Critical Review Report:

MDMB-4en-PINACA

Expert Committee on Drug Dependence
Forty-third Meeting
Geneva, 12–20 October 2020

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

MDMB-4en-PINACA (CAS: not available), methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate, is a synthetic cannabinoid with an indazole core and a terminal alkene on the side-chain. It is structurally similar to 5F-MDMB-PINACA (5F-ADB). MDMB-4en-PINACA has a chiral centre. The enantiomers have not been separated experimentally, but the S-enantiomer has been identified in samples. The compound is not readily converted into other controlled substances and has not been previously reviewed by the WHO Expert Committee on Drug Dependence.

The most likely routes of administration for MDMB-4en-PINACA in humans are inhalation via smoking the chemical after it has been sprayed onto plant material or vaping it after formulation in liquid. It has been identified in seized material formulated for smoking. The dosage required to elicit pharmacological effects in humans is unknown. With the exception of two studies, scientific investigation of MDMB-4en-PINACA has been sparse. These two studies focused on identification of biomarker(s) that could serve in forensic investigations as indicators of use. Like many other synthetic cannabinoids, MDMB-4en-PINACA is extensively metabolized. However, unlike many other synthetic cannabinoids, the parent product has been identified in authentic urine samples. Analysis of human liver microsomes, hepatocytes and authentic urine samples showed that M3 (C\textsubscript{19}H\textsubscript{27}N\textsubscript{3}O\textsubscript{5}) was the most abundant metabolite.

MDMB-4en-PINACA binds to human cannabinoid type 1 (hCB\textsubscript{1}) receptors with a K\textsubscript{i} of 3.26 nM. Further, it is a full and potent agonist, decreasing forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP) (half maximal effective concentration (EC\textsubscript{50}) = 0.33 nM). No reports of in vivo pharmacological or toxicological effects of MDMB-4en-PINACA have been published. Unpublished data suggest that MDMB-4en-PINACA produces substantial lethargy and hypothermia at higher doses (1–10 mg/kg). No studies demonstrating its abuse or dependence potential were identified.

In humans, MDMB-4en-PINACA has been detected in postmortem femoral vein blood samples taken following two deaths; however, the degree to which the drug contributed to the deaths could not be determined. MDMB-4en-PINACA has also been detected in products marketed as heroin and cannabis in the United States of America and in Wales.

MDMB-4en-PINACA was first identified in Europe in 2017. Since then, prevalence has increased dramatically, with the largest number of seizures reported in 2019, and a recent seizure in February 2020. Further, MDMB-4en-PINACA has been detected in Asia (3 countries), the European Union (17 countries), New Zealand, the Russian Federation and the United States of America. Currently, MDMB-4en-PINACA is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. It is under national control in Canada, Germany, Sweden and the United Kingdom.
1. Substance identification
   A. *International Nonproprietary Name (INN)*
      NA
   B. *Chemical Abstract Service (CAS) Registry Number*
      None available
   C. *Other chemical names*
      MDMB-PENINACA
      MDMB-PINACA N1-pentyl-4-en isomer
      5-CL-ADB-A
      ADB-PINACA-A
   D. *Trade names*
      NA
   E. *Street names*
      Reported in product labelled “Heavy Weight” (unpublished certificate of analysis from Commonwealth of Massachusetts, Department of State Police, February 2020). This product also contained other substances, including fentanyl.
   F. *Physical appearance*
      MDMB-4en-PINACA is described as a powder (1) white powder (2, 3); yellow/brown powder (3); tan powder (unpublished certificate of analysis from Commonwealth of Massachusetts, Department of State Police, February 2020).
   G. *WHO review history*
      MDMB-4en-PINACA has not previously been reviewed by the WHO Expert Committee on Drug Dependence (ECDD). It is classified as a high priority submission for the forty-third annual meeting of the ECDD.

2. Chemistry
   A. *Chemical name*
      IUPAC name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate
      CA Index name: NA
B. Chemical structure

![Chemical structure of MDMB-4en-PINACA]

**Molecular formula:** $C_{20}H_{27}N_3O_3$

**Molecular weight:** 357.5 g/mol

C. Stereoisomers

MDMB-4en-PINACA has one chiral centre, with two enantiomers (S and R). The S-enantiomer has been synthesized as an in-house standard for forensic analysis (4); however, it was unclear whether the samples analysed contained only this enantiomer or the racemate.

D. Methods and ease of illicit manufacturing

No information is available on methods for synthesis or ease of illicit manufacturing.

E. Chemical properties

- Melting point
  - No data

- Boiling point
  - No data

- Solubility
  - Soluble in CH$_2$Cl$_2$, MeOH and H$_2$O. (1)

F. Identification and analysis

Various methods have been used to identify and/or analyse MDMB-4en-PINACA. They include gas chromatography-mass spectrometry (GC-MS) (1, 4), high-performance liquid chromatography-time of flight (HPLC-TOF) (1), ultra-high-pressure liquid chromatography with photodiode array and quadrupole time of flight mass spectrometry (UPLC-PDA-QToF-MS) (4), nuclear magnetic resonance (NMR) spectroscopy (4), liquid chromatography and quadrupole time of flight mass spectrometry (LC-QToF-MS) (2), and liquid chromatography-high-resolution mass spectrometry (LC–HRMS) (5).
3. **Ease of convertibility into controlled substances**

Convertibility into a controlled, but non-cannabinoid substance, is unlikely.

4. **General pharmacology**

   **A. Routes of administration and dosage**

   MDMB-4en-PINACA has been identified in herbal material obtained for research from online purchases or law enforcement seizures (5). Most users who have posted on the effects of MDMB-4en-PINACA in online forums report that they smoked or vaped the product containing the compound and one reported sublingual administration (6).

   Recently, Norman et al. (4) reported analysis and identification of MDMB-4en-PINACA infused onto paper that was mailed to inmates in Scottish prisons. Since the ban on smoking in prisons, inmates had been inserting small pieces of paper infused with MDMB-4en-PINACA and other synthetic cannabinoids into their e-cigarette devices for subsequent vaping. Concentration of MDMB-4en-PINACA on a single card ranged from <0.07–0.58 mg/cm$^2$. The dosage of MDMB-4en-PINACA required to elicit pharmacological effects in humans is unknown.

   **B. Pharmacokinetics**

   No information on the absorption and distribution of MDMB-4en-PINACA is available. Two studies have examined its metabolism, with an emphasis on the identification of biomarker(s) that could serve during forensic investigations as indicators of use. Like many other synthetic cannabinoids, MDMB-4en-PINACA is extensively metabolized. However, unlike many other synthetic cannabinoids, the parent product has also been detected in authentic urine samples (2, 5). Analysis of human liver microsomes revealed 14–31 phase I metabolites resulting from various chemical reactions, including ester hydrolysis, double-bond oxidation and hydroxylation (2, 5). Follow-up analysis of authentic human urine samples showed that M3 (C$_{19}$H$_{27}$N$_{3}$O$_{5}$) was the most abundant metabolite (5).

   **C. Pharmacodynamics**

   MDMB-4en-PINACA binds to human cannabinoid type 1 (hCB$_1$) cannabinoid receptors (expressed in human embryo kidney cells), with $K_i$ (CB$_1$) = 3.26 ± 0.81 nM (7). When evaluated for functional activation of the CB$_1$ receptor, MDMB-4en-PINACA was shown to be a full and potent agonist, decreasing forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP): half maximal effective concentration ($EC_{50}$) = 0.33 ± 0.11 nM; $E_{max}$ = 112.7 ± 5.5% (7).

   To date, no reports on the in vivo effects of MDMB-4en-PINACA have been published; however, an unpublished preclinical study tested the compound in male ICR mice ($n = 6$) (Wiley JL and Marusich JA. RTI International, Durham, NC, USA, unpublished data). In this experiment, MDMB-4en-PINACA (0.1, 1 or 10 mg/kg) was injected intraperitoneally. Rectal temperature was measured at 30, 45 and 60 minutes post-injection and overt behaviour was observed over the same period. Whereas the dose of 0.1 mg/kg did not reduce temperature at any time point, 1 and 10 mg/kg decreased temperature, with maximal decreases of $-4.6 ± 0.62$ °C and $-8.15 ± 0.41$ °C, respectively. In addition, some mice that received either 1 or 10 mg/kg were lethargic and exhibited seizures upon handling. At 1 mg/kg, cage behaviour normalized within 2 hours; however, at 10 mg/kg, mice were still
lethargic at 5 hours post-injection. The 10 mg/kg dose also led to gasping and aggression in some mice. These effects had worn off by 3 hours post-injection.

5. Toxicology

No preclinical toxicology studies on MDMB-4en-PINACA have been conducted.

6. Adverse reactions in humans

Although adverse reactions to MDMB-4en-PINACA have not been widely reported, some information was available. For example, analysis of postmortem femoral vein blood samples by the Center for Forensic Science Research and Education (Willow Grove, PA; 12 September 2019) following two deaths, revealed the presence of MDMB-4en-PINACA. However, the degree to which the drug contributed to the deaths could not be confirmed, as circumstances related to the deaths were not reported. Bizarre and impulsive behaviour following consumption of heroin that had been cut with MDMB-4en-PINACA was reported by Massachusetts Police in Holyoke (8). Although the United Nations Office on Drugs and Crime (UNODC) Tox-Portal was searched, no cases related to MDMB-4en-PINACA were identified.

Of the user forums searched, Reddit (sub-reddit r/noids) contained the most information about user-reported effects (6). Users reported cannabis-like euphoria at moderate levels of intake, with dissociation occurring at higher concentrations. Some users reported sedation whereas others reported stimulation. Memory loss, confusion and agitation have also been reported by some users (9).

7. Dependence potential

A. Animal studies

No in vivo animal studies to evaluate the dependence potential of MDMB-4en-PINACA have been conducted.

B. Human studies

No human studies to evaluate the dependence potential of MDMB-4en-PINACA have been conducted.

8. Abuse potential

A. Animal studies

No animal studies on the abuse potential of MDMB-4en-PINACA have been published. However, unpublished drug discrimination data (Wiley JL and Marusich JA, RTI International, Durham, NC, USA, unpublished data) show that intraperitoneal MDMB-4en-PINACA substituted for Δ^9-tetrahydrocannabinol (THC) in male (n = 8) and female (n = 2) C57/Bl6 mice trained to discriminate 5.6 mg/kg THC (intraperitoneal) from vehicle in a two nose-poke drug discrimination procedure. Substitution was dose-dependent, with maximal substitution (97% THC-aperture responding) occurring at 0.1 mg/kg and was not accompanied by effects on response rates. The ED_{50} for THC-like discriminative stimulus effects for MDMB-4en-PINACA was 0.071 µmol/kg.
B. Human studies

No human studies to evaluate the dependence potential of MDMB-4en-PINACA have been conducted.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

NA

10. Listing on the WHO Model List of Essential Medicines

MDMB-4en-PINACA is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

MDMB-4en-PINACA has no marketing authorizations as a medicinal product.

12. Industrial use

NA

13. Nonmedical use, abuse and dependence

MDMB-4en-PINACA was first identified in Europe in 2017 (10). Since then, prevalence has increased dramatically, with the largest number of seizures (143 cases (89%)) reported in 2019 and a recent seizure in February 2020 (10). As of August 2020, more than 70 product samples had been submitted and found to contain MDMB-4en-PINACA by the Welsh Emerging Drugs and Identification of Novel Substances Project (Wedinos.org) (9). Whereas most samples contained only MDMB-4en-PINACA, a few samples contained additional substances, including nicotine, 5F-MDMB-BINACA, flubromazolam or pregabalin. Other specific information on MDMB-4en-PINACA use/abuse was not found.

The prevalence of chronic use and dependence on MDMB-4en-PINACA has not been reported.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Specific information on the nature and magnitude of public health problems associated with use of MDMB-4en-PINACA is not available. Adverse effects reported by individual users have been described in section 6 of this document.

15. Licit production, consumption and international trade

NA

16. Illicit manufacture and traffic and related information

MDMB-4en-PINACA has been detected in 17 countries in the European Union: Austria, Belgium, Bulgaria, Cyprus, France, Germany, Hungary, Latvia, Lithuania, the Republic of Moldova, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey and the United Kingdom (10, 11). Of these countries, 12 (70%) reported the identification of the substance for the first time in 2019 (10). Identification of MDMB-4en-PINACA has also been reported
in Asia (China, Kyrgyzstan and Singapore) (11), the Russian Federation (11), New Zealand (3) and the United States (11).

Information provided by the WHO ECDD confirmed traffic to the United States. For example, a situation report from the United States District of Columbia Department of Forensic Science (dated 16 December 2019) stated that MDMB-4en-PINACA had been identified for the first time in Washington, DC. Similarly, a report from the Center for Forensic Science Research and Education (Willow Grove, PA; 12 September 2019) analysed postmortem biological fluid taken in July 2019 from two individuals in Indiana and reported the presence of MDMB-4en-PINACA.

17. Current international controls and their impact

MDMB-4en-PINACA is not currently under international control.

18. Current and past national controls

Sweden entered MDMB-4en-PINACA into its list of controlled substances in 2018. It is also controlled in Canada, Germany and the United Kingdom.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

MDMB-4en-PINACA has been detected as an adulterant in substances marketed as heroin or cannabis/THC (8, 9, 12).
References


Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 35 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on MDMB-4en-PINACA

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of countries without information</th>
<th>Number of countries with information on substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Region</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>European Region</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total 92</td>
<td>57</td>
<td>35</td>
</tr>
</tbody>
</table>

LEGITIMATE USE

No countries reported approved human medical products or veterinary products containing MDMB-4en-PINACA.

One country (Region of the Americas) reported MDMB-4en-PINACA being currently used in medical or scientific research (excluding use as an analytical standard), specifically in cell line studies (binding/functional assays) and animal studies.

Two countries (one European Region, one Western Pacific Region) reported MDMB-4en-PINACA being used in industrial or other non-medical or non-scientific use.

No countries reported approved therapeutic indications for MDMB-4en-PINACA.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Sixteen countries reported that MDMB-4en-PINACA is being misused or abused for its psychoactive properties/recreational use.
The most common known route of administration reported was smoking (Table 2).

Table 2. Common routes of administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td>Injection</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation</td>
<td>2</td>
</tr>
<tr>
<td>Sniffing</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>14</td>
</tr>
<tr>
<td>Don’t know</td>
<td>18</td>
</tr>
</tbody>
</table>

The most common known formulation of MDMB-4en-PINACA reported was powder (Table 3).

Table 3. Common formulations reported by countries

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>9</td>
</tr>
<tr>
<td>Tablets</td>
<td>0</td>
</tr>
<tr>
<td>Liquid for oral use</td>
<td>2</td>
</tr>
<tr>
<td>Solution for injection</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>16</td>
</tr>
</tbody>
</table>

To the above, countries added:
- herbal material/paper
- plant mixture sprayed with active substance
- solution for smoking – e-liquid
- blotters.

Eleven countries reported the level of negative health impact due to MDMB-4en-PINACA’s non-medical consumption as “serious” or “substantial” (Table 4).

Table 4. Numbers of countries reporting levels of negative health impact of MDMB-4en-PINACA

<table>
<thead>
<tr>
<th>Serious</th>
<th>Substantial</th>
<th>Negligible</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

One country (Western Pacific Region) stated, “The social harm caused by MDMB-4en-PINACA is substantial”. Another country (European Region) reported “use by minors (15 years for the youngest) with electronic cigarettes (e-liquid)”. Another country (European Region) was concerned that “… there may be unknown cases of negative health impacts because … there is no reporting obligation by hospitals, poison centers, etc.”. One country (European Region) reported, “Recent increase in use, reflected in increase in emergency room visits and increase in seizures.”
Mainly used by the population of 'high-risk' and homeless drug users in combination with other substances”. One country (Region of the Americas) stated, “MDMB-4en-PINACA has been identified in seized drug evidence both alone and mixed with fentanyl and/or heroin. It has also been associated with overdoses.”

Five countries (four European Region, one Region of the Americas) reported emergency room admissions related to the non-medical use of MDMB-4en-PINACA.

Several countries reported specific adverse effects. One country (European Region) listed the adverse effects as “drowsiness, dizziness, nausea, pallor, derealization, euphoria, visual disturbances (‘zoom’)”. However, they also noted the difficulty specifying the adverse effects associated with MDMB-4en-PINACA because of multiple drug use. Another country (European Region) reported “agitation, anxiety, hallucination, convulsions, tachycardia and large pupils”. A third country (Region of the Americas) noted “body/muscle spasms similar to seizure, violence towards EMS personnel, tachycardia, PCP-like adverse effects, hypertension, erratic behavior”.

No countries reported users of MDMB-4en-PINACA presenting for drug dependence treatment.

Regarding mortality, only two countries (two European Region) reported deaths involving MDMB-4en-PINACA:
- one fatal case where other substances were also involved (2019)
- one fatal case where this substance was the only substance involved (2019).

**STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL**

Nineteen countries responded that MDMB-4en-PINACA is currently controlled under national legislation to regulate its availability.
Table 5 shows the main reported activities involving MDMB-4en-PINACA.

**Table 5. Reported illicit activities involving MDMB-4en-PINACA**

<table>
<thead>
<tr>
<th>Activities</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smuggling from other countries</td>
<td>8</td>
</tr>
<tr>
<td>Manufacture of substance by chemical synthesis</td>
<td>1</td>
</tr>
<tr>
<td>Manufacture of substance by extraction from other products</td>
<td>0</td>
</tr>
<tr>
<td>Production of consumer products containing the substance</td>
<td>2</td>
</tr>
<tr>
<td>Trafficking</td>
<td>5</td>
</tr>
<tr>
<td>Diversion from legal supply chain</td>
<td>0</td>
</tr>
<tr>
<td>Internet sales – seller or website located in country</td>
<td>2</td>
</tr>
<tr>
<td>Internet sales – from abroad to buyers in country</td>
<td>2</td>
</tr>
<tr>
<td>Internet sales – other, or location of sellers and website unknown</td>
<td>4</td>
</tr>
<tr>
<td>Direct sales to people who use the substance</td>
<td>3</td>
</tr>
<tr>
<td>Don’t know</td>
<td>20</td>
</tr>
</tbody>
</table>

In addition to the above, countries added:
- trafficking through postal services
- seizures in prisons.

Fifteen countries reported seizures (Table 6).

**Table 6. Reported seizures of MDMB-4en-PINACA**

<table>
<thead>
<tr>
<th>Year</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>554</td>
</tr>
<tr>
<td>2019</td>
<td>1321</td>
</tr>
<tr>
<td>2018</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>1888</td>
</tr>
</tbody>
</table>

Twenty-eight countries have the forensic laboratory capacity to analyse MDMB-4en-PINACA.