

Expert Committee on Drug Dependence
Thirty-sixth Meeting
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1. Comments based on the review report

a. Evidence on dependence and abuse potential

AM-2201 is an aminoalkylindole and an agonist of cannabinoid receptor type 1 (CB 1) and type 2 (CB 2). The data from *in vitro* studies demonstrate that it is more potent than Δ9-tetrahydrocannabinol (THC) at CB1 and CB2 receptors. Based on Ki values AM-2201 is about 40 and 18 times higher affinity than THC for CB1 and CB2 receptors, respectively. Human effects observed with use of AM-2201 are sedation, cognitive dysfunction, tachycardia, postural hypotension, dry mouth, ataxia, immunosuppression and psychotropic effects. These effects are very similar to those which are expected by stimulation of CB 1 receptor. However, preclinical data for the effects of AM-2201 on the central nervous system, neurobehavioral including cognition, cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems are lacking. Human data for pharmacological properties of AM-2201 are also not sufficient.

Several active metabolites of AM-2201 are identified which are full agonists at cannabinoid receptor. These metabolites are more potent than THC.

Toxicological studies are limited to only cell lines. AM-2201 showed dose dependent cytotoxicity in primary neuronal cells of the forebrain. Pre-incubation with the CB1 selective antagonist AM-251 suppressed AM-2201 cytotoxicity (30 μM), indicating an important role of CB1 receptors in the induction of cytotoxicity. Furthermore, a strong neurotoxic effect is also noted. However, considering the concentrations tested in the above study (10 μM and 30 μM AM-2201), conclusions on the cytotoxicity *in vivo* have to be drawn with care, as serum concentration levels published in the literature or from routine sample analysis (own unpublished data) are not higher than 33.4 nM (12 ng/ml) and are therefore about 300-fold lower than the concentrations applied by Tomiyama et al. Nevertheless, due to the lipophilic character of AM-2201, it can not be excluded that higher concentrations may occur in deeper compartments or in epithelial cells.

The dependence potential of AM-2201 was evaluated in monkeys. Data indicate that the probability of abuse potential of AM-2201 may be high and that abuse and dependence liability may be linked with its active metabolites JWH-018 and JWH-073.

Tolerance can occur with synthetic cannabinoids. Acute cessation of high dose intake may lead to withdrawal symptoms including nocturnal nightmares, profuse sweating, nausea, tremor, headache, anxiety, unstable mood, crying fits, feeling of inner emptiness,

spatial disorientation, hyperacusis, somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness

b. Risks to individual and society because of misuse

AM2201 is usually consumed as herbal mixtures that may contain synthetic cannabinoid chemicals JWH-018, JWH-081 and JWH-250 and other psychoactive substances. These chemicals can cause non-fatal and fatal hazardous effects in users. The presence of JWH-018, JWH-073 and AM-2201 without THC was detected in urine analysis in some cases. Fatality, one each in Germany, USA and Sweden are reported. In all three, AM 2201 was detected in post mortem blood samples along with other synthetic cannabinoids and psychoactive drugs. Thus it is apparent that AM 2201 is a popular constituent chemical of "herbal mixtures" which are very detrimental for the health of users.

According to the report of WHO questionnaire survey, one respondent in 2012 reported two deaths due to AM-2201. This same respondent reported 10 emergency room visits in 2012 and another reported 5 visits. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by AM-2201. Recreational/harmful use of AM-2201 was confirmed by 22 out of 66 responder states. Six respondents also mention that AM-2201 is often found in herbal mixtures.

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

AM2201 is a popular synthetic cannabinoid as recreation drug. The use and supply is widespread all over the world. The major regions are Asia (China and India), followed by Europe (Czech Republic, Hungary, Netherlands, Portugal, Spain, Ukraine and United Kingdom), the Americas, Africa and Oceania. The emergence of AM 2201 has been found in 27 countries up to December 2013. Detection of metabolites of synthetic cannabinoids in urine samples of athletes indicates its misuse by sport person (Heltsley et al.) The synthetic cannabinoids are more in demand as a substitute for cannabis and may be due to their non-detectability, easy availability and strong effects.

The most popular mode of procurement is through internet. There is tremendous increase in online shops for recreation drugs. WHO questionnaire report states that 11 respondents reported processing into the consumer product, 18 reported trafficking, three reported diversion and 16 an internet market.

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

No use reported.

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

No use reported.

f. Measures taken by countries to curb misuse

Of the responders to WHO questionnaire, 26 reported that AM-2201 was controlled under legislation that was intended to regulate its availability; among these 18 under “controlled substance act”, five under “medicines law”, one “temporary ban” and two under “other” laws

European countries have taken a lead to curb the misuse of Synthetic cannabinoids including AM 2201.

g. Impact if this substance if scheduled

No impact on availability for legitimate use.

2. Additional information to critical review report

No.

3. Other comments or opinions

More preclinical studies may be conducted to provide direct evidence regarding toxicity and abuse potential. Moreover, the metabolism of AM 2201 needs attention.

4. Expert reviewer's view on scheduling with rationale

AM 2201 has no medical use and indirect evidence based on use of mixtures of synthetic cannabinoids suggest abuse potential and toxicity both nonfatal as well as fatal. Since its effects have similarity to cannabis, AM 2201 may be placed under schedule 1 of 1961 convention.