Critical Review Report:

ADB-CHMINACA

Expert Committee on Drug Dependence
Forty-first Meeting
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Executive Summary

Substance identification: ADB-CHMINACA (CAS: 1863065-92-2 for racemate or 1185887-13-1 for the (S)-enantiomer) is a synthetic cannabinoid that was first documented in international patent WO 2009/106980-A2 issued to Ingrid Buchler and colleagues at Pfizer on September 3, 2009.\(^1\) ADB-CHMINACA is also referred to as MAB-CHMINACA.

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

Chemistry: ADB-CHMINACA is N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide. The racemate is comprised of two enantiomers: (S) and (R). Based upon hypothesized synthesis methods, the (S)-enantiomer is likely to predominate in products available on the street.

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

Similarity to known substances / Effects on the central nervous system: ADB-CHMINACA 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-CHMINACA 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. Investigation of the pharmacokinetics of ADB-CHMINACA has focused on delineation of its metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Ten metabolites of ADB-CHMINACA have been identified in human hepatocytes, with verification of the major metabolites in authentic human urine samples from living individuals. ADB-CHMINACA undergoes extensive biotransformation that is focused on hydroxylation of its cyclohexylmethyl tail. Other metabolites are also formed through biotransformation focused on the cyclohexylmethyl tail, including ketolization, tert-butyl hydroxylation, and dihydroxylation. Neither glucuronidation nor other phase II processes occurred with ADB-CHMINACA; hence, phase II metabolites were absent. Specific information on other pharmacokinetic parameters (absorption, distribution, elimination, and time course) for ADB-CHMINACA was not available in the literature.

ADB-CHMINACA is a potent CB\(_1\) receptor agonist, with reported binding affinities ranging from 0.289 nM to 0.49 nM. It is a full agonist in functional tests of CB\(_1\) and CB\(_2\) receptor activation, as demonstrated by its efficacy for inhibition of forskolin-stimulated release of cyclic adenosine monophosphate (cAMP) and its potency in increasing recruitment of β-arrestin 2. In vivo assessment of ADB-CHMINACA has been sparse. Available data show that ADB-CHMINACA fully substituted for THC in male rats trained to discriminate THC from vehicle, and that it suppresses
locomotor activity in male mice. Rimonabant reversibility suggests that the THC-like effects of ADB-CHMINACA in the drug discrimination procedure are CB₁ receptor-mediated.

**Toxicology:** Preclinical evaluation of the acute or chronic toxicological effects of ADB-CHMINACA has not been conducted.

**Adverse reactions in humans:** Case studies and reports of mass intoxication indicate that acute administration of ADB-CHMINACA has the potential to produce severe adverse reactions in humans up to, and including, death. Symptoms of ADB-CHMINACA overdose may include tachycardia, unresponsiveness, seizures, delirium, slurred speech, vomiting, agitation and combativeness. In the spring of 2015, ADB-CHMINACA was associated with several drug-induced clusters of severe illness and death in the U.S. It has also been associated with 13 deaths in the European Union and one death in Japan.

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

**Abuse potential:** The abuse potential of ADB-CHMINACA has not been evaluated in humans.

ADB-CHMINACA (i.p.) produces an inverted U-shaped substitution dose-effect curve in male rats trained to discriminate 3 mg/kg delta⁹-tetrahydrocannabinol (THC) from vehicle, with dose-dependent increased in THC-lever responding to a peak of full substitution at 0.18 mg/kg. A higher 0.25 mg/kg dose decreased responding; however, it also substantially decreased overall responding. Peak effect of the 0.18 mg/kg dose was observed at 30 min after injection.

**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-CHMINACA 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, Australia, New Zealand, 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. ADB-CHMINACA, specifically, has been associated with several clusters of mass intoxication, illness and death in the U.S. and in Europe. Agitation and aggressive behavior are common in individuals with analytically confirmed use of ADB-CHMINACA, although causality is difficult to determine.
History of mental illness or substance abuse disorder may be associated with more severe reactions.

**Licit production, consumption, and international trade:** None

**Illicit manufacture and traffic:** ADB-CHMINACA has been detected in 17 Member States of the European Union and in the U.S. Underreporting is likely due to lack of routine screening for the compound. 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-CHMINACA 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:** ADB-CHMINACA is regulated as a Schedule 1 substance in the United State. In May 2018, ADB-CHMINACA was placed under regulatory control in the European Union. It is also subject to control measures in Canada and Singapore.
1. Substance identification

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

1863065-92-2: racemate
1185887-13-1: (S)-enantiomer

C. Other Chemical Names

MAB-CHMINACA; (S)-ADB-CHMINACA; N-(1'-(aminocarbonyl)-2',2'-dimethylpropyl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide; N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide

D. Trade Names

N/A

E. Street Names

Bionic is one street name that has been associated with ADB-CHMINACA. The compound has also been detected in GM Sapphire. Other specific street names for ADB-CHMINACA 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

White powder or crystalline solid

G. WHO Review History

WHO has not previously reviewed ADB-CHMINACA.

2. Chemistry

A. Chemical Name

IUPAC Name: N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide

CA Index Name: n/a
B. **Chemical Structure**

Molecular Formula: $\text{C}_{21}\text{H}_{30}\text{N}_{4}\text{O}_{2}$

Molecular Weight: 370.5 g/mol

C. **Stereoisomers**

ADB-CHMINACA racemate contains two enantiomers: (S)-ADB-CHMINACA and (R)-ADB-CHMINACA. The enantiomer composition of ADB-CHMINACA in products available on the street is unknown; however, based upon the presumed precursors, it is likely to be largely (S)-ADB-CHMINACA.\(^3\)

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

Specific synthesis methods for ADB-CHMINACA (compound 13) were not provided in the original patent filed for the compound.\(^1,3\) Based upon risk assessment conducted on behalf of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), one general method of synthesis is initiated using standard techniques that have been used previously for cannabinoids with similar indazole structures.\(^3\) Potential precursors include 1H-indole-3-carboxylic acid and methyl 1H-indazole-3-carboxylate.\(^4\) The final reaction step described in the patent involves coupling of an acid intermediate with L-tert-leucinamide. This process yields the (S)-enantiomer of ADB-CHMINACA.\(^3\)

Manufacture in illicit laboratories is straightforward and dependent primarily upon availability of suitable precursors. Impurities in the precursors could result in impurities in the resulting product and possible resultant toxicity. To date, illicit manufacture has not been prominent in the European Union or in the United States, but rather, is believed to occur primarily in China.\(^3\)

E. **Chemical Properties**

Melting point: 141.5°\(^{\circ}\)C\(^4\)

Boiling point: not determined
Solubility: ADB-CHMINACA is soluble in dichloromethane and methanol. Like many cannabinoids, it is poorly soluble in water. Solubility in other solvents ranges from 1 mg/mL in ethanol to 10 mg/ml in dimethyl sulfoxide. It is also soluble in dimethyl formamide up to 5 mg/ml.

F. Identification and Analysis

Various methods have been used to identify and/or analyze ADB-CHMINACA. These methods have included gas chromatography–mass spectrometry (GC-MS), liquid chromatography–mass spectroscopy/mass spectroscopy (LC-MS/MS), liquid chromatography quadrupole time-of-flight/mass spectrometry (HPLC-QTOF-MS), liquid chromatography-high resolution tandem mass spectrometry (LC-HRMS/MS), gas chromatography-electron ionization high resolution mass spectrometry (GC–EI-HRMS), electrospray–mass spectrometry (ESI-MS), electrospray-tandem–mass spectrometry (ESI-MS/MS), liquid chromatography-electrospray-tandem mass spectrometry (LC-ESI-MS/MS), nuclear magnetic resonance spectroscopy (NMR), and infrared (IR) and ultraviolet (UV) spectroscopy. In addition to these analytical chemistry methods, a biological activity method (CB₁ and CB₂ reporter assays) has also been used to detect ADB-CHMINACA.

3. Ease of Convertibility Into Controlled Substances

Ease of convertibility of ADB-CHMINACA 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-CHMINACA 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. Recently, the U.S. Drug Enforcement Agency reported the identification of ADB-CHMINACA in liquid formulation suitable for use in vaping. Dosage required for pharmacological effects in humans is unknown. In four individuals with confirmed ADB-CHMINACA intoxication, blood concentrations ranged from 1.3 – 14.6 ng/mL, with concentration correlated with degree of intoxication in this small sample.

B. Pharmacokinetics

Investigation of the pharmacokinetics of ADB-CHMINACA has focused on delineation of its metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Similar to other synthetic cannabinoids, ADB-CHMINACA undergoes extensive biotransformation catalyzed by cytochrome P450
enzymes prior to elimination of metabolites in the urine. In a study using human hepatocytes, ten metabolites for ADB-CHMINACA were identified.⁸ The primary reaction in the phase I metabolism of ADB-CHMINACA was hydroxylation of its cyclohexylmethyl tail.⁸ Other metabolites were also formed through biotransformation focused on the cyclohexylmethyl tail, including ketolization, tert-butyl hydroxylation, and dihydroxylation. Neither glucuronidation nor other phase II processes occurred with ADB-CHMINACA; hence, phase II metabolites were absent.⁸ Metabolites recommended for forensic identification of ADB-CHMINACA include ADB-CHMINACA 4‴-hydroxycyclohexyl, ADB-CHMINACA hydroxycyclohexylmethyl, and ADB-CHMINACA hydroxycyclohexylmethyl.⁸

These in vitro results in human hepatocytes were compared to results of analysis of authentic human urine in a single post-mortem sample from an individual who died after consuming ADB-CHMINACA and another synthetic cannabinoid.⁵ Because the person died shortly after smoking, only two metabolites of ADB-CHMINACA were identified in the urine specimen. Whereas cyclohexylmethyl hydroxylation was responsible for formation of ADB-CHMINACA’s predominant metabolites in human hepatocytes, dihydroxylation seemed to play a larger role in the authentic human urine sample.⁵ This reversal of predominance of metabolites in the urine may be related to lipophilicity of the metabolites, which would affect their facility in crossing cell membranes.⁵ However, Cannaert and colleagues¹⁰ reported that this reversal did not occur in authentic human urine samples from living individuals. Rather, major metabolites in their study were confirmatory of the Carlier et al study.⁸ Specific information on other pharmacokinetic parameters (absorption, distribution, elimination, and time course) for ADB-CHMINACA was not available in the literature, with the exception of a single study in which distribution of ADB-CHMINACA was measured in post-mortem tissues from one individual.¹³

C. Pharmacodynamics

ADB-CHMINACA is a full agonist of the CB₁ receptor, with reported binding affinities (Kᵢ) of 0.289 nM¹ or 0.49 nM.¹²,¹⁴ Efficacy for inhibition of forskolin-stimulated release of cyclic adenosine monophosphate (cAMP) was comparable to that of the full agonist WIN55,212-2, with EC₅₀ values of 0.620 nM¹ and 0.214 nM.¹²,¹⁴ ADB-CHMINACA was also potent in an assay measuring recruitment of β-arrestin 2, with EC₅₀ values of 1.49 and 2.2 nM for the CB₁ and CB₂ receptor, respectively.¹⁰ ADB-CHMINACA is one of the most potent synthetic cannabinoids to date.⁸

In vivo assessment of ADB-CHMINACA has been sparse. Published data are confined to results from a drug discrimination study in which ADB-CHMINACA was found to fully substitute for THC in male Sprague-Dawley rats, with an ED₅₀ of 0.07 mg/kg¹⁵ (further details in Section 8A of the present report). Rimonabant reversal of these effects suggests CB₁ receptor mediation. Unpublished data showed that ADB-CHMINACA decreased locomotor activity in male Swiss-Webster mice in a time- and dose-dependent manner.¹⁶ Suppression of activity occurred within 10 min of injection within a dose range of 0.1 – 1.0 mg/kg. The effect lasted from 40-80 minutes.
5. **Toxicology**

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

6. **Adverse Reactions in Humans**

In humans, the acute psychological effects of synthetic cannabinoids (including ADB-CHMINACA) 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.\(^{11, 17-20}\) 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 and reports of mass intoxication suggest that acute administration of ADB-CHMINACA has the potential to produce severe adverse reactions in humans up to, and including, death.\(^{3, 6, 7, 18, 21, 22}\) In a series of case studies (n=11) from a U.S. hospital emergency room, symptoms that were shared by many of these individuals with confirmed ADB-CHMINACA exposure include tachycardia, unresponsiveness, agitation and combativeness.\(^{21}\) Seizures, hyperemesis, slurred speech, delirium and sudden death have also been reported with use of synthetic cannabinoids (in general) and with ADB-CHMINACA (specifically).\(^{3, 6}\) In the spring of 2015, ADB-CHMINACA was associated with several drug-induced clusters of severe illness and death in the U.S.\(^{7, 18, 21, 22}\) In the European Union, 13 deaths with confirmed use of ADB-CHMINACA were reported over a two-year period from 2014-2016, and another death occurred in Japan.\(^{3, 4, 12}\)

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

7. **Dependence Potential**

   A. **Animal Studies**

   No available data.
8. Abuse Potential

A. Animal Studies

ADB-CHMINACA was tested in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle in a standard two-lever drug discrimination procedure. At doses from 0.025 to 0.18 mg/kg, ADB-CHMINACA (i.p.) produced dose-dependent increases in responding on the THC-associated lever to a peak of 83% (full) THC-lever responding at the 0.18 mg/kg dose ($ED_{50} = 0.07$ mg/kg). At a higher 0.25 mg/kg dose, responding on the THC lever decreased, producing an overall U-shaped dose-effect curve. This dose was also associated with significant decreases in response rate. Examination of the time course for effects of the 0.18 and 0.25 mg/kg doses in a different group of rats showed that full substitution and absence of substitution, respectively, was replicated at the original 30-min pre-session injection interval, although the 0.25 mg/kg dose did not substantially alter response rates in this second group of rats. Data from the time course experiment showed that the 0.18 mg/kg dose of ADB-CHMINACA increased substitution from 5 to 30 min post-injection (with a peak of full substitution at the 30-min time point) followed by sharp decreases from 60 to 240 min. Substitution of ADB-CHMINACA for THC was blocked by pre-treatment with rimonabant, suggesting that this effect was CB$_1$ receptor-mediated. ADB-CHMINACA has not been assessed in a self-administration procedure.

B. Human Studies

No available data.

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-CHMINACA 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.\textsuperscript{11} 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.\textsuperscript{23-27}


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. ADB-CHMINACA, specifically, has been associated with several clusters of mass intoxication, illness and death in the U.S. and in Europe.\textsuperscript{3, 6, 7, 12, 18, 21, 22} Agitation and aggressive behavior are common in individuals with analytically confirmed use of ADB-CHMINACA, although causality is difficult to determine.\textsuperscript{12, 21} Six analytically confirmed cases of driving under the influence of ADB-CHMINACA were reported in Hungary,\textsuperscript{4} with the likely probability of underreporting worldwide.\textsuperscript{12} Finally, based upon autopsies provided by the U.S. Drug Enforcement Agency for use in preparation of this report, as well as on published reports, a number of persons who have been hospitalized or who have died following use of ADB-CHMINACA have shown signs of other serious medical disorders (e.g., history of mental illness or substance abuse disorder, cardiovascular disease, morbid obesity),\textsuperscript{3, 12, 22} suggesting that co-morbidities may contribute to the overall public health burden related to the abuse of ADB-CHMINACA.

15. Licit Production, Consumption and International Trade

N/A

16. Illicit Manufacture and Traffic and Related Information

ADB-CHMINACA was first detected in Hungary in August 2014.\textsuperscript{3} Since then, ADB-CHMINACA has been detected in 17 Member States of the European Union, Norway and Turkey.\textsuperscript{3} As of 2017, the vast majority of ADB-CHMINACA seizures had occurred in Turkey.\textsuperscript{4} ADB-CHMINACA has also been detected in the United States.\textsuperscript{3, 12} Similar to other synthetic cannabinoids, underreporting is likely due to lack of routine screening for specific compounds.

Synthesis of ADB-CHMINACA (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{11} 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. There may also be trade within the
European Union, as indicated by seizures of packages of synthetic cannabinoids including those
containing ADB-CHMINACA.

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

17. Current International Controls and Their Impact
ADB-CHMINACA 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

**European Union:** EU Early Warning System report⁴ and subsequent risk assessment³
resulted in the decision to subject ADB-CHMINACA to control measures on May 14, 2018.
Seventeen Member States have already placed ADB-CHMINACA under regulatory control.
³ Other states will have one year from the May 2018 ruling to develop their own
regulations for this compound.

**United States:** Effective February 5, 2016, the U.S. Drug Enforcement Agency issued a
statement that placed ADB-CHMINACA under temporary Schedule I control.
Subsequently, an 8-factor analysis was performed, with report released in January 2018,¹²
and ADB-CHMINACA was placed under Schedule 1 control.

**Canada:** ADB-CHMINACA is classified as a Schedule II controlled substance under
Canada’s Controlled Drugs and Substances Act which was originally passed in 1996.

**Singapore:** ADB-CHMINACA is listed in the Fifth Schedule of the Misuse of Drugs Act
(MDA), effective May 2015.

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

None
References

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CB1 receptors. Portland, Oregon: Drug Enforcement Agency/Department of Veterans Affairs Medical Center, 2014.


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