Expert Committee on Drug Dependence

Thirty-eighth Meeting

Geneva, 14-18 November 2016

World Health Organization

Expert Peer Review No.2 for 5F-APINACA (5F-AKB-48)

1. Comments based on the review report

a. Evidence on dependence and abuse potential

5F-APINACA binds to cannabinoid CB_1 and CB_2 with greater potency than THC and activates the CB_1 receptor as a full agonist and more strongly than at the CB_2 receptor. 5F-APINACA induces a prolonged release of dopamine in the shell of the nucleus accumbens in awake mice. The CB_1 cannabinoid antagonist/inverse agonist, AM251, blocks several *in vivo* effects of 5F-APINACA in mice including its induced spontaneous and stimulated aggressiveness, hypothermic effects, and antinociceptive effects. The *in vitro* binding and functional activity effects of 5F-APINACA, along with its *in vivo* effects of hypothermia and antinociceptive effects that are antagonizable by AM251, are consistent with a THC-like cannabinoid compound.

No pertinent animal studies regarding dependence or abuse potential appear to have been reported using 5F-APINACA. User reports indicate compulsive re-dosing, tolerance development, craving, and physical withdrawal symptoms, the latter of which appeared resolved with the re-administration of 5F-APINACA.

b. Risks to individual and society because of misuse

Pre-clinical: The toxicological effects of 5F-APINACA include the ability to cause chromosomal damage without inducing gene mutation. High doses (3 and 6 mg/kg, i.p.) of 5F-APINACA induce spontaneous and handling-induced convulsions, hyperreflexia and myoclonus in mice (in contrast to THC) that are blockable by AM251. 5F-APINACA inhibits sensory responses reducing the visual object and acoustic response in mice, and the pinnae, corneal and vibrissae reflexes in mice. 5F-APINACA, similar to THC, induces a marked catalepsy in mice. These neurological effects are also antagonizable by AM251. Overall, these preclinical toxicological effects, which are likely translatable in some form to humans, provide health risks to individuals who use 5F-APINACA.

Clinical: Few toxicity data appear available with 5F-APINACA. Anxiety, paranoia, dry mouth, headache, hyperthermia have been reported by users. Long term use of

5F-APINACA has been characterized by users with a loss of appetite, cognitive impairment, breathlessness, cardiac conditions requiring medication, skin ablations, tooth decay, lethargy, apathy, tremors and insomnia, which are all exacerbated when attempting to reduce use. Chest pain, agitation, hypertension, and tachycardia were reported in one case of acute toxicity after inhalation of 5F-APINACA (it was unspecified if other drugs were involved). In another case involving smoked 5F-APINACA, myocardial infarction was reported in a 26-year-old man who had smoked 5F-APINACA. Other instances of hospitalizations were reported in the Critical Review involving the use of 5F-APINACA or admantyl synthetic cannabinoids that possibly included 5F-APINACA, but often other drugs were simultaneously detected making inferences regarding the contribution to toxicity of 5F-APINACA difficult.

The Norwegian Institute of Public Health reported four driving under the influence of drug cases in which 5F-APINACA was detected. Only one case of fatal 5F-APINACA use has been reported, and in this case, nine other synthetic cannabinoids were also detected and the decedent had been suffering from diabetic ketoacidosis.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc.)

5F-APINACA is sold over the Internet. It has been detected in commercial or seized products in several countries in Europe, the U.S., and Korea. Seizures in South America, Australasia, Japan or other countries in the East except Korea were not reported in the Critical Review. Perhaps the most notable seizure reported in the Critical Review was that from the EU in 2013 of 114 kg of 5F-APINACA. Few reports of analytical confirmation of the use of 5F-APINACA in biosamples exist and appear limited to 8 cases in Norway and a few cases in the UK and a case possibly in Germany.

d. Need of the substance for medical (including veterinary) practice

5F-APINACA is not marketed or licensed as a medicinal product.

e. Need of the substance for other purposes (e.g. industrial)

There appear no industrial uses for 5F-APINACA.

f. Measures taken by countries to curb misuse

The Critical Review identifies 13 countries that are directly controlling 5F-APINACA or include it under more generic legislation such as under their analogue control acts.

g. Impact if this substance is scheduled

Because 5F-APINACA does not appear to have an industrial application or an approved medical use, and because no special research interest possibilities were identified within the Critical Review, there appear not to be important ramifications if the drug were scheduled.

2. Are there absent data that would be determinative for scheduling?

More evidence of toxicity, specifically death-associated toxicity is needed, along with evidence of a more pervasive abuse.

3. Other comments or opinions

It would be helpful to provide information how routinely 5F-APINACA would be detected in current routine forensic screens, and whether we are currently getting accurate indications of its usage.

4. Expert reviewer's view on scheduling with rationale

Despite any properties of 5F-APINACA being similar to that which cannabis can produce, which is in Schedule I of the Single Convention on Narcotic Drugs, 1961, and in keeping with the observation that THC and synthetic cannabinoids such as JWH-018 and AM-2201 are controlled under the Convention on Psychotropic Substances of 1971, 5F-APINACA should be evaluated according to the requirements of the 1971 Convention. To this reviewer, there is insufficient evidence at present that 5F-APINACA is being or is likely to be abused to constitute a *substantial* risk to public health. Evidence of associated fatalities is minimal. Evidence of abuse outside of Europe or the US is minimal. Thus, this reviewer would not consider the use of 5F-APINACA consistent with Schedules I-III compounds. Perhaps 5F-APINACA satisfies Schedule IV requirements of, "Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little to great." However, this reviewer does not find that there is evidence of an "international" need for control, or that the controls of the Convention are suitable to solve or alleviate the present problem, that could likely be contained by individual country regulations. It is suggested that 5F-APINACA be kept under surveillance.