1. **Comments based on the critical review report**

Ketamine is an anesthetic used in human and veterinary medicine. Sub-anesthetic doses produce psychotropic effects in humans. Based on many years of clinical experience, ketamine is generally considered a safe anesthetic. Nevertheless, it can produce adverse reactions in humans during awakening from anesthesia including vivid dreams, hallucinations, floating sensations, and delirium. These effects can be reduced by concurrent use of a benzodiazepine and leaving the patient in a low stimulus room during awakening.

a. **Evidence on dependence and abuse potential**

Animal studies have shown that ketamine is readily self-administered, that tolerance may develop upon repeated administration and that withdrawal symptoms may be observed.

Human studies have shown that ketamine in sub-anesthetic doses affects perception of body, time, surroundings and reality, and that it produces a state of mind that resembles a schizophrenic psychosis. For these effects, ketamine is called a dissociative anesthetic. Ketamine also produces a biphasic effect on anxiety, reducing anxiety at low doses and increasing anxiety at high doses. The dissociative effects of ketamine in combination with its effects on anxiety at high doses may discourage experimental users from continued use.

Tolerance to ketamine may develop in humans and ketamine dependence is increasingly reported in survey studies (Winstock et al., 2012). However, cases of ketamine dependence described in the literature are limited in number and a withdrawal syndrome has not been defined (Morgan and Curran, 2012). Published case studies indicate that some users may be unable to stop ketamine use (Wei and Yang, 2013).

b. **Risks to individual and society because of misuse**

Ketamine acutely affects cognitive performance, including attention, working memory and semantic memory. Short-term exposure, however, does not produce long-term effects on cognition, mood and personality. Chronic use of ketamine may selectively impair cognitive processes. In recreational users, semantic memory impairments may be reversible; attentional impairment may be long-lasting.
An acute adverse effect of recreational ketamine use is aberrant behaviour, which poses a risk for accidents and injury to the user. Since 2007, urinary tract problems and bladder disease have become apparent as adverse effects of chronic ketamine use. Secondary renal damage may occur in severe cases. Upon cessation of ketamine use, symptoms usually resolve over time but in a few individuals, symptoms may progress despite stopping ketamine use.

Few deaths following a ketamine overdose have been described. In ketamine-associated fatalities, additional substances are frequently found post mortem, which makes the contribution of ketamine difficult to assess.

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

Ketamine has been misused as a recreational drug in specific populations and subcultures since the early seventies. However, solid epidemiological data on ketamine misuse at present is not available. Although levels of misuse in the general population may be very low, recent publications suggest that the levels have increased and that it has become more mainstream. Ketamine abuse is mainly reported in China, Hong Kong, Taiwan, UK, Australia and the USA.

Data on dependence in ketamine users is largely lacking. In contrast, there is increasing evidence for physical adverse effects - in particular urinary tract problems - after prolonged use of ketamine in high doses.

Based on the WHO questionnaire for Review of Psychoactive Substances for the 36th ECDD, twenty-eight respondents (out of 64 having information on ketamine) reported that there was recreational/harmful use of ketamine, while 12 respondents reported that there was no such use. One respondent reported an overdose death in 2012. Three respondents reported on emergency room visits (3, 5, and 12 in 2012; 1550 in 2011). Two respondents reported on enrollment in an addiction programme (25 and 869 persons, respectively).

INCB (2011) reported that 99% of all ketamine seizures worldwide in 2009 took place in Asia. Illicit manufacture mainly occurs in China and India.

On illicit activities involving ketamine, four respondents to the WHO questionnaire reported processing of ketamine into the consumer market, 15 reported trafficking, 14 reported diversion and 12 reported an internet market. The total number of seizures was 2150 (quantity: 5549 kg and 45 L) in 2011 (11 respondents), and 2070 (quantity: 4199 kg and 31 L) in 2012 (12 respondents). The number of seizures appears to be stable.

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

Sixty-two respondents to the WHO questionnaire stated that ketamine is currently authorized as a medical product used for anesthesia, sedation, and in animals for immobilization.
Ketamine is widely used in developing countries due to its relative safety, in particular in settings with paucity of skilled medical personnel, poor equipment, and lack of inexpensive alternatives. In Africa, ketamine was used in 10% to 90% of cases in hospitals visited for the 35th ECDD report in 2012. There are no indications that this situation has changed since 2012. Six respondents to the WHO questionnaire indicated that the availability of ketamine would be affected if placed under international control.

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

Not applicable.

f. Measures taken by countries to curb misuse

Fifty-five respondents to the WHO questionnaire reported that ketamine was controlled under national legislation that was intended to regulate its availability. In 2009, 48 countries and in 2008, 34 countries reported on such legal measures. It may be argued that over the years a situation of international control has emerged due to international resolutions and data on illicit activities and misuse.

g. Impact if this substance if scheduled

Six respondents to the WHO questionnaire reported that the availability of ketamine for medical use will be affected if ketamine is placed under international control.

Ketamine has acquired a unique place in human and veterinary medicine. It is used as an anesthetic in many different procedures and surgeries. In developing countries with poor medical facilities, ketamine has a prominent place as an anesthetic in human medicine due to its safety and ease of use. Several member states have indicated that ketamine is indispensable as a veterinary medicine.

2. Additional information to improve the critical review report

There is increased concern over ketamine’s neurotoxicity. Dose-dependent abnormalities of white matter in temporoparietal brain regions have been found following chronic ketamine use (Liao et al., 2010; Liao et al., 2011). In chronic ketamine users, cognitive impairments (verbal and visual) have been found (Morgan et al., 2009; Morgan et al., 2010; Chan et al., 2013; Liang et al., 2013; Tang et al., 2013). However, most ketamine users are poly-drug users. Therefore, the contribution of ketamine is hard to establish (Liang et al., 2013; Chan et al. 2013). Studies that reported on the persistence of the cognitive impairments are scarce and inconclusive. In usual clinical practice, ketamine does not induce neurotoxicity (Mion and Villevieille, 2013).

There is evidence that ketamine misuse is increasing and that dependence may develop. Morgan and Curran (2012) cited that last-year use in young UK people aged 16-24 had increased from 0.9% in 2007/08 to 1.7% in 2009/10, and that in the USA ever use was 1-2% of 10th- and 12th-graders. McCambrigde et al. (2007) reported an increase of current
use prevalence from 3.9% in 1999 to 16% in 2003 among respondents to a UK music magazine survey (Mixmag).

In an internet-based survey in 2010, 17% of 1285 recent (last year) ketamine users (poly-drug users; 92% of respondents were from UK and USA) were found to be dependent (Winstock et al., 2012). This is consistent with the 22% of respondents reporting physical tolerance to ketamine in an Australian study in 2003 among 100 recreational users (Dillon et al., 2003). In an interview study of 90 ketamine users, 57% of frequent users, 43% of infrequent users and 60% of ex-users reported experiences of or concerns about addiction/dependence (Muetzelfeldt et al., 2008).

References

3. **Other comments or opinions**

No further comments.

4. **Expert reviewer’s view on scheduling with rationale**

Ketamine is widely used as an anesthetic in human and veterinary medicine. According to the WHO critical review in 2012 (including annexes 2 and 3), ketamine is a main agent for anesthesia in many surgical and obstetric procedures in several developing countries in Africa. The popularity of ketamine is due to its safety and ease of use under difficult circumstances. There are no data presented that indicate that this situation has changed since 2012. Placing ketamine under international control may therefore create a public health crisis in these countries as it will likely reduce the availability of ketamine.

There is evidence of urinary tract problems after chronic ketamine abuse, but recent epidemiological data on the prevalence of abuse is largely lacking. Traditionally, ketamine abuse occurred mainly in specific subcultures but it has become more mainstream in specific regions/countries, in particular in the UK, the USA and in East Asia. Most countries facing problems due to ketamine abuse have taken legislative control measures to regulate its availability.

Considering the medical need for ketamine in developing countries and the consequences of international control on the availability of ketamine in such countries, the reviewer’s recommendation is not to place ketamine under international control. Instead, ketamine may be kept under surveillance and to study the prevalence of abuse and dependence, and its adverse effects on individual and public health.