



# Critical Review Report:

## AB-FUBINACA

Expert Committee on Drug Dependence  
Forty-second Meeting  
Geneva, 21-25 October 2019

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## Acknowledgements

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This document was produced for the WHO Expert Committee on Drug Dependence (ECDD) under the overall direction of the WHO Secretariat led by Dr Gilles Forte (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The document was written by Dr Jenny Wiley under the technical direction of Dr Dilkushi Poovendran (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The report was edited by Professor Kim Wolff. The member state questionnaire was produced under the technical direction of Ms Judith Sprunken (Division of Access to Medicines, Vaccines, and Pharmaceuticals).

The WHO Secretariat would also like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA), INCB, UNODC, and Member States for providing relevant information for the review of substances.

## Executive Summary

AB-FUBINACA (CAS: 1185282-01-2), N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide, is a synthetic cannabinoid in the S-conformation with unresolved stereochemistry. It was first reported in Pfizer patent WO 2009/106982. While synthetic methods for AB-FUBINACA were not described specifically in this patent, a synthesis method was published subsequently. 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 route of administration for AB-FUBINACA in humans is inhalation via smoking the chemical after it has been sprayed on plant material or vaping it after formulation in liquid. Dosage required for pharmacological effects in humans is unknown. Little is known about its absorption, distribution, elimination or time course. Pharmacokinetic investigation has focused on metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Based upon results of experiments in human liver cells and analysis of urine from verified users, major metabolites included hydroxylation at the amino-oxobutane moiety, on the indazole ring, and of the primary amide. In addition, consistent with results from rats, the metabolism of AB-FUBINACA was notably slow in humans compared to other synthetic cannabinoids in both human liver microsomes and in authentic urine assays.

AB-FUBINACA binds to hCB<sub>1</sub> and hCB<sub>2</sub> receptors, with K<sub>i</sub> = 0.734 and 0.933 nM, respectively. Functional activity at both receptors was also indicated by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) in hCB<sub>1</sub> and hCB<sub>2</sub> receptors (IC<sub>50</sub> = 1.36 and 1.95 nM, respectively). It was a full agonist at both receptors. Consistent with its activation of CB<sub>1</sub> receptors, AB-FUBINACA produced an in vivo pharmacological profile in mice that was typical of psychoactive cannabinoids, including suppression of locomotor activity, antinociception, hypothermia and catalepsy. Reversal by a CB<sub>1</sub>-receptor antagonist suggested that these effects were CB<sub>1</sub> receptor-mediated. Suppression of locomotor activity in mice (ED<sub>50</sub> = 1.71 mg/kg) occurred within 10 min of i.p. injection and lasted for 50-60 min.

Although its dependence potential has not been evaluated, AB-FUBINACA was tested in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle, where it fully substituted (ED<sub>50</sub> = 0.18 mg/kg). Full substitution occurred at 15 min, remained at 60% or greater for 1 h, and was absent at 2 h post-injection. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans. AB-FUBINACA has not been examined for its abuse potential in self-administration in animals nor has it been evaluated in humans.

Systematic preclinical evaluation of the toxicology of AB-FUBINACA has not been undertaken, although it has been tested in several studies. In one study, acute AB-FUBINACA (tested over the dose range of 0.1 – 6 mg/kg, i.p.) produced increased neurological signs in male ICR mice, including spontaneous and handling-induced convulsions, hyperreflexia, myoclonias, altered sensorimotor effects, and spontaneous aggressiveness. These neurological signs were most prominent at the 6 mg/kg dose. All neurological effects were prevented by pre-administration of a CB<sub>1</sub> receptor antagonist. In vitro, AB-FUBINACA did not produce signs of nephrotoxicity; however,

disrupted mitochondrial functioning indicative of cellular toxicity was reported in neuro-2a cells that endogenously express CB<sub>1</sub> receptors. In rat heart and liver, analysis of a quantitative real-time polymerase chain reaction (PCR) gene expression array following five days of daily i.p. injection of 5 mg/kg AB-FUBINACA revealed significant up- or down-regulation of cellular immune response genes in the liver and pro-inflammatory response genes in the heart, suggesting that repeated dosing may have adverse effects on the cardiovascular and hepatic systems.

AB-FUBINACA is a synthetic cannabinoid that likely shares a profile of centrally mediated effects with other synthetic cannabinoids, including THC-like intoxication. Examination of the in vivo effects of this compound specifically is limited, and formal surveys of adverse reactions in humans consequent to acute administration of AB-FUBINACA specifically are lacking, although at least one death has been reported to be associated with its use. Specific information on the nature and magnitude of public health problems associated with AB-FUBINACA also is not available; however, it is a synthetic cannabinoid, a class of chemicals that have become a global issue with potential for serious public health problems. While the magnitude of these challenges is difficult to determine, issues that have been reported with synthetic cannabinoids include impaired driving, acute psychiatric distress, polysubstance abuse, and increased aggressiveness.

AB-FUBINACA was first identified in samples originating from Japan in 2013. The magnitude of illicit manufacture and trafficking is unknown; however, similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific compounds. Synthesis of the compound occurs predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped. Direct marketing and purchase over the internet also are common.

Currently, AB-FUBINACA is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. It is controlled as a schedule I substance in the United States (final ruling 2016) and is also under national control in Germany and Canada.

## 1. Substance identification

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

N/A

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

1185282-01-2

**C. Other Chemical Names**

No other common chemical names.

**D. Trade Names**

N/A

**E. Street Names**

Street names specific for AB-FUBINACA are not known.

**F. Physical Appearance**

(For example: color, taste and smell)

White powder<sup>1</sup>

**G. WHO Review History**

AB-FUBINACA has not been previously reviewed by the WHO.

## 2. Chemistry

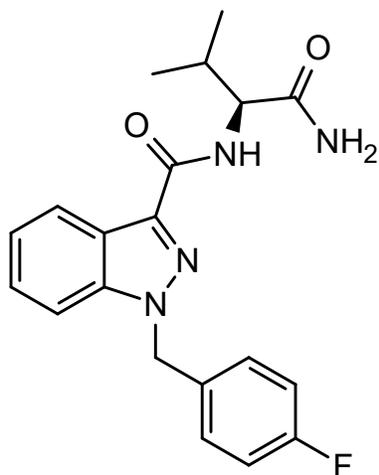
**A. Chemical Name**

**IUPAC Name:** N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide

**CA Index Name:** N/A

## B. Chemical Structure

**Figure 1:** Chemical structure of AB-FUBINACA



**Molecular Formula:**

C<sub>20</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>2</sub>

**Molecular Weight:**

368.4 g/mol

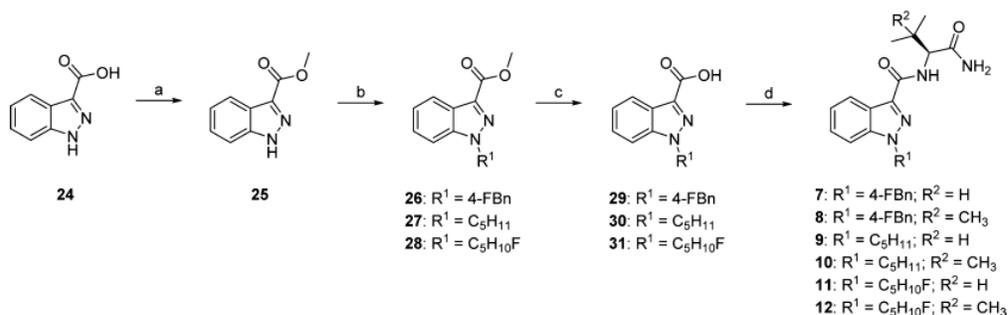
## C. Stereoisomers

The (S)-enantiomer of AB-FUBINACA is claimed in Pfizer patent WO 2009/106982.<sup>2</sup> Although the stereochemistry of AB-FUBINACA is not resolved, a R-AB-FUBINACA enantiomer is probable. Based upon patent data, it is likely that the S-enantiomer has most cannabimimetic activity.<sup>3</sup>

## D. Methods and Ease of Illicit Manufacturing

Synthetic methods for AB-FUBINACA were not described specifically in the patent under which it is covered.<sup>2</sup> However, a synthesis method has been published subsequently (AB-FUBINACA is compound **7** in Scheme 2 presented below).<sup>3</sup>

**Scheme 2. Synthesis of Indazole SCs 7–12<sup>a</sup>**



<sup>a</sup>Reagents and conditions: (a) conc. H<sub>2</sub>SO<sub>4</sub>, MeOH, reflux, 4 h, 76%; (b) BrR<sup>1</sup>, *t*-BuOK, THF, 0 °C to rt, 48 h, 67–77%; (c) NaOH, MeOH, rt, 24 h, 76–96%; (d) EDC·HCl, HOBT, DIPEA, 19 or 20, DMF, rt, 24 h, 31–63%.

**E. Chemical Properties**

Melting point No data

Boiling point No data

Solubility 100 µg/mL in methanol (advertised for sale by Sigma Aldrich as analytical standard)

**F. Identification and Analysis**

Various methods have been used to identify and/or analyze AB-FUBINACA. These methods have included liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS),<sup>4</sup> gas chromatography-mass spectrometry (GC-MS),<sup>1, 5, 6</sup> liquid chromatography-mass spectrometry-mass spectrometry (LC/MS/MS),<sup>7-11</sup> liquid chromatography quadrupole tandem time of flight mass spectrometry,<sup>12</sup> high performance liquid chromatography / mass spectrometry (HPLC-ESI-MS),<sup>13</sup> gas chromatography–electron ionization–triple quadrupole mass spectrometry (GC-EI-MS/MS),<sup>14</sup> liquid chromatography (LC)-electrospray ionization (ESI)-linear ion trap mass spectrometry (LIT-MS) and LC-ESI-triple quadrupole mass spectrometry (QqQ-MS),<sup>15</sup> gas chromatography with Fourier transform infrared detection (GC-FT-IR)<sup>16</sup> <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectroscopy,<sup>1, 6</sup> infrared spectroscopy,<sup>1</sup> and ultraviolet-visible spectroscopy.<sup>6</sup>

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

Ease of its convertibility into a controlled, but non-cannabinoid substance, is low.

**4. General Pharmacology**

**A. Routes of administration and dosage**

The primary route of administration for AB-FUBINACA is presumed to be the same as for other synthetic cannabinoids: inhalation via smoking or vaping. Inhalation of smoke from chemical sprayed on herbal material is the most common route of administration for synthetic cannabinoids.<sup>17</sup> Dosage required for pharmacological effects in humans is unknown.

**B. Pharmacokinetics**

Information on the absorption and distribution of AB-FUBINACA is not available. Several studies have examined its metabolism, with emphasis on discovery of biomarker(s) that could serve forensics as indicators of use. One preclinical study assayed the urine of rats injected intraperitoneally (i.p.) with AB-FUBINACA.<sup>18</sup> Of note, AB-FUBINACA exhibited slow metabolism compared to many other synthetic cannabinoids. While results showed that the concentration of AB-FUBINACA decreased gradually over time since injection, detection of the parent compound in the urine was still at 50% up to 3 h after i.p. injection.

In addition, this study identified two hydroxylated metabolites in rat urine, with the major metabolite involving hydroxylation and elimination of the 4-fluorobenzyl substituent.<sup>18</sup> Work with human samples, however, suggests that this metabolite may be species specific. Assays that used human liver microsomes, human hepatocytes, or authentic urine samples from human users reported hydroxylations, but not at the 4-fluorobenzyl moiety. The number of identified metabolites varied from 2-18, dependent upon the type of sample assayed;<sup>12, 19-22</sup> however, results from a study that used both human liver microsomes and authentic urine samples revealed 5 common metabolites across assay.<sup>12</sup> Major metabolites identified across studies included hydroxylation at the amino-oxobutane moiety, on the indazole ring, and of the primary amide.<sup>12, 20-23</sup> Proposed biomarkers include AB-FUBINACA carboxylic acid, hydroxy AB-FUBINACA carboxylic acid, dihydrodiol AB-FUBINACA, and dihydrodiol ABFUBINACA carboxylic acid.<sup>12, 19</sup> In addition, consistent with results from rats, the metabolism of AB-FUBINACA was notably slow in humans compared to other synthetic cannabinoids in both human liver microsomes and in authentic urine assays.<sup>12</sup>

### C. *Pharmacodynamics*

AB-FUBINACA is a potent and fully efficacious agonist at hCB<sub>1</sub> receptors, with a binding affinity (K<sub>i</sub>) of 0.9 nM and an EC<sub>50</sub> value of 23.2 nM in [<sup>35</sup>S]GTPγS binding reported in the original Pfizer patent.<sup>2</sup> A later study reported a similar affinity (K<sub>i</sub>) for hCB<sub>1</sub> receptors of 0.734 nM and an affinity of 0.933 nM for hCB<sub>2</sub> receptors.<sup>24</sup> In mCB<sub>1</sub> and mCB<sub>2</sub> receptors, corresponding K<sub>i</sub>s were 1.26 and 1.12 nM.<sup>24</sup> Further, functional activity (full agonism) at both receptors was indicated by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) in hCB<sub>1</sub> and hCB<sub>2</sub> receptors expressed in CHO cells (IC<sub>50</sub> = 1.36 and 1.95 nM, respectively)<sup>24</sup> and in hCB<sub>1</sub> receptors expressed in HEK293T cells.<sup>25</sup> Similarly, AB-FUBINACA was a high potency full agonist at both receptors in a fluorometric assay of membrane potential.<sup>3</sup>

In vivo, AB-FUBINACA produced the tetrad of pharmacological effects in mice that is characteristic of psychoactive cannabinoids, including suppression of locomotor activity, antinociception, hypothermia and catalepsy, effects that were reversed by CB<sub>1</sub> antagonism.<sup>24</sup> The ED<sub>50</sub> for locomotor suppression in mice was 1.71 mg/kg, with decreased activity occurring within 10 min of i.p. injection and lasting for 50-60 min.<sup>25</sup> Schreiber et al.<sup>26</sup> reported that AB-FUBINACA also impaired coordination and balance in mice. In adolescent rats, AB-FUBINACA decreased distance travelled in a locomotor assay, increased anxiogenic activity, and decreased normal weight gain.<sup>27</sup> Residual impairment two weeks later was observed in object recognition memory, but not on the motor or anxiogenic measures.<sup>27</sup> In adult male rats, AB-FUBINACA fully and dose-dependently substituted for THC in a drug discrimination procedure,<sup>25</sup> as described in more detail in section 8 of this document.

## 5. Toxicology

Systematic preclinical evaluation of the toxicology of AB-FUBINACA has not been undertaken. Several studies have examined specific aspects of AB-FUBINACA-induced toxicity. In one study, AB-FUBINACA was evaluated acutely in a battery of pharmacology/

toxicology assays designed to examine toxicology in the CNS.<sup>24</sup> Results show that AB-FUBINACA (tested over the dose range of 0.1 – 6 mg/kg, i.p.) produced increased neurological signs in male ICR mice, including spontaneous and handling-induced convulsions, hyperreflexia, myoclonias, sensorimotor alterations, and spontaneous aggressiveness. These neurological signs were most prominent at the 6 mg/kg dose. All neurological effects were prevented by pre-administration of a CB<sub>1</sub> receptor antagonist (AM-251), suggesting that they were mediated by activation of this receptor.<sup>24</sup>

Other studies examined the effects of AB-FUBINACA in vitro. While AB-FUBINACA did not affect renal cell viability or produce other signs of nephrotoxicity that have been observed with other synthetic cannabinoids,<sup>28</sup> disrupted mitochondrial functioning indicative of cellular toxicity has been reported in neuro-2a cells that endogenously express CB<sub>1</sub> receptors.<sup>24</sup> In rat heart and liver, analysis of a quantitative real-time polymerase chain reaction (PCR) gene expression array following five days of daily i.p. injection of 5 mg/kg AB-FUBINACA revealed significant up- or down-regulation of cellular immune response genes in the liver and pro-inflammatory response genes in the heart,<sup>18</sup> suggesting that repeated dosing may have adverse effects on the cardiovascular and hepatic systems.

## 6. Adverse Reactions in Humans

Formal surveys of adverse reactions in humans consequent to acute administration of AB-FUBINACA do not exist; however, at least one death has been reported to be associated with use of AB-FUBINACA.<sup>29</sup> Further, the chemical and pharmacological data that are available suggest that it would produce adverse reactions that are similar to those reported for other synthetic cannabinoids. In humans, the acute psychological effects of synthetic cannabinoids may resemble those reported during acute intoxication with cannabis, ranging from a relaxed and unfocused euphoria to feelings of distress (e.g., confusion, anxiety, and fear). Time perception may be distorted, and in susceptible individuals, hallucinations, paranoia, and more serious psychiatric disorder may occur. Physical effects may include bloodshot eyes (as is characteristic of THC), tachycardia, somnolence, mydriasis, nausea, vomiting, seizures, and impaired motor performance. Because synthetic cannabinoids are usually more potent (and also may be more efficacious) than phytocannabinoids, their effects occur at lower doses, and overdose may be more common, as suggested by increased reports of deaths and serious adverse reactions compared to cannabis.<sup>29-33</sup> Since users usually are unaware of which synthetic cannabinoid is contained in a product, they may administer a chemical with greater potency than the chemical contained in previous products. Further, the chemical may not be evenly distributed throughout the plant material, creating “hot spots” containing higher concentrations of synthetic cannabinoid. For these reasons, dose (in THC equivalents) often exceeds intended dose. Contaminants (e.g., pesticides, heavy metals, rodent feces) may also be present and may contribute to adverse reactions.

As discussed in a single case report, clinical features of acute AB-FUBINACA intoxication included psychological (confusion, agitation, somnolence) and physical (hypertension, tachycardia) symptoms.<sup>34</sup> However, while AB-FUBINACA was analytically confirmed

through testing of the product and urine and blood of the patient, ADB-FUBINACA was also present, complicating determination of the agent responsible for symptoms.

Reports on the pharmacological effects of AB-FUBINACA in humans after chronic use are not available.

## 7. Dependence Potential

### A. *Animal Studies*

AB-FUBINACA has not been assessed for dependence potential in animals.

### B. *Human Studies*

AB-FUBINACA has not been assessed for dependence potential in humans.

## 8. Abuse Potential

### A. *Animal Studies*

The abuse potential of AB-FUBINACA has been assessed in drug discrimination in one study. Results showed that AB-FUBINACA fully substituted in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle ( $ED_{50} = 0.18$  mg/kg).<sup>25</sup> Unlike for THC, substitution by AB-FUBINACA was accompanied by significant response rate suppression at doses that substituted. Full substitution occurred at 15 min after intraperitoneal injection but was absent at 2 h after injection. Substitution remained at 60% or greater for up to 1 h post-injection. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans.<sup>35</sup>

### B. *Human Studies*

AB-FUBINACA has not been assessed for abuse potential in humans.

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

N/A. No known medical / therapeutic usage.

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

Not listed.

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

N/A

## 12. Industrial Use

N/A

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

The prevalence of non-medical use of AB-FUBINACA has not been determined specifically, primarily because the chemicals contained in packages of synthetic cannabinoids are not labeled. Hence, users may not even know which synthetic cannabinoids they are using. Prevalence estimates for specific synthetic cannabinoids rely upon analysis of seized materials and bodily fluids of persons who appear in hospital or morgue following administration, both of which undoubtedly underestimate actual use. In a report covering the period from January 2016 to December 2017, synthetic cannabinoids represented the largest group of substances monitored by the European Union (EU) Early Warning System.<sup>17</sup> Non-medical use and abuse of synthetic cannabinoids has also been reported outside of the EU, including in the United States, Australia, New Zealand, and Asia.<sup>36-40</sup>

In a report that covered identifications from 2015-2018 (provided by the UNODC to the ECDD Secretariat), AB-FUBINACA was detected in 5 regions and 37 countries. Numbers of detections decreased over the time period, with 26 detections in 2015 and 5 detections in 2018. A similar pattern was observed in the U.S. DEA Emerging Threat reports. While 64 identifications of AB-FUBINACA occurred in 2016, only 1 identification was reported in 2018. The mid-year 2019 report did not list any identifications for AB-FUBINACA.

The prevalence of chronic use and dependence of synthetic cannabinoids has not been reported.

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

Although specific information on the nature and magnitude of public health problems associated with AB-FUBINACA is not available, misuse and abuse of synthetic cannabinoids is a global issue with potential for serious public health problems.<sup>17, 40, 41</sup> The magnitude of these challenges is difficult to determine; however, newer compounds (i.e., “second and third generation” synthetic cannabinoids) may have increased potential for harm.<sup>42</sup> Issues that have been reported include impaired driving,<sup>43-45</sup> acute psychiatric distress,<sup>23, 46</sup> and polysubstance abuse with several synthetic cannabinoids and/or synthetic cannabinoids and other substances (e.g., alcohol).<sup>47, 48</sup> Increased aggressiveness has also been reported with some of the newer compounds,<sup>49</sup> but a definitive causal link is lacking. This increase could conceivably be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons and the homeless,<sup>50-52</sup> the former of whom might already be prone to be more aggressive. Co-morbidity also may be an issue with synthetic cannabinoids in general (as suggested by emergency room reports and autopsies).<sup>48</sup>

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

N/A

## 16. Illicit Manufacture and Traffic and Related Information

AB-FUBINACA was first identified in samples originating from Japan in 2013.<sup>53</sup> The magnitude of illicit manufacture and trafficking is unknown; however, similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific compounds. Detection of AB-FUBINACA has been reported in Italy,<sup>8</sup> Turkey,<sup>5</sup> United States,<sup>7</sup> and Serbia.<sup>13</sup>

Synthesis of AB-FUBINACA (and many other synthetic cannabinoids) is believed to occur predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.<sup>17</sup> This hypothesis is supported by the observation that shipments confiscated by law enforcement organizations frequently originate from China. Direct marketing and purchase over the internet also are common.

More recent email correspondence (August 13, 2019) from the International Narcotic Control Board Secretariat, United Nations Office on Drugs and Crime, to the ECDD Secretariat stated that survey of the IONICS platform revealed 303 contact incidents with AB-FUBINACA to date. Most of these incidents (n=294) occurred in Latvia between 2014 and 2015. The other 9 incidents were reported from five countries (3 from Greece, 2 from the United Kingdom, 1 from Spain, 1 from Australia and 1 from the United States).

See Annex 1 for additional information on illicit manufacture and traffic in WHO Member States.

## 17. Current International Controls and Their Impact

AB-FUBINACA is not currently under international control.

## 18. Current and Past National Controls

United States: On September 17, 2016, the U.S. Drug Enforcement Administration issued an order for permanent placement (final rule) of AB-FUBINACA under Schedule I control.<sup>54</sup> It had been under temporary control since early 2014.

European Union: The EMCDD has not issued an Early Warning System report or risk assessment on AB-FUBINACA; however, the compound is regulated under German law (Anlage II).

Canada: AB-FUBINACA is classified as a Schedule II controlled substance under Canada's Controlled Drugs and Substances Act passed in 1996.

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

AB-FUBINACA was detected (and analytically confirmed) in cannabidiol oil that was purchased from an online vendor.<sup>4</sup> The contamination was brought to the attention of medical personnel following an ER visit by a minor child who had been given the oil as treatment for recurrent seizures. This incident highlights the danger of synthetic cannabinoids showing up as contaminants in other non-regulated products.

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## **Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances**

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances