

**AB-CHMINACA**  
**Critical Review Report**  
**Agenda Item 4.1**

**Expert Committee on Drug Dependence**  
**Thirty-ninth Meeting**  
**Geneva, 6-10 November 2017**



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WHO would like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for providing information on AB-CHMINACA from the European Union Early Warning System, which includes data reported by the Reitox National Focal Points in the EU Member States, Turkey, and Norway.

## Summary

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AB-CHMINACA is a synthetic cannabinoid receptor agonist (SCRA) with an aminoalkylindazole structure used as an active ingredient of products sold as cannabis substitutes. AB-CHMINACA has no known therapeutic or medical use. In different regions it is being used and abused for non-medical purposes. Furthermore, some countries have put AB-CHMINACA under national control.

When smoked, AB-CHMINACA produces cannabimimetic effects like  $\Delta^9$ -tetrahydrocannabinol (THC). Doses needed to produce these effects are much lower than for THC. Many of the risks linked to cannabis use are also present in the case of AB-CHMINACA, among them complications in patients suffering from cardiovascular diseases and triggering of acute psychosis. The abuse potential seems to be higher than for other SCRAs.

## 1. Substance identification

### A. *International Nonproprietary Name (INN)*

Not applicable

### B. *Chemical Abstract Service (CAS) Registry Number*

1805788-79-7      AB-CHMINACA racemate  
1185887-21-1      (S)-AB-CHMINACA

### C. *Other Chemical Names*

*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide

*N*-(1-carbamoyl-2-methyl-propyl)-1-(cyclohexylmethyl)-indazole-3-carboxamide

*N*-[(1*S*)-1-carbamoyl-2-methyl-propyl]-1-(cyclohexylmethyl)-indazole-3-carboxamide (*S* enantiomer)

### D. *Trade Names*

None

### E. *Street Names*

Spice, K2, legal weed, synthetic cannabis, herbal incense are common terms for SCRAAs containing products.

AB-CHMINACA has been detected in the following brands: Red Dub Herbal Blend, Vertex Pirate edition, Vertex Space cadet. <sup>1</sup>

Mixtures sold under specific brand names do not always contain the same substance or mixture of substances over time.

### F. *Physical Appearance*

White crystalline solid (in pure form)

### G. *WHO Review History*

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

Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

## 2. Chemistry

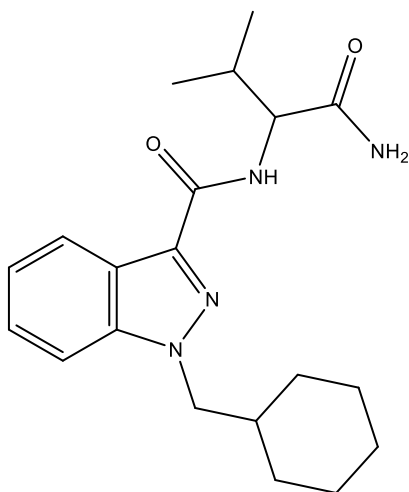
### A. Name

**IUPAC Name:** N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide

**CA Index Name:** N-[1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide;  
N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (S enantiomer)

### B. Chemical Structure

**Free base: Chemical**



**Molecular Formula:** C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>  
**Molecular Weight:** 356.47

### C. Stereoisomers

AB-CHMINACA contains a chiral center at the C-2 carbon of the oxobutan-2-yl sidechain, so that two enantiomers exist: R- AB-CHMINACA and S-AB-CHMINACA. Based on the literature and the most likely precursors to be used, an (S)-configuration of the stereocenter could be expected.

AB-CHMINACA also has a positional isomer, where the cyclohexylmethyl tail is attached to the nitrogen at position 2 of the indazole.<sup>2</sup> It is unknown whether this positional isomer represents a manufacturing impurity or was intentionally synthesized.



#### ***D. Methods and Ease of Illicit Manufacturing***

The synthesis of (S)-AB-CHMINACA was first described in a 2009 patent.<sup>3</sup> The starting compound is methyl-1H-indazole-3-carboxylate, which is commercially available and can be prepared from 1H-indole-2,3-dione.<sup>4</sup>

More recently, the synthesis of (S)-AB-CHMINACA has been described by Longworth et al.<sup>2</sup> The synthesis started with 1H-indazole-3-carboxylic acid, which was subjected to Fischer esterification to give the corresponding methyl ester (methyl 1H-indazole-3-carboxylate). Alkylation of the ester with the appropriate bromoalkane ((bromomethyl)cyclohexane), in the presence of potassium tert-butoxide produced methyl 1-(cyclohexylmethyl)-1H-indazole-3-carboxylate. Saponification of the ester gave the acid 1-(cyclohexylmethyl)-1H-indazole-3-carboxylic acid, which was then reacted with L-valinamide to produce (S)-AB-CHMINACA.

#### ***E. Chemical Properties***

Melting point: 88.5-92.5° C

Boiling point: not available

Solubility: AB-CHMINACA is soluble in organic solvents such as ethanol, dimethyl sulfoxide and dimethyl formamide. The solubility of AB-CHMINACA in these solvents is approximately 3, 10 and 5 mg/ml respectively. AB-CHMINACA is sparingly soluble in aqueous buffers.<sup>5</sup>

#### ***F. Identification and Analysis***

Quantification of AB-CHMINACA in products can be carried out according to the general procedure described by United Nations Office on Drugs and Crime (UNODC).<sup>6</sup>

The analytical profile of AB-CHMINACA has been described in various papers. Utilized methods include gas chromatography–mass spectrometry (GC-MS)<sup>7, 8, 9, 10</sup>, liquid chromatography–tandem mass spectrometry (LC-MS)<sup>8, 10</sup>, fourier-transform infrared spectroscopy (FTIR)<sup>2, 9</sup>, nuclear magnetic resonance spectroscopy (NMR)<sup>2, 3, 9</sup>, ultraviolet–visible spectroscopy (UV-VIS)<sup>9</sup>, mass spectrometry (both high and low resolution)<sup>2</sup> and direct analysis in real time (DART-MS) and liquid chromatography/electrospray ionization quadrupole time-of-flight mass spectrometry.<sup>11</sup>

Detection of AB-CHMINACA in biological matrices was described in serum<sup>12, 13</sup>, whole blood<sup>14</sup> and hair<sup>15</sup>. In urine samples, the main metabolites are the analytical targets.<sup>16, 17</sup>

### **3. Ease of Convertibility Into Controlled Substances**

AB-CHMINACA is not readily converted into other internationally controlled substances.

## 4. General Pharmacology

AB-CHMINACA is a synthetic cannabinoid receptor agonist (SCRA). It has an indazole core, which is a common structural feature in a number of the SCRA's monitored by the EMCDDA and the UNODC.

### A. *Routes of administration and dosage*

AB-CHMINACA is mainly offered on the Internet either in the form of 'herbal mixtures', where the chemical has been sprayed on plant material, as a powder, or in a liquid to be used in e-cigarette devices. Based on user reports and on the dosage forms offered, the primary route of administration is inhalation either by smoking the 'herbal mixture' as a joint or utilizing a vaporizer, or vaping through an e-cigarette.

The effects of AB-CHMINACA are felt on doses as small as 0.5 mg-1 mg on your cigarettes or buds.<sup>18</sup> Users reported cannabimimetic effects after smoking the drug. Doses for oral application can be assumed to be significantly higher due to lower bioavailability.

### B. *Pharmacokinetics*

Erratico et al. were the first to study the human *in vitro* and *in vivo* metabolism of AB-CHMINACA.<sup>16</sup> They used human liver microsomes (HLMs) and monitored the formation of AB-CHMINACA metabolites using LC-TOF-MS. In total 26 metabolites were identified. Major *in vitro* metabolites were formed by mono-hydroxylation of the cyclohexyl ring and by hydrolysis of the outer amide group of AB-CHMINACA resulting in a carboxylated metabolite (M21). Furthermore six di-hydroxylated metabolites, five mono-hydroxylated metabolites of M21 and five glucuronidated metabolites were formed. An interesting finding is that glucuronidation takes place at a carboxyl group and not at one of the hydroxyl groups formed during Phase I metabolism. In a second part of the study they used panel of seven human recombinant CYPs (rCYPs). rCYP3A4 was the major CYP enzyme involved in the metabolism of AB-CHMINACA. In the last part of their study they analyzed a human urine sample from an AB-CHMINACA user. Most of the *in vitro* metabolites of AB-CHMINACA were also present in the urine sample. Thus, the *in vitro* model was a good predictor of AB-CHMINACA *in vivo* metabolism.

Comparing results from different publications is not always easy. A good example is the article by Wurita et al.<sup>17</sup> They reported on an autopsy case in which the cause of death was judged as poisoning by multiple NPS, including AB-CHMINACA. Unchanged AB-CHMINACA could be detected from 8 solid tissues, but not in blood or urine samples. They could however detect and identify two metabolites in the urine sample, called M1 and M3. M1 was described as 4-hydroxycyclohexylmethyl AB-CHMINACA and M3 as *N*-[[1-(cyclohexylmethyl)-1H-indazol-3-yl]carbonyl]-l-valine. Their concentrations were  $52.8 \pm 3.44$  and  $41.3 \pm 5.04$  ng/ml (n=10) respectively. Unfortunately, the naming of the metabolites differs from the Erratico paper and also from the naming of AB-CHMINACA as found on the Cayman website. So, comparing the results is hardly possible.

For forensic applications Sim et al. developed and validated a method for detection of AB-CHMINACA and six of its metabolites in hair by using a LC-MS/MS system.<sup>15</sup> After validation, the method was applied to 37 hair samples from suspected SCRA users. AB-CHMINACA and two metabolites, AB-CHMINACA M2 and AB-CHMINACA M4, were detected. The concentration of the parent drug was much higher than those of the metabolites, and the amount of AB-CHMINACA M2 was greater than that of AB-CHMINACA M4 in all samples. Again, a caveat is the naming of the metabolites might differ from the study by Erratico.

### C. *Pharmacodynamics*

Wiley et al. studied three novel SCRA, AB-CHMINACA, AB-PINACA, and FUBIMINA, for *in vitro* biochemical effects and *in vivo* pharmacological effects.<sup>19</sup> In a binding assay AB-CHMINACA displaced [<sup>3</sup>H]CP55,940 at the CB1 receptor binding site with an inhibition constant ( $k_i$ ) of 0.78 nM for AB-CHMINACA and of 0.59 nM for CP55,940. In the stimulated [<sup>35</sup>S]GTPg turnover assay AB-CHMINACA exhibited enhanced efficacy compared with CP55,940. It was about three times more potent than CP55,940. The affinity at the CB2 receptor binding site is 0.45 nM for AB-CHMINACA and 0.30 nM for CP55,940. Although the affinity of all tested compounds for the CB2 receptor exceeded those obtained at the CB1 receptor by 1.7- to 12.6-fold, they showed reduced efficacy at the CB2 receptor compared with the CB1 receptor. In the stimulated [<sup>35</sup>S]GTPg turnover assay, AB-CHMINACA was 111-fold less potent than CP55,940.

Using the tetrad test rodents can be screened for the effects of THC and SCRA. The four components of the tetrad are spontaneous activity, catalepsy, hypothermia, and analgesia. In the second part of the study Wiley et al. demonstrated that Delta-9-THC, AB-CHMINACA, and AB-PINACA exhibited the complete profile of cannabinoid effects in the tetrad tests in mice. Each compound produced dose-dependent suppression of spontaneous activity, antinociception, hypothermia, and ring immobility. Across the four tests, AB-CHMINACA was 11- to 58-fold more potent than Delta-9-THC, whereas AB-PINACA was 2- to 14-fold more potent than Delta-9-THC. These effects could be antagonized by concomitant administration of rimonabant.

In humans smoking of cannabis and SCRA is the most used method of administration. Recently vaping has become more popular due to the increase in available e-cigarette devices. But in animal experiments an injection is the preferred method of administration.

To bridge the gap between street and lab Lefever et al decided to use vaping as method of administration for a number of SCRA, including AB-CHMINACA.<sup>20</sup> After building their own device the SCRA CP 55,940, AB-CHMINACA, XLR-11, and JWH-018 were administered either by aerosol or injection to mice. They used the same test battery as in the tetrad test but without catalepsy. The most potent cannabinoids (CP 55,940, AB-CHMINACA) produced the full cannabinoid profile (i.e., hypothermia, hypolocomotion, and analgesia), after both methods of

administration. Time course analysis for hypothermia showed that aerosol exposure to CP 55,940, and AB-CHMINACA produced faster onset of effects and shorter duration of action than injection.

## 5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of AB-CHMINACA.

## 6. Adverse Reactions in Humans

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, conjunctival injection (“red eyes”), tachycardia, and nausea and vomiting. Similar effects to cannabis have been reported for SCRAAs such as AB-CHMINACA. In some cases, the effects are reported to be more pronounced/severe.<sup>21</sup>

Compared to cannabis, severe and fatal poisoning appears to be more common with SCRAAs.<sup>21,22</sup> 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.

### *Acute intoxications*

Between 2014 and 2016 a total of 7 acute intoxications with confirmed exposure to AB-CHMINACA were reported to the EMCDDA.<sup>23</sup> In four cases details were available (Belgium (1), France (1) and the United Kingdom (2)). In 2 of the cases, no other substances were detected. In the other 2 cases other substances detected included SCRAAs and an opioid. In all 4 cases, the clinical features of the poisoning were typical of those reported for SCRAAs. For the other 3 cases, all from Hungary, no further details were available.

During a very short period in 2014 (less than two weeks) there was an outbreak of SCRAA induced non-fatal toxicity in Florida.<sup>24</sup> A total of 35 patients were evaluated and treated following reported exposure to a SCRAA containing product obtained from a common source.<sup>24</sup> Patients demonstrated acute delirium and 14 patients had seizures. Ventilator support and ICU-level care was required in 5 patients. The presence of AB-CHMINACA, or one of its predicted metabolites was confirmed in 15 of 21 cases.

Abouchdid et al.<sup>12</sup> describe a series of cases presented at an Emergency Department in 2015 with analytical confirmation of recreational drugs. In a six month period 179 patients with acute recreational drug toxicity were enrolled. In 18 (10%) out of the 179 patient samples SCRAAs were detected in serum. The most common SCRAA present was MDMB-CHMICA (7/18, 80-8000 pg/mL) and also AB-CHMINACA (3/18, 50-1800 pg/mL) has been found. But only 9 of 18 (50%) patients were aware of the use of SCRAAs.

Klavž et al.<sup>25</sup> report a suicide attempt with a mix of two SCRAs (AB-CHMINACA, AB-FUBINACA) and 3 synthetic cathinones (alpha-PHP, alpha-PVP and 4-CMC). All of these substances were not only detected in urine but also in stomach content, with the exception of 4-CMC (only urine). The 38 year old male survived the attempt.

### ***Deaths***

Between 2014 and 2017 a total of 31 deaths with confirmed exposure to AB-CHMINACA were reported to the EMCDDA (Croatia (1), Germany (4), Hungary (11), Poland (2), Sweden (5), and the United Kingdom (8)). In at least 7 cases, AB-CHMINACA was the cause of death or contributed to the death.<sup>23</sup> Of the deaths, 24 were male, 1 was female; in 6 cases the sex was not described. The males were aged 16 - 66 years (n=23; mean 29.7, median 26.5); the female was aged 38. In 6 cases, no other substances were detected. In 2 cases, it was unknown if other substances were detected. In the remaining 23 cases other substances were detected such as alcohol, SCRAs, opioids and benzodiazepines.

Hess et al.<sup>26</sup> present a case of fatal diabetic ketoacidosis in a male.

In blood from a femoral vein eleven (11!) SCRAs (AB-CHMINACA, AB-FUBINACA, AM-2201, 5F-AMB, 5F-APINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135 and THJ 2201) were detected by LC-MS/MS. It is not clear if death due to hyperglycaemia could have been induced by skipping of insulin doses due to his intoxicated state or by the combination of SCRAs which were described to be able to produce hyperglycaemia themselves.

In a recent fatal case, use of AB-CHMINACA is associated with non-cardiogenic pulmonary edema.<sup>27</sup> Shortly after ingesting an herb product containing SCRAs a young man died. Analyses of blood revealed high levels of AB-CHMINACA ( $7.61 \pm 0.59$  ng/mL) and its metabolites (M2,  $56.73 \pm 4.16$  ng/mL; M4,  $2.29 \pm 0.14$  ng/mL). Furthermore, trace amounts of three other SCRAs were detected, 5-fluoro-AMB, FUB-PB-22 and AB-FUBINACA. The high blood ratio of the M2 metabolite to the parent compound, AB-CHMINACA, demonstrates rapid metabolism.

Urine levels of SCRAs in unchanged forms are usually much lower than their blood and tissue levels. Therefore Minakata et al.<sup>28</sup> developed a new sensitive LC-MSMS method for the identification and quantitation of parent forms of six SCRAs in urine samples of human cadavers. Using this method they could detect urine levels of AB-CHMINACA (239 pg/mL) in one victim.

## **7. Dependence Potential**

### **A. *Animal Studies***

No data available.

### **B. *Human Studies***

No data available.

## 8. Abuse Potential

### A. *Animal Studies*

Wiley et al.<sup>19</sup> studied a number of SCRAs, including AB-CHMINACA, in a drug discrimination model for THC. Mice were trained in a nose poke procedure and after completing the training schedule the drugs were administered intraperitoneally. All compounds tested substituted for THC. Rank order of potency correlated with CB1 receptor-binding affinity. AB-CHMINACA produced full, dose-dependent substitution for THC and was 16 times more potent than THC.

Of the tested compounds, the effects of AB-CHMINACA bore the most resemblance to those of THC. At the lowest dose (0.3 mg/kg) AB-CHMINACA produced full substitution without affecting response rates. Full substitution also occurred at a dose of 1 mg/kg AB-CHMINACA, but this effect was accompanied by an overall reduction in response rates. Only one out of seven mice tested at this dose responded on either aperture during the entire session.

### B. *Human Studies*

No data available.

One particular concern with quick-onset and short-acting SCRAs, such as AB-CHMINACA, is that users will smoke or vape more frequently to maintain their high, thereby also exposing themselves to greater potential for adverse events of these substances.

## 9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

AB-CHMINACA has not been used in therapy.

## 10. Listing on the WHO Model List of Essential Medicines

AB-CHMINACA is not listed on the WHO Model List of Essential Medicines (20<sup>th</sup> List) or the WHO Model List of Essential Medicines for Children (6<sup>th</sup> List).

## 11. Marketing Authorizations (as a Medicinal Product)

AB-CHMINACA has never been marketed as a medicinal product.

## 12. Industrial Use

AB-CHMINACA has no industrial use.

### 13. Non-Medical Use, Abuse and Dependence

Similar to other SCRA<sub>s</sub>, AB-CHMINACA is sold and used as a ‘legal’ substitute for cannabis.<sup>23,29</sup> The most common way of using it is by smoking a joint or vaping through an e-cigarette. Because these products rarely state the ingredients, most users will be unaware that they are using AB-CHMINACA.

People who use AB-CHMINACA may include recreational users, high-risk drug users, and groups who experiment with the substance (such as psychonauts). Furthermore, individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) may use AB-CHMINACA because routine drug tests/screens will be unable to detect SCRA<sub>s</sub>.

### 14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Around 2014 AB-CHMINACA appeared on the international drug markets. Since then investigators in Japan<sup>30</sup>, Hungary<sup>31</sup> and USA<sup>32</sup> have looked at the presence of SCRA<sub>s</sub> in persons suspected of driving under the influence of drugs (DUID) and persons involved in traffic incidents.

In Japan in the period from 2012 to 2014, 214 cases of motor vehicle collisions were attributed to the use of illegal drugs.<sup>30</sup> In 93 out of 96 investigated cases, one or more SCRA<sub>s</sub> were found. The following observations were made on the appearance of the drivers just after the collision:

- impaired consciousness 73 cases;
- excited states such as agitation, shouting, confusion, and continuous stereotyped behaviors 16 cases.

In 24 cases blood samples and in 17 cases urine samples were available.

- AB-CHMINACA was involved in 11 cases.
- AB-CHMINACA was detected in blood in 4 cases (1.3–31 ng/mL (n = 3), median 2.7 ng/mL).
- AB-CHMINACA was detected in urine in 3 cases.

The prevalence and pattern of psychoactive substances use among drivers suspected of DUID in Hungary in the period 2014–2015 was subject to a study by Institóris et al.<sup>31</sup> Blood and/or urine samples of 1252 suspected drivers were analyzed for traditional illicit drugs, NPS (novel psychoactive substances) and medicinal products, with around 79% positive cases for at least one substance. But only in around 37% of the tested drivers’ impairment was proven, based on the legal criteria of Hungary. The average age of users of traditional drug was 30 years, while the mean age of users of SCRA<sub>s</sub> was 26.5 years. In about 10% both alcohol and at least one drug was found and in around 37% multi-drug use could be proven. Cannabis was the most frequent used drug (432). The use of SCRA<sub>s</sub> was much lower, for instance AB-CHMINACA (46) and MDMB-CHMICA (30).

Peterson et al.<sup>32</sup> reviewed 58 suspected DUID cases that were positive for the SCRA<sub>s</sub> AB-CHMINACA or AB-PINACA. All cases were submitted in 2014. The population of

drivers was predominantly male (95%), with a mean age of 28 years (18-61 years). In 33 case AB-CHMINACA was detected (0.6->10 ng/mL).

While there are limited data for AB-CHMINACA, the social risks might share similarities with other SCRA. Of particular note is that SCRA are increasingly used by vulnerable groups, such as prisoners. Reports suggest that this has caused new health and social problems as well as exacerbation of existing ones. For example, in prisons, alongside the adverse health effects, the market in SCRA 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.<sup>33; 34, 35, 36</sup>

## **15. Licit Production, Consumption and International Trade**

Not applicable.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

## **16. Illicit Manufacture and Traffic and Related Information**

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

## **17. Current International Controls and Their Impact**

AB-CHMINACA is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

## **18. Current and Past National Controls**

Controlled in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Slovakia, Slovenia, Sweden and Turkey.<sup>1</sup>

Also controlled in China, Japan and Switzerland.

Placed under temporary control in USA.<sup>37</sup>

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

## **19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**

No data.



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**Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of AB-CHMINACA**

Please refer to separate Annex 1 document published on ECDD website