Critical Review Report:

ADB-FUBINACA

Expert Committee on Drug Dependence
Forty-first Meeting
Geneva, 12-16 November 2018

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
© World Health Organization 2018
All rights reserved.

This is an advance copy distributed to the participants of the 41st Expert Committee on Drug Dependence, before it has been formally published by the World Health Organization. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.
Contents

Acknowledgements ........................................................................................................................................... 5

Summary .......................................................................................................................................................... 5

1. Substance identification .............................................................................................................................. 9
   A. International Nonproprietary Name (INN) ............................................................................................ 9
   B. Chemical Abstract Service (CAS) Registry Number ........................................................................... 9
   C. Other Chemical Names ........................................................................................................................... 9
   D. Trade Names ........................................................................................................................................... 9
   E. Street Names .......................................................................................................................................... 9
   F. Physical Appearance .............................................................................................................................. 9
   G. WHO Review History ............................................................................................................................ 9

2. Chemistry .................................................................................................................................................. 9
   A. Chemical Name ..................................................................................................................................... 9
   B. Chemical Structure ............................................................................................................................... 10
   C. Stereoisomers ....................................................................................................................................... 10
   D. Methods and Ease of Ilicit Manufacturing ......................................................................................... 10
   E. Chemical Properties ............................................................................................................................ 11
   F. Identification and Analysis .................................................................................................................. 11

3. Ease of Convertibility Into Controlled Substances .................................................................................... 11

4. General Pharmacology .............................................................................................................................. 11
   A. Routes of administration and dosage ................................................................................................. 11
   B. Pharmacokinetics ............................................................................................................................... 11
   C. Pharmacodynamics ............................................................................................................................ 12

5. Toxicology .................................................................................................................................................. 12

6. Adverse Reactions in Humans ................................................................................................................ 12

7. Dependence Potential .............................................................................................................................. 13
   A. Animal Studies ..................................................................................................................................... 13
   B. Human Studies ..................................................................................................................................... 13

8. Abuse Potential ........................................................................................................................................ 13
   A. Animal Studies ..................................................................................................................................... 13
   B. Human Studies ..................................................................................................................................... 13

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use .............. 14

10. Listing on the WHO Model List of Essential Medicines ....................................................................... 14

11. Marketing Authorizations (as a Medicinal Product) ............................................................................. 14

12. Industrial Use ........................................................................................................................................... 14

13. Non-Medical Use, Abuse and Dependence ............................................................................................ 14
15. Licit Production, Consumption and International Trade ......................................................14
16. Illicit Manufacture and Traffic and Related Information....................................................15
17. Current International Controls and Their Impact...............................................................15
18. Current and Past National Controls ..................................................................................15
19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance ......................................................................................................................15

References .................................................................................................................................. 16
Acknowledgements

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a critical review for the 41st Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge Jenny Wiley for the literature review and drafting and Jurgen Rehm, Astrid Otto, and Jakob Manthey for questionnaire analysis and report drafting.

WHO would like to thank the US Drug Enforcement Agency for providing information on ADB-FUBINACA.
Executive Summary

**Substance identification:** ADB-FUBINACA (CAS: 1445583-51-6) is a synthetic cannabinoid that was first documented (as (S)-enantiomer) in international patent WO 2009/106980-A2 issued to Ingrid Buchler and colleagues at Pfizer on September 3, 2009.\(^1\)

**WHO Review History:** The WHO has not previously reviewed ADB-FUBINACA.

**Chemistry:** ADB-FUBINACA is N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide. It is in the S-configuration. Although the stereochemistry of ADB-FUBINACA is not resolved, a R-ADB-FUBINACA enantiomer is probable. Based upon patent data, it is likely that the S-enantiomer has mostly cannabimimetic activity.

**Ease of convertibility into controlled substances:** ADB-FUBINACA is not readily converted into other controlled substances.

**Similarity to known substances / Effects on the central nervous system:** ADB-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.

**General pharmacology:** The most likely route of administration for ADB-FUBINACA is inhalation via smoking the chemical after it has been sprayed on plant material or vaping it after formulation in liquid. The dosage required for pharmacological effects in humans is unknown.

Little information is available about the pharmacokinetics of ADB-FUBINACA. Work using human liver microsomes and hepatocytes revealed extensive hepatic metabolism with 23 metabolites identified. It was predicted that metabolites would be measurable in urine for several days after intake. Unique ADB-FUBINACA metabolites suggested as biomarkers for intake were ADB-FUBINACA hydroxy-alkyl, ADB-FUBINACA hydroxydehydroalkyl, and ADB-FUBINACA hydroxylindazole. Additional information on the specific pharmacokinetics (absorption, distribution, metabolism, or elimination) of ADB-FUBINACA is not available.

ADB-FUBINACA is a potent and fully efficacious agonist at hCB1 receptors, with a binding affinity (K\(_i\)) of 0.36 nM and an EC\(_{50}\) value of 0.98 nM in [35S]GTP\(_\gamma\)S binding reported in the original Pfizer patent. In both CB1 and CB2 receptors expressed in mouse AtT20-FipIN neuroblastoma cells, ADB-FUBINACA efficacy and potency was substantially greater than THC as measured by agonist-stimulated opening of G protein-gated inwardly rectifying potassium channels (GIRKs). Potency for GIRK channel activation was greater at CB1 vs CB2 receptors, with EC\(_{50}\) values of 1.2 nM and 3.5 nM, respectively. ADB-FUBINACA also potently activated the \(\beta\)arrestin-2 signaling pathway, with EC\(_{50}\) values of 0.69 nM and 0.59 nM in CB1 and CB2 receptors, respectively. Results of any in vivo assessment of ADB-FUBINACA have not been reported.
Toxicology: Preclinical evaluation of the acute or chronic toxicological effects of ADB-FUBINACA has not been conducted.

Adverse reactions in humans: Although sparse in number, extant case studies suggest that acute administration of ADB-FUBINACA has contributed to severe adverse reactions in humans up to, and including, death. In each case (or case series), ADB-FUBINACA was analytically confirmed through testing of the product and/or urine or blood of the patient; however, in most cases, other substances, including other synthetic cannabinoids, were also present. Clinical features of acute intoxication included psychological (confusion, agitation, somnolence) and physical (hypertension, tachycardia) symptoms. Although symptoms resolved in most patients, at least two patients had more severe effects: one patient died and another suffered a stroke with lasting neurological damage. In each case, pulmonary or cardioembolism likely contributed to the outcome. The highest known serum concentration of ADB-FUBINACA (34 ng/mL) was measured in an inmate who was hospitalized when balloons containing cannabis and synthetic cannabinoids (including ADB-FUBINACA) ruptured in his stomach.

Dependence potential: The dependence potential of ADB-FUBINACA has not been evaluated in humans or in animals.

Abuse potential: The abuse potential of ADB-FUBINACA has not been evaluated in humans or in animals.

Therapeutic applications / usefulness: None

Listing on WHO Model List of Essential Medicines: Not listed as an essential medicine.

Marketing authorizations: None

Industrial use: None

Non-medical use: The prevalence of non-medical use of ADB-FUBINACA specifically has not been determined; however, synthetic cannabinoids (as a class) is the largest group of substances monitored by the European Union Early Warning System, and user exposure to specific synthetic cannabinoids is not often analytically confirmed. Non-medical use has also been reported outside of the European Union, including in the United States and Asia.

Nature and magnitude of public health problems: Use of synthetic cannabinoids has 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, and increased aggressiveness.

Licit production, consumption, and international trade: None

Illicit manufacture and traffic: ADB-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.

**Current international controls and their impact:** ADB-FUBINACA is not been subject to international control under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

**Current and past national controls:** In April 2017, the U.S. Drug Enforcement Agency issued a statement of temporary placement of ADB-FUBINACA under Schedule 1 control measures. The EMCDDA has not issued an Early Warning System report or risk assessment on ADB-FUBINACA. The compound is scheduled in Germany (Anlage II) and is subject to control regulations in Canada.
1. Substance identification

A. International Nonproprietary Name (INN)
   N/A

B. Chemical Abstract Service (CAS) Registry Number
   1445583-51-6

C. Other Chemical Names
   No other common chemical names

D. Trade Names
   N/A

E. Street Names
   ADB-FUBINACA has been detected in samples of products labeled Black Mamba,2
   VaperFi,3 Freeze,4 and Mojo.5 Other specific street names for ADB-FUBINACA are not
   available. However, there are dozens of street names for synthetic cannabinoids (which
   may contain one or more unidentified synthetic cannabinoids). These names include K2,
   K2XXX, barely legal, iBlaze, spice, cloud 10, herbal incense, fake weed, kush, and zombie,
   among others.

F. Physical Appearance
   Crystalline solid\textsuperscript{6}
   White powder\textsuperscript{7}

G. WHO Review History
   ADB-FUBINACA has not previously been reviewed by the WHO.

2. Chemistry

A. Chemical Name
   IUPAC Name: N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-
   indazole-3-carboxamide
   CA Index Name: n/a
B. Chemical Structure

Figure 1: Chemical structure of ADB-FUBINACA

![Chemical Structure Diagram]

Molecular Formula: $C_{21}H_{23}FN_4O_2$

Molecular Weight: 382.4 g/mol

C. Stereoisomers

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

D. Methods and Ease of Illicit Manufacturing

Synthetic methods for ADB-FUBINACA were not described specifically in the patent under which it is covered, but have been described in a recent research paper. Scheme 1 was copied from this publication and delineates steps in the chemical reaction necessary to synthesize ADB-FUBINACA (compound 8).

Scheme 1. Synthesis of indazole cannabinoids (including ADB-FUBINACA)

- Reagents and conditions: (a) conc. H$_2$SO$_4$, MeOH, reflux, 4 h, 76%; (b) B$_2$R$_3$, t-BuOK, THF, 0°C to rt, 48 h, 67–77%; (c) NaOH, MeOH, rt, 24 h, 76–96%; (d) EDC•HCl, HOBr, DIPEA, 19 or 20, DMF, rt, 24 h, 31–63%.
E. Chemical Properties

Melting point: 135-137°C

Boiling point: No data

Solubility: No data

F. Identification and Analysis

Various methods have been used to identify and/or analyze ADB-FUBINACA. These methods have included Fourier Transform Infrared Spectroscopy with Attenuated Total Reflection sampling (FTIR-ATR), low resolution mass spectra recorded with electrospray ionization (LRMS-ESI), liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS), liquid chromatography-mass spectrometry, liquid chromatography-tandem mass spectrometry (LC-MS/MS), gas chromatography-mass spectrometer (GC-MS), gas chromatography, high performance liquid chromatography (HPLC), high-performance liquid chromatography with photodiode array detection (HPLC-DAD), ion trap time-of-flight mass spectrometry (IT-TOF/MS), ultraperformance liquid chromatography with electrospray ionization – tandem mass spectrometry (UPLC/ESI-MS/MS), and nuclear magnetic resonance spectroscopy (NMR).

3. Ease of Convertibility Into Controlled Substances

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

4. General Pharmacology

A. Routes of administration and dosage

The primary route of administration for ADB-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. Dosage required for pharmacological effects in humans is unknown.

B. Pharmacokinetics

Little information is available about the pharmacokinetics of ADB-FUBINACA. To date, published analysis of blood or urine from confirmed users has not been available. Hence, extant work has relied on human liver microsomes and hepatocytes. An initial study using human liver microsomes identified a single hydroxylated metabolite of ADB-FUBINACA, with oxidation hypothesized to occur on the N-(1-amino-3,3-dimethyl-1-oxobutan) moiety. Further investigation of metabolism of ADB-FUBINACA using co-incubated human liver microsomes and hepatocytes revealed additional metabolites for a
Hepatic metabolism was extensive, and it was predicted that metabolites would be measurable in urine for several days after intake. Primary biotransformation processes included hydroxylation at the dimethylpropane chain or the indazole ring, amide hydrolysis after glucuronide conjugation, and dehydrogenation. Unique ADB-FUBINACA metabolites suggested as biomarkers for intake were ADB-FUBINACA hydroxy-alkyl, ADB-FUBINACA hydroxydehydroalkyl, and ADB-FUBINACA hydroxylindazole. Additional information on the specific pharmacokinetics (absorption, distribution, metabolism, or elimination) of ADB-FUBINACA is not available.

C. **Pharmacodynamics**

ADB-FUBINACA is a potent and fully efficacious agonist at hCB1 receptors, with a binding affinity (Ki) of 0.36 nM and an EC50 value of 0.98 nM in [35S]GTPγS binding reported in the original Pfizer patent.1 In both CB1 and CB2 receptors expressed in mouse AtT20-FlpIN neuroblastoma cells, ADB-FUBINACA efficacy and potency was substantially greater than THC as measured by agonist-stimulated opening of G protein-gated inwardly rectifying potassium channels (GIRKs).8 Potency for GIRK channel activation was greater at CB1 vs CB2 receptors, with EC50 values of 1.2 nM and 3.5 nM, respectively.8 ADB-FUBINACA also potently activated the β-arrestin-2 signaling pathway, with EC50 values of 0.69 nM and 0.59 nM in CB1 and CB2 receptors (expressed in human embryonic kidney (HEK) 293 cells), respectively.16 Results of any in vivo assessment of ADB-FUBINACA have not been reported.

5. **Toxicology**

Preclinical evaluation of the acute or chronic toxicological effects of ADB-FUBINACA has not been conducted.

6. **Adverse Reactions in Humans**

In humans, the acute psychological effects of synthetic cannabinoids (including ADB-FUBINACA) 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, 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 with this class of cannabinoids as compared to cannabis.15,17-20 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.

Case studies suggest that acute administration of ADB-FUBINACA has contributed to severe adverse reactions in humans up to, and including, death.\textsuperscript{2-5,10} In each case (or case series), ADB-FUBINACA was analytically confirmed through testing of the product and/or urine or blood of the patient; however, in most cases, other substances, including other synthetic cannabinoids, were also present. Clinical features of acute intoxication included psychological (confusion, agitation, somnolence) and physical (hypertension, tachycardia) symptoms.\textsuperscript{2-4} Although symptoms resolved in most patients, at least two patients had more severe effects: one patient died\textsuperscript{5} and another suffered a stroke with lasting neurological damage.\textsuperscript{4} In each case, pulmonary or cardioembolism likely contributed to the outcome. The highest known serum concentration of ADB-FUBINACA (34 ng/mL) was measured in an inmate who was hospitalized when balloons containing cannabis and synthetic cannabinoids (including ADB-FUBINACA) ruptured in his stomach.\textsuperscript{10}

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

7. Dependence Potential

   A. Animal Studies

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

   B. Human Studies

   ADB-FUBINACA has not been evaluated for its dependence potential in humans.

8. Abuse Potential

   A. Animal Studies

   ADB-FUBINACA has not been assessed for abuse potential in animal studies. It has not been tested in drug discrimination or self-administration.

   Although ADB-FUBINACA has not been assessed for abuse potential, a closely related structural analog AB-FUBINACA fully substituted for THC in male Sprague-Dawley rats trained to discriminate THC from vehicle.\textsuperscript{21} ADB-FUBINACA differs from AB-FUBINACA in chemical structure by a replacement of an isopropyl moiety with a tert-butyl moiety.

   B. Human Studies

   ADB-FUBINACA has not been evaluated for abuse potential in humans.
9. **Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use**
   No known medical use or therapeutic applications.

10. **Listing on the WHO Model List of Essential Medicines**
    N/A

11. **Marketing Authorizations (as a Medicinal Product)**
    None

12. **Industrial Use**
    None

13. **Non-Medical Use, Abuse and Dependence**
    The prevalence of non-medical use of ADB-FUBINACA has not been determined specifically, primarily because the chemicals contained in packages of synthetic cannabinoids are not labeled or are mislabeled.\(^2\) 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.\(^15\) Non-medical use and abuse of synthetic cannabinoids has also been reported outside of the EU, including in the United States and Asia.\(^11, 22-26\)

14. **Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence**
    Use of synthetic cannabinoids is a global issue with potential for serious public health problems.\(^15, 26, 27\) 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.\(^28\) Issues that have been reported include impaired driving,\(^29, 30\) acute psychiatric distress,\(^31, 32\) and polysubstance abuse with several synthetic cannabinoids and/or synthetic cannabinoids and other substances (e.g., alcohol).\(^33, 34\) Increased aggressiveness has also been reported with some of the newer compounds,\(^35\) but a definitive causal link is lacking. This increase could conceivably could be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons\(^10\) and the homeless,\(^36-38\) the former of whom might already be prone to be more aggressive.

15. **Licit Production, Consumption and International Trade**
    N/A
16. Illicit Manufacture and Traffic and Related Information
ADB-FUBINACA was first identified in samples originating from Japan in 2013.\textsuperscript{11} 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 ADB-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.\textsuperscript{15} 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.

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

17. Current International Controls and Their Impact
ADB-FUBINACA is not subject to international controls under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and Past National Controls
United States: On April 10, 2017, the U.S. Drug Enforcement Agency issued an order for temporary placement of ADB-FUBINACA under Schedule I control.\textsuperscript{39}

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

Canada: ADB-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
None.
References

6. Cayman Chemicals. ADB-FUBINACA. Available at: https://www.caymanchem.com/product/142922018
7. Drug Enforcement Agency. ADB-FUBINACA. Available at: http://swgdrug.org/Monographs/ADB-FUBINACA.pdf; 2017


