDMB-4en-PINACA has been identified in 850 detections across 20 Member States, Turkey, and Norway. These relate to 768 seizures, 13 collected samples and 69 biological samples. In addition, three detections were reported by Slovenia⁽¹³⁾ after the data submission deadline, which have not been included in the dataset.

Information from seizures

In total, 768 seizures of MDMB-4en-PINACA, amounting to over 63 kg, were reported to the EMCDDA by 20 Member States and Norway, as follows: the United Kingdom (380 seizures), Hungary (223), Germany (40), France (35), Sweden (20), Belgium (12), Poland (11), Bulgaria (10), Latvia (7), Lithuania (7), Slovakia (5), Slovenia (4), Spain (3), Austria (2), Cyprus (2), Romania (2), Croatia (1), Greece (1), the Netherlands (1), Portugal (1), and Norway (1). In addition, Turkey reported 663 additional cases that may contain duplicates and have not been included in the count.

The majority of the seizures comprise police cases (730), with 108 (15%) of the seizures taking place in prisons and other custodial settings. There were 38 customs cases reported.

¹³ Slovenia reported three seizures of herbal material made by the police in prison, which contained also 4F-MDMB-BICA (3), 5F-MDMB-PICA (3), 5F-EMB-PICA (3), Cumyl-PeGaClone (1), Cumyl-5F-PINACA (1), MDMB-PINACA (1), 4F-MDMB-BICA (1) and traces of JWH-210 (1).

Seizures included smoking mixtures, powders, liquids, blotters and unspecified physical forms. A summary is provided below.

Customs seizures

A total of 38 customs seizures of MDMB-4en-PINACA were reported by France (13), Belgium (12), Poland (4), Germany (3), Sweden (2), Bulgaria (1), Lithuania (1), the Netherlands (1), and Norway (1). When reported, the seizures occurred between May 2019 and September 2020. In the majority of cases (36) no other substances were reported as identified in the seizures.

MDMB-4en-PINACA was detected in powders, and smoking mixtures. A summary is provided below.

- Powders

In total, 22 customs seizures, amounting to 44.5 kg were in powder form. Overall, most of the quantities seized by customs were made in 2020 (44.36 kg; 99.7%), while only 115 grams were seized in 2019.

In total, Belgian customs reported 11 seizures of MDMB-4en-PINACA amounting to 44.3 kg of powder. These included two single seizures amounting to 16 kg each. All the seizures reported by Belgium originated in China and the destinations were reported as: Turkey (for each of the 16 kg seizures); the United Kingdom (for 3 seizures amounting to 7.2 kg); Israel (2, 2.7 kg); Reunion (France) (1, 500 grams); Netherlands (1, 1.5 kg); Belgium (1, 300 grams); and Romania (1, 100 grams). No other substances were reported as identified in any of the seizures.

Lithuanian customs reported a seizure of shipment from Spain of MDMB-4en-PINACA in a package labelled '5CL'.

- Smoking mixtures

Four of the seizures, amounting to 287 grams, were in herbal form. In 2 of them 5F-MDMB-PICA was also detected.

- Other

The physical form for 12 of the seizures was reported as an 'other' or not specified and amounts to approximately 2.5 kg.

Police seizures

A total of 730 seizures made by police were reported by 18 Member States, as follows: the United Kingdom (380 seizures), Hungary (223), Germany (37), France (22), Sweden (18), Bulgaria (9), Latvia (7), Poland (7), Lithuania (6), Slovakia (5), Slovenia (4), Spain (3), Austria (2), Cyprus (2), Romania (2), Croatia (1), Greece (1), and Portugal (1).

Seizures occurred between 2017 and September 2020. Where known, seizures occurred in 2017 (1), 2018 (14), 2019 (325), and 2020 (388). The police seizures amounted to approximately 15.9 kg. In terms of quantity, material containing MDMB-4en-PINACA was seized mainly in 2020 (9.7 kg) and 2019 (6.2 kg).

Out of the 730 police seizures, 108 seizures occurred in prisons, including correction houses and were reported by: the United Kingdom (98), Slovenia (4), Lithuania (3), Cyprus (1), France (1) and Germany (1). The seizures occurred between June 2019 and July 2020. In 100 cases, the seizures were in blotter form, including all cases reported by the United Kingdom, and amounted to 135 blotters. In 4 seizures, reported by Slovenia, MDMB-4en-PINACA was detected in herbal material amounting to 5.2 grams. Other synthetic cannabinoids were detected in 10 of the seizures; these included: 5F-MDMB-PICA (8), 4F-MDMB-BICA (3), and 4F-MDMB-BINACA (3). In the case reported by Cyprus, 14 impregnated sheets of A4 sized paper which had been concealed inside a television were seized in a delivery of a package to a prison.

The remaining 622 seizures reported by the police were detected in smoking mixtures, powders, blotters, and liquids. A summary is provided below.

- *Smoking mixtures*

A total of 301 seizures of smoking mixtures amounting to 4.5 kg were reported by: Hungary (194), the United Kingdom (49), Germany (32), Latvia (7), Sweden (7), Slovakia (5), Poland (3), Lithuania (2), Greece (1), and Croatia (1). Seizures occurred between 2017 and September 2020. In 67 cases, other synthetic cannabinoids were detected: mainly 5F-MDMB-PICA (39), 4F-MDMB-BICA (11), and 4F-MDMB-BINACA (11). In 3 cases reported by the United Kingdom, cannabis and THC were detected. In 4 cases reported by the United Kingdom, nicotine was detected. Seizures ranged from 0.03 grams to 842 grams, being most of the seizures (260) under 10 grams. Germany reported MDMB-4en-PINACA in branded 'legal-high' type products: 'Pico Bello Extra Strong' (seized in 2017, containing 5-ADB and 5-ADB-PINACA), 'Pico Bello Made In Holland' (3 seizures, containing also 5F-MDMB-PICA). Mixtures were also found in joints, in small non-branded grip-seal clear bags and inside paper wrappers.

- *Powders*

In total, 45 seizures of powder amounting to 2.6 kg were reported by: Hungary (17), Sweden (11), the United Kingdom (5), Germany (3), Spain (3), Poland (2), Cyprus (1), Lithuania (1), Portugal (1), and Romania (1). Seizures ranged from 0.01 grams to approximately 1 kg, being most of the seizures (28) under 10 grams. Only three seizures were reported to contain other substances: 2.7% of dimethylsulphone (1); 4F-MDMB-BINACA (1), and 5F-MDMB-2201 (1).

- *Blotters*

A total of 41 seizures amounting to 150 blotters were reported by 3 Member States: the United Kingdom (30), Hungary (11), and Germany (1). In 11 cases, other synthetic cannabinoids were also detected, 5F-MDMB-PICA (9 cases), 4F-MDMB-BINACA (2) and AMB-FUBINACA (1).

- *Liquids*

In total, 15 seizures of liquid amounting to 39 ml were reported by 3 Member States: France (11), the United Kingdom (3) and Hungary (1). Of these, in 11 seizures other psychoactive substances were detected including mainly synthetic cannabinoids. The liquids were found

in most cases in a vial, as e-liquids for vaping (10 cases), and in one case in an e-cigarette with a half empty cartridge.

- *Other*

For 219 seizures amounting to close to 8.8 kg the physical form was not specified, reported as 'other' or unknown. These included 5 single seizures amounting to close to 1 kg each, reported by the United Kingdom, which occurred in February 2020.

Information from collected samples

A total of 13 collected samples were reported by 5 Member States: France (5 samples), Poland (3), Germany (2), Slovenia (2) and Belgium (1). Of these, 7 samples were in powder form, 4 samples were in liquid form and for the remaining 2 samples the form was reported as 'other'.

Powders were collected as beige or yellow solids. In one case reported by Slovenia MDMB-4en-PINACA was purchased from an internet website as '5-CL-ADB-A' for the price of 21 dollars per gram.

All the cases where MDMB-4en-PINACA was detected in liquid form, which were reported by France (3) and Belgium (1), were recovered from poisoning cases.

The 3 liquid samples reported by France were collected between September 2019 and January 2020 and were collected from patients with acute non-fatal poisonings. One of the three samples, sold under the street name 'PTC' (from the French, 'pète ton crane'), was related to poisonings with probable exposure to MDMB-4en-PINACA of two males, aged 16. In the remaining 2 samples of liquid, 4F-MDMB-BINACA was also detected. One of the e-liquids, labelled 'Born to DIY', was sold among school students.

The sample reported by Belgium, was in an e-liquid for vaping found on an poisoned patient. The sample also contained 4F-MDMB-BINACA, 5CI-AKB48, 4-cyano-CUMYL-BUTINICA, 5F-MDMB-PICA, 5F-CUMYL-PINACA and benzylone in lower concentrations than 4F-MDMB-BINACA. The case occurred in July 2020.

Two additional samples reported by France, which also contained 5F-MDMB-PICA, were collected in the overseas department and region of Mayotte and sold as 'Chimique'.

Information from biological samples

Serious adverse events with confirmed exposure to MDMB-4en-PINACA from biological samples (11 acute intoxications reported by the United Kingdom, and 4 deaths reported by United Kingdom (3) and Sweden (1)) are discussed in section 3.1.2.

In addition to these, 54 detections of MDMB-4en-PINACA in biological samples were reported by Turkey (36) and Hungary (18)¹⁴. Detections included:

- 3 samples associated with non-fatal intoxications, reported by Hungary;

¹⁴ In addition, Turkey reported 101 samples associated with non-fatal intoxications which may contain duplicates and therefore have not been included in the total count.

- 4 cases of persons suspected of driving under the influence of drugs (including two traffic accidents), reported by Hungary;
- 11 cases of drug consumption, reported by Hungary;
- 36 samples taken by the law enforcement agencies, reported by Turkey.

3.1.2. Health problems

Acute poisonings

A total of 11 acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA were reported by the United Kingdom ⁽¹⁵⁾. The cases occurred during 2020. Of the cases, nine were male and two were female. The males were aged between 19 and 60 (mean 36; median 32.5). The females were aged 31 and 35.

All the cases included clinical features of poisoning similar to those reported for synthetic cannabinoids. In all cases other substances were identified.

In ten of the cases, the poisoning was considered life-threatening and required hospitalisation of the patient.

Deaths

A total of 4 deaths with confirmed exposure to MDMB-4en-PINACA were reported by the United Kingdom (3) and Sweden (1). The cases occurred between 2019 and 2020.

Of the deaths, two were male and two were female. The males were aged 37 and 41; the females were aged 31.

In all cases, other substances were identified, including central nervous system depressants (such as alcohol, opioids, synthetic cannabinoids and benzodiazepines). In 2 cases, metabolites of fluoro-MDMB-PICA metabolites were detected post-mortem. Three of the cases were found dead, in one case the individual fell from a balcony. In three cases MDMB-4en-PINACA was the cause of death or contributed to the death; in the remaining case the cause of death was trauma from a fall where the contribution from drugs present could not be determined.

ECDC reported that currently they do not have any information on MDMB-4en-PINACA.

3.1.3. Social problems

While there is limited data for MDMB-4en-PINACA, the social risks might share some similarities with cannabis and other synthetic cannabinoids.

Of particular note is that synthetic cannabinoids are increasingly used by vulnerable groups, such as prisoners and people experiencing homelessness. Reports suggest that this has caused new health and social problems as well as exacerbated existing ones for these

¹⁵ In addition, France reported two acute intoxications with probable exposure to MDMB-4en-PINACA. These cases are not discussed further in this report.

groups. For example, in prisons, alongside the adverse health effects, the market in 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 (Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016). As such, it is a concern given that six Member States reported seizures of MDMB-4en-PINACA in prisons and other custodial settings, and, that overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings.

3.1.4. Patterns of use

There is limited information on the patterns of use of MDMB-4en-PINACA. As MDMB-4en-PINACA is a synthetic cannabinoid, it could be expected that suppliers as well as users who are looking for 'legal' substitutes for cannabis and replacements for controlled synthetic cannabinoids, may be interested in the substance. This may include 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 prisoners and people experiencing homelessness, may specifically seek out synthetic cannabinoids as they are readily available and have gained a reputation for causing profound intoxication while being comparatively cheaper to other drugs. In addition, synthetic cannabinoids, particularly when impregnated on to paper, can be easy to smuggle into prison and other custodial settings.

Detections of MDMB-4en-PINACA in prisons and other custodial settings have been reported both in the scientific literature (Norman et al., 2020; Yeter et al., 2020) and cases reported to the EMCDDA. Six Member States reported seizures of MDMB-4en-PINACA in prisons and other custodial settings to the EMCDDA; overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings. In addition, according to information reported by the United Kingdom, MDMB-4en-PINACA is currently the most prevalent synthetic cannabinoid in prisons in Scotland (McKenzie 2020).

Although limited, there is some information to suggest a recent increase in vaping of synthetic cannabinoids using electronic cigarettes by young people, including teenagers, in some Member States.

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').

Although MDMB-4en-PINACA may be deliberately sought after by some users, in most cases, such as those that purchase it at street-level, they are likely to be unaware that they are using the substance which presents an inherent risk to the individuals.

There are three main types of products containing MDMB-4en-PINACA that are sold on the drug market. The most common products are smoking mixtures, where MDMB-4en-PINACA is mixed with herbal plant material or tobacco that is then smoked or inhaled from a vaporiser (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint')). There are also e-liquids, where a solution of MDMB-4en-PINACA is

prepared by mixing it with a solvent, which is then vaped using an electronic cigarette (Gaulier et al., 2020). In addition, MDMB-4en-PINACA is 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, users may prepare their own similar products using MDMB-4en-PINACA purchased from a vendor or dealer.

3.2. Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction

3.2.1. Chemical description and names

MDMB-4en-PINACA is a synthetic cannabinoid receptor agonist. It contains an indazole core, a common structural feature in many of the synthetic cannabinoids monitored by the EMCDDA, a carboxamide link, a dimethyl methyl butanoate linked group and a pent-4-ene moiety on a pentyl tail.

MDMB-4en-PINACA appears not to have been described in the scientific or patent literature prior to the first identification on the drug market in Europe in 2017.

MDMB-4en-PINACA shares structural features with a number of substances, including: 5F-MDMB-PICA (¹⁶), 4F-MDMB-BINACA (¹⁶), 5F-MDMB-PINACA (¹⁷), and 4F-MDMB-BICA (¹⁸).

Structurally, MDMB-4en-PINACA differs in the tail (4-fluorobutyl) from 4F-MDMB-BINACA and (5-fluoropentyl) from 5F-MDMB-PINACA; in the core (indole) and tail (5-fluoropentyl) from 5F-MDMB-PICA; and in the core (indole) and tail (4-fluorobutyl) from 4F-MDMB-BICA.

The molecular structure, molecular formula and molecular mass of MDMB-4en-PINACA are provided in Figure 1.

¹⁶ 5F-MDMB-PICA and 4F-MDMB-BINACA were critically reviewed by the WHO's Expert Committee on Drug Dependence (ECDD) in 2019 and have been added to Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances, which will come into force on 3 November 2020.

¹⁷ 5F-MDMB-PINACA was critically reviewed by ECDD in 2017 and is internationally controlled under Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.

¹⁸ 4F-MDMB-BICA is the subject of an EMCDDA initial report.

Figure 1. Molecular structure, molecular formula, and molecular mass of MDMB-4en-PINACA. Information on 4F-MDMB-BINACA, 5F-MDMB-PINACA, 5F-MDMB-PICA and 4F-MDMB-BICA is provided for comparison.

	MDMB-4en-PINACA	4F-MDMB-BINACA ⁽¹⁹⁾	5F-MDMB-PINACA ⁽²⁰⁾	5F-MDMB-PICA ⁽²¹⁾	4F-MDMB-BICA ⁽²²⁾
Molecular formula	C ₂₀ H ₂₇ N ₃ O ₃	C ₁₉ H ₂₆ FN ₃ O ₃	C ₂₀ H ₂₈ FN ₃ O ₃	C ₂₁ H ₂₉ FN ₂ O ₃	C ₂₀ H ₂₇ FN ₂ O ₃
Molecular mass	357.45	363.43	377.453	376.47	362.44

Common name:

MDMB-4en-PINACA

Systematic (IUPAC) name:

Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate

Other chemical names:

Methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1H-indazol-3-yl]formamido]butanoate

Methyl 3,3-dimethyl-2-[(1-pent-4-enylindazole-3-carbonyl)amino]butanoate

Methyl 3-methyl-N-[1-(pent-4-en-1-yl)-1H-indazole-3-carbonyl]valinate

Other names:

MDMB-4EN-PINACA

MDMB-PENINACA

MDMB-PINACA N1-pentyl-4-en isomer

5CI-ADB-A ⁽²³⁾

¹⁹ Methyl 2-(1-(4-fluorobutyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate

²⁰ Methyl 2-[[1-(5-fluoropentyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate

²¹ Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate

²² Methyl 2-[[1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl]amino)-3,3-dimethylbutanoate

ADB-PINACA-A

Chemical Abstracts Service (CAS) registry numbers:

Not registered

IUPAC International Chemical Identifier Key (InCHI Key):

LWOCBHBFWNGPGM-UHFFFAOYSA-N

Simplified Molecular-Input Line-Entry System (SMILES):

COC(=O)C(NC(=O)c1nn(CCCC=C)c2ccccc12)C(C)(C)C

3.2.2. Physical description

There is no information available on the solubility, lipophilicity, melting and boiling points or other physico-chemical properties of MDMB-4en-PINACA.

MDMB-4en-PINACA is reported to be soluble in methanol (MeOH) (NPS Discovery, 2019; Norman et al., 2020a), deuterated chloroform (CDCl₃) (Norman et al., 2020a) and due to its similarity to 5F-MDMB-PINACA, MDMB-4en-PINACA is also expected to be soluble in ethanol (EtOH), dimethyl sulfoxide (DMSO) and partially soluble in water.

To date, seizures and collected samples containing MDMB-4en-PINACA, reported to the EMCDDA, have been in white, beige, yellow and orange powders and in herbal material. MDMB-4en-PINACA has also been identified in blotters, papers impregnated with the substance and in liquids contained in vape cartridges.

MDMB-4en-PINACA has been detected in combination with other synthetic cannabinoids including: 5F-MDMB-PICA, 4F-MDMB-BICA, 4F-MDMB-BINACA, 5CI-AB-PINACA, 5F-EMB-PICA, AMB-FUBINACA, AB-FUBINACA, Cumyl-PeGaClone, CUMYL-4CN-BINACA, Cumyl-5F-PINACA and JWH-210.

In at least some of the detections, the free base of MDMB-4en-PINACA was identified.

A more detailed description of seizures and collected samples can be found in section 3.1.1.

3.2.3. Methods and chemical precursors used for the manufacture or extraction

No information was reported by the Member States, Norway, or Turkey about the chemical precursors or manufacturing methods used to make the MDMB-4en-PINACA which has been identified within Europe.

The synthesis of the *S*-enantiomer of MDMB-4en-PINACA has recently been published in the literature (Norman et al., 2020a). The authors reported that MDMB-4en-PINACA, 5F-MDMB-PINACA and 4F-MDMB-BINACA can be prepared using similar synthetic routes (Norman et al., 2020a).

²³ MDMB-4en-PINACA has, in some instances, been incorrectly advertised online as '5CI-ADB-A'.

The synthesis of MDMB-4en-PINACA may be carried out in analogy to the synthesis of 5F-MDMB-PINACA, described by Banister et al., starting with methyl 1*H*-indazole-3-carboxylate which was reacted with methyl *L-tert*-leucinate, yielding (S)-5F-MDMB-PINACA (Banister et al., 2016). The (*R*)-enantiomer might be synthesised under identical conditions using methyl *D-tert*-leucinate instead of methyl *L-tert*-leucinate. Using methyl *tert*-leucinate as a racemate would lead to the production of the racemic substance.

Potential precursors of MDMB-4en-PINACA are methyl 1*H*-indazole-3-carboxylate, 5-bromo-1-pentene, and *L-tert*-leucine methyl ester (for the synthesis of the (S) enantiomer).

There is no information on the actual manufacturing methods used to make the MDMB-4en-PINACA which has been identified in Europe.

3.2.4. Detection and analysis

Methods documented in the literature for the identification of MDMB-4en-PINACA in physical samples include: gas chromatography–mass spectrometry (GC-MS) (NPS Discovery, 2019; Cayman Chemical, 2020; RESPONSE, 2018; Norman et al., 2020a); Fourier transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC) and ¹H, ¹³C and ¹⁹F nuclear magnetic resonance spectroscopy (NMR) (RESPONSE 2018); ultra-performance liquid chromatography-photodiode detector-quadrupole/time of flight-mass spectrometry (UPLC-PDA-Q/TOF-MS) and Ion mobility spectrometry (IMS) (Norman et al., 2020a; Norman et al., 2020b).

In an analysis of 360 individual seized paper samples from three Scottish prisons between 1 June 2018 and 27 September 2019, 146 samples (41%) were found to contain at least one synthetic cannabinoid. Of these, 22 samples (15%) were found to contain MDMB-4en-PINACA ranging in concentration from $<0.07 \pm 0.01$ to 0.58 ± 0.09 mg/cm² paper (Norman et al., 2020a).

Concentration mapping data from two seized paper samples in this study, found to contain AMB-CHMICA (²⁴) and 5F-MDMB-PICA, demonstrated that in the case of AMB-CHMICA ‘concentrations across papers were ‘highly variable (0.47 - 2.38 mg/cm² paper) making consistent dosing by users, and representative sampling by laboratory analysts, difficult’ (Norman et al., 2020a).

The variation in synthetic cannabinoid concentration in these papers has been attributed to the method employed for the preparation of synthetic cannabinoid impregnated papers and indicates that the synthetic cannabinoid was likely added to the centre of the paper with the solution moving outward (Norman et al., 2020a). In a simulated test, the authors demonstrated that the distribution of a synthetic cannabinoid across an impregnated paper was less variable when the paper was laid flat compared to when hung up to dry, with concentrations considerably higher at the bottom of the papers hung up to dry (Norman et al., 2020a).

In the same study, it was noted that between April and May 2019, 73% (16 samples) of all MDMB-4en-PINACA detections were also found to contain 4F-MDMB-BINACA as a major

²⁴ methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3-methyl-butanoate

component. The authors also highlighted the increasing prevalence of MDMB-4en-PINACA in detections over the course of their studies from June 2018 to September 2019 and from September to 18 December 2019 (Norman et al., 2020a; Norman et al., 2020b).

MDMB-4en-PINACA was identified in a ratio 'per plant material of 1.56% to 2.09% w/w' in a seizure of three 'Spice' samples, in July 2020, in the UK. In the report submitted by the UK, it was noted that this was between 1.5 to 2 times the ratio of MDMB-4en-PINACA found in seized samples tested in June 2020.

Quantification of MDMB-4en-PINACA in products can be carried out according to the general procedure described by the UNODC (UNODC, 2013).

Methods documented in the literature for the identification of MDMB-4en-PINACA in biological samples include: liquid chromatography-quadrupole time of flight-mass spectrometry (LC-QTOF-MS) (NPS Discovery, 2019; Krotulski et al., 2020); liquid chromatography-high-resolution mass spectrometry (LC-HRMS) (Yeter et al., 2020); and liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) (Watanabe et al., 2020).

Krotulski et al. noted the importance of the detection of MDMB-4en-PINACA 3,3-dimethylbutanoic acid in blood samples, highlighting that the detection of butanoic acid metabolites was 'as the result of instability of parent synthetic cannabinoids, especially with methyl ester species' (Krotulski et al., 2020). The authors indicated that MDMB-4en-PINACA may be susceptible to matrix instability and as a result suggested that MDMB-4en-PINACA 3,3-dimethylbutanoic acid may be an 'equally appropriate target when testing blood samples for synthetic cannabinoids, even after just short periods of time when blood samples are refrigerated' (Krotulski et al., 2020). The authors recommended that cases be interpreted as MDMB-4en-PINACA ingestion if a blood sample is positive for MDMB-4en-PINACA 3,3-dimethylbutanoic acid but negative for MDMB-4en-PINACA, once other similar alkylated analogues have not been detected on the drugs market and while also taking note of the case history and post-mortem findings (Krotulski et al., 2020).

Krotulski et al. additionally flagged the potential requirement in toxicology testing for emerging synthetic cannabinoids for 'high sensitivity platforms (e.g., LC-MS/MS) due to increased potency over compounds from previous generations and corresponding lower concentrations' (Krotulski et al., 2020).

MDMB-4en-PINACA contains a stereocentre thus allowing for the existence of a pair of enantiomers, (*R*)- and (*S*)-MDMB-4en-PINACA. The *S*-enantiomer of MDMB-4en-PINACA is available as a reference standard, in the form of a neat solid (²⁵). Methods documented in the literature for the characterisation of (*S*)-MDMB-4en-PINACA include: GC-MS (Cayman Chemical, 2020; Norman et al., 2020a) and NMR spectroscopy (Norman et al., 2020a).

There is no representative information on the enantiomeric composition of the samples of MDMB-4en-PINACA detected within the European Union, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Based on

²⁵ <https://www.caymanchem.com/product/26097/mdmb-4en-pinaca>

the literature of similar compounds (Banister et al., 2016) and the most likely precursors to be used, an (S)-configuration of the stereocentre could be expected.

Differentiation of enantiomers is possible using the following techniques: chiral chromatography, vibrational circular dichroism (VCD) spectroscopy and/or electronic circular dichroism (ECD) spectroscopy.

MDMB-4en-PINACA and MBA-CHMINACA⁽²⁶⁾, also known as AB-CHMINACA metabolite M2, are isomers therefore it is important to note that GC-MS analysis of these substances will result in very similar mass spectrometry fragmentation patterns. The ability to distinguish between isomers requires the use of analytical reference standards, access to reference spectra for both substances, and/or additional analytical methods⁽²⁷⁾.

MDMB-4en-PINACA is currently screened for in some, but not all, forensic and toxicology laboratories in Europe. As a result, some cases of MDMB-4en-PINACA are likely to be undetected and under reported, leading to incomplete data regarding detections of MDMB-4en-PINACA in Europe.

3.3. Pharmacological and toxicological description of the new psychoactive substance

MDMB-4en-PINACA is a synthetic cannabinoid receptor agonist. Limited data suggests that MDMB-4en-PINACA is a CB₁ receptor agonist (Antonides et al., 2020; ECDD 2020; Krotulski et al., 2020; NBFM and PHA, 2019) that shares some similarities with the major psychoactive constituent of cannabis Δ^9 -tetrahydrocannabinol (THC) and other synthetic cannabinoids.

The acute effects of THC (and consequently cannabis) include: relaxation, euphoria, lethargy, depersonalisation, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, reddening of the conjunctivae of the eyes, tachycardia, and, nausea and vomiting. THC also has an abuse liability and dependence potential (Pertwee, 2014; Wiley et al., 2016). Similar effects to cannabis have been reported for synthetic cannabinoids such as MDMB-4en-PINACA. In some cases, the effects are reported to be more pronounced/severe (EMCDDA, 2017).

Compared to cannabis, severe and fatal poisoning appears to be more common with synthetic cannabinoids (EMCDDA, 2017; Tait et al., 2016). Poisoning may include rapid loss of consciousness/coma, cardiovascular effects (such as hypertension, tachycardia, bradycardia, chest pain, myocardial infarction, and stroke), seizures and convulsions, vomiting/hyperemesis, delirium, agitation, psychosis, and, aggressive and violent behaviour. Sudden death has also been reported. The mechanisms of this toxicity are poorly understood (Tai and Fantegrossi, 2016), but factors that are likely to play an important role are the potency of the substances and the doses that users are exposed to. In addition, some of the effects of poisoning — such as loss of consciousness or behavioural effects — may place users at additional risks such as choking on vomitus, drowning, or self-harm.

²⁶ 2-[[1-(Cyclohexylmethyl)indazole-3-carbonyl]amino]-3-methyl-butanoic acid

²⁷ <https://www.caymanchem.com/product/16389/ab-chminaca-metabolite-m2>

Currently there is no antidote to poisoning caused by synthetic cannabinoids.

In general, the use of smoking mixtures containing synthetic cannabinoids appears to pose a high risk of poisoning. This is because manufacturers guess the amount of cannabinoids(s) to add to the herbal material, and the manufacturing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the material. This can result in mixtures that contain a large amount of highly potent cannabinoid, as well as 'hot pockets' where the cannabinoid is highly concentrated within parts of the herbal material (Schäper, 2016). Together, this makes it difficult for users to control the dose that they are exposed to. As these mixtures are typically smoked as cigarettes ('joints'), users can inadvertently administer a toxic dose; in some cases, a small number of puffs from a cigarette have been sufficient to cause severe poisoning. Reflecting these risks, smoking mixtures have caused a large number of outbreaks of mass poisonings in recent years (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Trecki et al., 2015; Tyndall et al., 2015). Such outbreaks have the potential to overwhelm local healthcare systems, which is of particular concern considering the ongoing COVID-19 pandemic.

While there is limited data for MDMB-4en-PINACA, the chronic health risks might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

ECHA reported to the EMCDDA that they do not currently have any information on MDMB-4en-PINACA at their disposal, in particular any data on its toxicological properties. EFSA reported to the EMCDDA that they do not currently have any information on MDMB-4en-PINACA, including both describing the hazard and concerning human exposure.

3.4. Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance

Europol received replies from 19 Member States: Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Portugal, Slovakia, Slovenia, Spain and the United Kingdom.

Replies were also received from the United States (US) Drug Enforcement Administration (DEA) ⁽²⁸⁾ and New Zealand ⁽²⁹⁾.

No information was received on the involvement of criminal groups in the manufacture or distribution of MDMB-4en-PINACA.

Belgium reported 11 seizures of MDMB-4en-PINACA by customs at Liege airport. One shipment contained two separate quantities of 16 kilograms of MDMB-4en-PINACA. Belgium remarked that they are a transit country for MDMB-4en-PINACA from China to other EU Member States, such as Hungary, the Netherlands, Romania and the United Kingdom.

²⁸ The U.S. DEA reported seizures of MDMB-4en-PINACA in 2020. The substance was mixed with fentanyl, heroin, tramadol and cocaine. The substance was seized in powder, plant and tablet form.

²⁹ New Zealand reported a seizure of 500 grams of MDMB-4en-PINACA, by customs, on 9 June 2020. The substance was identified in air cargo which was en-route from China and it was also reported that it is likely that the MDMB-4en-PINACA was produced there. New Zealand indicated that the amount of MDMB-4en-PINACA seized could be used to prepare at least one million doses and it was noted that MDMB-4en-PINACA is incorrectly known as 5-CL-ADB-A and has been described as both a white and yellow-brown powder (internationally).

Bulgaria reported that MDMB-4en-PINACA was identified in 1 gram seized by customs in 2020. The substance was detected in a courier parcel.

France reported a few seizures of MDMB-4en-PINACA by customs in recent months. MDMB-4en-PINACA was identified in 1.008 kilograms of beige powder seized by customs at Roissy Airport, on 8 August 2020. The substance was contained in a heat-sealed bag, labelled as 'polypropylene pigment12 (Yellow), HS 3213100000', which was en-route via express freight, from China to Hungary. MDMB-4en-PINACA was also identified in five seizures at St Denis Airport, in Reunion since June 2020. The five seizures amounted to a total of 2.073 grams which were en-route, via express freight, from China to Reunion.

France also highlighted that MDMB-4en-PINACA has in recent months been identified in 'La Chimique', a term given to plant/herbal material which had been mostly found to contain the synthetic cannabinoids AB-CHIMINACA, AB-FUBINACA. They reported that following the national lockdown in France, as a result of Covid-19, seizures of 'La Chimique' were subsequently found to contain the synthetic cannabinoids MDMB-4en-PINACA, 4F-MDMB-BINACA and 5F-MDMB-PICA. 'La Chimique' is reportedly ordered online and delivered by post from China and is considered to be popular amongst young people (18 and 25 years old) in both the Mayotte and Reunion region of France.

Latvia reported that MDMB-4en-PINACA was identified in 7 seizures in the first 6 months of 2020. Whilst no information was available on the origin of the substance, they noted that detections occurred within one district, suggesting a single distributor of MDMB-4en-PINACA in that region.

Portugal did not report any seizures of MDMB-4en-PINACA by police however they reported a case of MDMB-4en-PINACA, from 4 January 2020, associated with hospital admissions of some individuals.

Romania reported that MDMB-4en-PINACA has been identified since between April and May 2020, in plant/herbal material or powder form.

Slovakia reported that MDMB-4en-PINACA was identified with 4F-MDMB-BICA and A-CHMINACA⁽³⁰⁾ in yellow crystalline material, contained in 2 plastic tubes, seized in postal consignments en-route from the Netherlands to Hong Kong, in September 2020.

Slovenia reported two seizures of 3.34 grams and 0.3 grams of MDMB-4en-PINACA in plant material, which occurred in a prison, on 25 August 2020.

In addition, the US DEA reported seizures of MDMB-4en-PINACA in 2020. The substance was mixed with fentanyl, heroin, tramadol and cocaine. The substance was seized in powder, plant and tablet form.

New Zealand reported a seizure of 500 grams of MDMB-4en-PINACA, by customs, on 9 June 2020. The substance was identified in air cargo which was en-route from China and it was also reported that it is likely that the MDMB-4en-PINACA was produced there. New Zealand indicated that the amount of MDMB-4en-PINACA seized could be used to prepare

³⁰ *N*-(1-adamantyl)-1-(cyclohexylmethyl)indazole-3-carboxamide

at least one million doses and it was noted that MDMB-4en-PINACA is incorrectly known as 5-CL-ADB-A and has been described as both a white and yellow-brown powder.

3.5. Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product

Based on the reported information from the EMA ⁽³¹⁾, it appears that MDMB-4en-PINACA is not an active substance in:

- a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/ EC of the European Parliament and of the Council, Directive 2001/82/EC of the European Parliament and of the Council or Regulation (EC) No 726/2004 of the European Parliament and of the Council;
- b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;
- c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority.

In addition, it appears that MDMB-4en-PINACA is not an active substance in the following, although the information, especially in relation to use in extemporaneously prepared products, is unknown in some cases:

- d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/ EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;
- e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council.

3.6. Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes

MDMB-4en-PINACA is used as an analytical reference material in clinical and forensic case work as well as scientific research. There is currently no information that suggests MDMB-4en-PINACA is used for other legitimate purposes.

ECHA and EFSA reported that MDMB-4en-PINACA did not retrieve any results in their databases.

³¹ 26 Member States, as well as Norway and Iceland provided a response to the EMA's request regarding human and/or veterinary medicinal products.

3.7. Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States

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

Drug control legislation

Nine Member States (Croatia, Cyprus, Finland, France, Latvia, Luxembourg, Poland, Sweden, and the United Kingdom) and Turkey reported that MDMB-4en-PINACA is controlled under drug control legislation.

- Croatia reported that MDMB-4en-PINACA is controlled within the List of drugs, psychotropic substances and plants used to produce drugs, and substances that can be used for the production of drugs (OG 13/19) since 2016.
- Cyprus reported that MDMB-4en-PINACA is controlled under drug control legislation (generic legislation) since 15 June 2018.
- Finland reported that MDMB-4en-PINACA is covered by the Government degree on psychoactive substances banned from the consumer market (1130/2014) since 15 August 2019.
- France reported that MDMB-4en-PINACA is controlled under drug control legislation (NOR: AFSP1710288A) since 31 March 2017.
- Latvia reported that MDMB-4en-PINACA is controlled under drug control legislation (the Law on Procedures for the Coming into force and Application of the Criminal Law) since 2013.
- Luxembourg reported that MDMB-4en-PINACA is controlled under drug control legislation (RGD du 20 avril 2009 modifiant le RGD modifié du 20 mars 1974 concernant certaines substances psychotropes) since 2009.
- Poland reported that MDMB-4en-PINACA is covered by generic definition of synthetic cannabinoids (Regulation of the Minister of Health on Regulation of the Minister of Health on list of psychotropic drugs, psychoactive substances and new psychoactive substances; main act: Act on Counteracting Drug Addiction) since July 2018.
- Sweden reported that MDMB-4en-PINACA is regulated as a narcotic since 11 February 2020.
- United Kingdom reported that MDMB-4en-PINACA is controlled under the Misuse of Drugs Act 1971 since 02 December 2016.
- Turkey reported that MDMB-4en-PINACA is included in Law on Drug Control No. 2313 (taken automatically under legal control with the generic legislation as the NPS detected in the country) as of March 2019.

New psychoactive substance legislation

Four Member States (Austria, Belgium, Germany, and Hungary) reported that MDMB-4en-PINACA is controlled under specific new psychoactive substances control legislation.

- Austria reported that MDMB-4en-PINACA is covered by the Austrian Act on New Psychoactive Substances.
- Belgium reported that MDMB-4en-PINACA is controlled under Belgian Generic Legislation, active since September 2017.
- Germany reported that MDMB-4en-PINACA is covered by the New Psychoactive Substances Act (NpSG).
- Hungary reported that MDMB-4en-PINACA is controlled under specific NPS control legislation (Regulation 55/2014 (XII.30) of the Ministry of Human Capacities).

Medicines legislation

Lithuania and Norway reported that MDMB-4en-PINACA is controlled under medicines legislation.

- Lithuania reported that MDMB-4en-PINACA is controlled under medicines legislation (falls under the definition of the generic group of synthetic cannabinoids) since 21 September 2015.
- Norway reported that MDMB-4en-PINACA is controlled under the Norwegian Law of Medicines.

3.8. Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific, and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

On 1 October 2020, the WHO informed the EMCDDA that MDMB-4en-PINACA will be assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held on 12–16 October 2020. At the time of writing this report a critical review had been published, however, a written recommendation had not been published.

During the data collection process, significant new data have been reported to the EMCDDA to suggest the need for a risk assessment at Union level. In particular, information on recent large scale seizures and health harms associated with MDMB-4en-PINACA indicate that MDMB-4en-PINACA might pose health and social threat at Union level.

3.9. Other relevant information

United Kingdom

In the United Kingdom, 84 samples containing MDMB-4en-PINACA were submitted to WEDINOS ⁽³²⁾ between August 2019 and September 2020. Of these, 76 samples (90%) were submitted in 2020. 57 (68%) of the samples submitted to WEDINOS were herbal material. The self-reported effects from users were consistent with synthetic cannabinoids, and included euphoria, relaxation, chest pains, irregular heartbeat, vomiting, confusion, agitation, auditory and visual hallucinations, and paranoia (WEDINOS, 2020).

Switzerland

In Switzerland, the drug checking service Saferparty reported 37 samples of cannabis adulterated with MDMB-4en-PINACA between May and September 2020. Nineteen samples contained other synthetic cannabinoids such as 5F-MDMB-PICA, 4F-MDMB-BINACA, 5F-ADBICA-A, 4F-MDMB-BICA and THJ-018 (Saferparty, 2020).

United States

In the United States, the Centre for Forensic Science Research and Education (CFSRE) reported the first identification of MDMB-4en-PINACA in July 2019. The report was related to two biological samples from post-mortem investigations from 2019. In one case the synthetic cannabinoid 5F-MDMB-PICA was also identified (NPS Discovery, 2019).

MDMB-4en-PINACA has been identified in 25 forensic toxicology cases in the United States. The majority of cases (n = 16, 64%) were submitted from postmortem investigations, followed by eight cases from suspected clinical toxicology investigations, and one case from an impaired driving investigation. The samples were collected between May 2019 and March 2020 and were from many regions across the United States. In seven cases, MDMB-4en-PINACA was the only drug reported, excluding incidental findings (e.g., caffeine and nicotine). Based on information from the death investigations, two death cases happened in prison settings and one case involved homeless individual. Authors reported that results from toxicology testing paired with case history show the potential for MDMB-4en-PINACA to cause or contribute to impairment or death (Krotulski et al., 2020).

4. Analysis and assessment

Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA) is a synthetic cannabinoid receptor agonist monitored by the EMCDDA as a new psychoactive substance in accordance with Regulation (EC) No 1920/2006 (as amended).

MDMB-4en-PINACA has been available on the drug market in Europe since at least 2017. The substance is sold as a 'legal' replacement for cannabis and other controlled synthetic cannabinoids. Limited information suggests that MDMB-4en-PINACA is a potent CB₁

³² WEDINOS is a drug testing service in the United Kingdom operated by Public Health Wales. http://www.wedinos.org/about_us.html

receptor agonist, and, as such, shares some pharmacological similarities with Δ^9 -tetrahydrocannabinol (THC), which is responsible for the major psychoactive effects of cannabis, and other synthetic cannabinoids, such as JWH-018, which are under international control.

The available information suggests that MDMB-4en-PINACA is manufactured by chemical companies based in 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 consumers products. There are three main types of products containing MDMB-4en-PINACA that are sold on the drug market: smoking mixtures, where MDMB-4en-PINACA is mixed with herbal plant material or tobacco that is then smoked or inhaled from a vaporiser (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint')); e-liquids, where a solution of MDMB-4en-PINACA is prepared by mixing it with a solvent, which is then vaped using an electronic cigarette; in addition, MDMB-4en-PINACA is 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, users may prepare their own similar products using MDMB-4en-PINACA purchased from a vendor or dealer.

As of October 2020, MDMB-4en-PINACA has been identified in twenty Member States as well as Turkey and Norway; 768 seizures have been reported, which includes 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 94% of the total amount of powder (44 kg) seized by customs during the year.

A total of eleven acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA have been reported by one Member State, 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 reported to be life-threatening and required hospitalisation of the patient.

A total of four deaths with confirmed exposure to MDMB-4en-PINACA have been reported by two Member States, Sweden and the United Kingdom. The deaths occurred between January 2019 and June 2020. In three 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 the presence of MDMB-4en-PINACA on the drug market and in serious adverse events may be undetected in Europe since the substance is not routinely screened for in some laboratories.

The available data suggests that MDMB-4en-PINACA may be used by cannabis users, by those who are regularly subjected to drug testing procedures (including those in prison), and by people who self-experiment with a range of psychoactive substances (so-called 'psychonauts'). MDMB-4en-PINACA may also be used by high risk drug users and other marginalised groups, such as people experiencing homelessness and prisoners, as

synthetic cannabinoids are typically readily available, and have gained a reputation for causing profound intoxication while being comparatively cheaper to other drugs. In addition, synthetic cannabinoids can be easy to smuggle into the prison environment. Although limited, there is some information to suggest a recent increase in vaping of synthetic cannabinoids using electronic cigarettes, including MDMB-4en-PINACA, by young people, including teenagers, in some Member States.

Because of their high potency and the unintentionally high doses that users may be exposed to, synthetic cannabinoids can pose a high risk of severe poisoning, which in some cases can be fatal. These factors can also be responsible for the outbreaks of mass poisonings seen with synthetic cannabinoids. Such outbreaks have the potential to overwhelm local healthcare systems, which is of particular concern given the ongoing COVID-19 pandemic and the additional burden already on healthcare systems. There is no approved antidote to poisoning caused by synthetic cannabinoids.

In prisons, alongside the adverse health effects, the market in 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 that six Member States reported seizures of MDMB-4en-PINACA in prisons and other custodial settings, and, that overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings.

There is no information whether or not criminal groups are involved in the manufacture, trafficking, and distribution of MDMB-4en-PINACA within Europe. However, based on information reported to the EMCDDA, there is evidence of criminal acts, such as supply offences, involving MDMB-4en-PINACA.

The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution, and use of MDMB-4en-PINACA is currently unknown. However, seizures of more than 44 kg of bulk powders by a European national customs agency during the pandemic suggests that attempts at large-scale importation into and distribution within Europe are continuing. It is also possible, that in case of a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including MDMB-4en-PINACA.

Based on the available information, it appears that MDMB-4en-PINACA is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe. However, 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 due to a lack of information. Aside from limited use as an analytical reference standard and in scientific research, there is currently no information that suggests MDMB-4en-PINACA is used for other legitimate purposes.

MDMB-4en-PINACA is subject to restrictive measures in fourteen Member States, Turkey, and Norway. 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.

MDMB-4en-PINACA is under assessment within the United Nations system. It will be assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in October 2020. At the time of writing this initial report, a critical review had

been published, however, a written recommendation had not. During the initial report process, significant new information was reported by the Member States to the EMCDDA that provides further evidence that MDMB-4en-PINACA might pose health and social threats at Union level. This includes seizures of large quantities of bulk powder of MDMB-4en-PINACA made in the last few months and recent cases of severe poisonings and deaths involving the substance in Europe.

Based on the information reported to the EMCDDA, there are indications that MDMB-4en-PINACA has the potential to continue to rapidly spread in Europe. Of note is that, similar to 4F-MDMB-BICA, which is also currently the subject of an initial report, 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.

The EMCDDA will continue to intensively monitor MDMB-4en-PINACA in order to ensure that new information is provided to the Member States, Europol, the Commission, and the EMA through the European Union Early Warning System in a timely manner in order to strengthen situational awareness as well as to continue to inform preparedness and response measures at both national and EU level in order to protect public health.

Based on the analysis of the available information, the EMCDDA considers that there are indications that MDMB-4en-PINACA may pose health or social risks at Union level. We conclude that the potential health and social risks posed by the use, manufacture, distribution and the involvement of criminal groups, could be thoroughly assessed through a risk assessment procedure in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended).

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