Report on the Risk Assessment of ketamine
in the Framework of the
Joint Action on New Synthetic Drugs
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On 17 April 2000, the Portuguese Presidency of the European Council formally notified KETAMINE (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) to the EMCDDA for risk assessment under Article 4 of the Joint Action on new synthetic drugs of 16 July 1997.

A meeting of the Scientific Committee of the EMCDDA extended with experts nominated by the Member States and representatives of the European Commission, Europol and the EMEA to assess the health and social risks as well as the possible consequences of prohibition of ketamine, was held on 25-26 September 2000.

The meeting considered the following documents:

I. Technical Annexes A and B: The Pharmacotoxicological Report on ketamine, Report to the EMCDDA
II. Technical Annex D: public health risks: epidemiological evidence, EMCDDA
III. Technical Annex C: sociological/criminological evidence, EMCDDA
IV. Europol contribution to the risk assessment of ketamine
V. EMEA contribution to the risk assessment of ketamine

These documents, in conjunction with further information and comments from the expert participants, formed the basis of the Risk Assessment reported below.

1. CHEMICAL DESCRIPTION

The chemical name of ketamine is 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, an arylcycloalkylamine. It is structurally related to phencyclidine (PCP—‘angel dust’) and cyclohexamine. It occurs in racemic form and also as the S-enantiomer.

Registered names (human use) are: KETALAR, Ketamine PANPHARMA, KETOLAR, KETANEST-S.

Registered names (veterinary use) are: KETALAR, Ketaminol Vet., Clorketam, Imalgene, Anesketin, Ketamine Ceva, Vetalar Vet., NARKETAN, KETASET.

Ketamine is known in Member States under the street names: K, Special K, KitKat, Tac et Tic, Cat Valium, Vitamine K, Ket, Super K, and others.

2. PHARMACEUTICAL DESCRIPTION

Ketamine was first synthesised in 1962 and patented in Belgium in 1963. As an anaesthetic and analgesic, ketamine has a recognised unique therapeutic value in veterinary practice and, to a lesser extent, in human medicine. For therapeutic purposes, ketamine usually is administered intravenously or intramuscularly.
In recreational use, typical doses are: 75-125 mg intramuscularly or subcutaneously; 60-250 mg intranasally; 50-100 mg intravenously; and 200-300 mg orally.

Ketamine is manufactured by the chemical industry for use in the manufacture of pharmaceutical products using as precursors cyclopentyl bromide, \( \alpha \)-chlorobenzonitrile, and methylamine. Due to the complicated multi-step synthesis, and the difficulty of purchasing the necessary precursors and numerous solvents and reagents, ketamine sold illicitly for recreational use appears to be mostly obtained by diversion of legitimate supplies of either the bulk drug or of pharmaceutical preparations containing it.

Pharmaceutical products may be injected or may be modified by evaporation after which the resultant powder may be snorted in pure form or mixed with other drugs and/or inactive components. In powder form, combination with cocaine has been observed. In the form of tablets, the concentration of ketamine and other substances are mostly unknown by users. These tablets are sold as ‘ecstasy’ in some Member States. Other substances reported to be present in ketamine-containing tablets are pseudoephedrine, ephedrine, caffeine, amphetamine, methamphetamine and MDMA. As the effects of ketamine are dose-dependent, the uncertainty about ketamine concentration in the powder, and \textit{a fortiori} in fake ‘ecstasy’ tablets, poses a risk in recreational use.

Preparations containing ketamine hydrochloride are used as an anaesthetic and analgesic agent in human and veterinary medicine, with important clinical applications in paediatric and ambulatory anaesthesia, treatment of burned wound patients, and for short anaesthetic procedures. However, the human use of ketamine in the EU is restricted to special indications, due to the occurrence of emergence reactions. Outside the EU, the ease of use gives ketamine a major advantage under difficult circumstances (developing countries and remote areas). Its use in veterinary anaesthesia, especially in small animals, is widespread and considered by several Member States and by the Federation of Veterinarians of Europe as indispensable in veterinary medicine.

3. HEALTH RISKS
   (Documents I, II and V)

3.1 Individual health risks

(a) Acute effects

Ketamine is a dissociative anaesthetic. The term ‘dissociative’ has a twin meaning. Firstly, it refers to an effect on the brain, inducing a lack of responsive awareness, not only to pain but also to the general environment. Secondly, it refers to a feeling of dissociation of the mind from the body (‘out of body experience’). Ketamine would be expected to block or interfere with sensory input to centres of the central nervous system (CNS) in a way the drug selectively interrupts association pathways of the brain before producing somesthetic (sensation of having a body) sensory blockade.

Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output and blood pressure. In recreational ketamine users, presenting to an emergency department, tachycardia was the most common finding. As a mild respiratory depressant, ketamine
is unlikely to produce respiratory depression at recreational doses, even if it cannot be wholly excluded. Cardiovascular effects usually do not pose a problem in patients without cardiovascular problems, but ketamine is contraindicated in patients with significant ischaemic heart disease and is to be avoided in those with a history of high blood pressure or cerebrovascular disorders.

The findings of neurotoxicity in the rat may indicate cause for concern in recreational users of ketamine. These users may not take ketamine in combination with protective agents like benzodiazepines as is usually the case in the clinical setting. Moreover, compounds increasing the neurotoxic potency of ketamine (like alcohol) might be co-administered. Recreational use also implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in chronic users of ketamine have been reported, though rarely, and include persisting impairment of attention and recall and a subtle visual anomaly. The Report on Risk Assessment of 4-MTA noted that ketamine increased the neurotoxicity of 4-MTA in mice. Neurotoxicity of repeated exposure to ketamine in primates including humans has not been studied.

(b) Clinical effects

Ketamine is considered as an anaesthetic with a good safety profile, based on extensive clinical experience. The major drawback, limiting clinical use, is the occurrence of emergence reactions in patients awakening from ketamine anaesthesia. These reactions include hallucinations, vivid dreams, floating sensations and delirium. However, preclinical data on the effects of repeated ketamine administration may be of greater importance for recreational use which, contrary to clinical practice, may present cases of long-term use.

A total of 12 deaths in which ketamine was identified, have been noted between 1987-2000 including seven from the USA. Only three reported fatal cases involving ketamine alone were identified. Two reports concern mixed drugs fatalities. In one case, ketamine had only a minor role. For the remaining six cases, insufficient details were available to be evaluated properly. In the three cases involving only ketamine, the routes of administration were intramuscular or intravenous and the cause of death was mainly due to overdose (multiple intramuscular doses or accidental intravenous overdose), in line with preclinical findings. In the other cases involving ketamine mixed with other drugs, the observed lower ketamine concentrations indicates that drug interaction may have contributed to these deaths. Substances with CNS/respiratory depressant effects, like ethanol, opioids, barbiturates, and benzodiazepines or drugs with cardiotonic effects, like cocaine or amphetamines, may increase ketamine acute toxicity.

Regarding non-fatal intoxications, potential dangerous interactions may also arise when different drugs are combined. Ketamine has sympathomimetic properties. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects. Serious side effects such as hypertension and pulmonary oedema have been reported, but such adverse effects appear to be rare and may be related to the combination of ketamine with other drugs, such as amphetamines and its analogues, ephedrine and cocaine.
(c) Dependence

Tolerance, dependence and withdrawal signs have been observed in a number of animal studies. Tolerance to the desired effects of ketamine develops quickly and may result in an escalation of the dose, the toxicological implications of which are unknown. A risk associated with the recreational use of ketamine, is the potential of the drug to cause psychological dependence in some individuals based on case reports and information from users. The prevalence of long-term use is unknown. There is no evidence that ketamine causes an abstinence syndrome in humans.

(d) Psychological effects

Ketamine may be experienced by the recreational user as an altered, ‘psychedelic’ state of mind (‘the K-hole’) that allows the user to travel beyond the boundaries of ordinary existence. The intensity of ‘psychedelic effects’ is dose-related. Ketamine in subanaesthetic doses produces a clinical syndrome which both neurophysiologically and behaviourally resembles that of a schizophrenic psychosis. Ketamine acutely affects cognitive performance, profoundly affects perception of the body, time, surroundings and reality.

The main effects of ketamine are neurobehavioural: anxiety, agitation, changes of perception (e.g., loss of notion of danger, visual disturbance) and impairment of motor function and the analgesic effects. In such a condition, the user may be at risk of injury to themselves (burns, falls) or to others (accidents).

3.2 Public health risks

(a) Availability and Quality

Ketamine preparations have marketing authorisations in most countries of the EU, except in Greece where the marketing authorisation was recalled in 1998.

Seizure data suggest mostly low levels of availability of ketamine for illicit use within different Member States, with a decrease occurring in the UK and an increase in two other Member States. A large proportion of ketamine seizures are in tablet form and the tablets carry the same logo as those often found in ecstasy tablets. It may also be found in powder form and sold as a stimulant such as amphetamine or cocaine. Forensic laboratories have found ketamine in variable doses mixed with manitol, caffeine, ephedrine and pseudo-ephedrine, MDMA, methamphetamines and amphetamines. In Belgium, 89 kilos of pure ketamine in powder were seized in September 1999 and a further 3 kg in January 2000. Four Member States (Belgium, Ireland, the Netherlands and the UK) seized significant amounts of ketamine. However, seizures of ketamine are small when compared to seizures of ‘regular’ types of synthetic drugs such as amphetamine, MDMA and MDA.

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1 Classification for the supply of medicinal products for human use is regulated by Directive 92/26/EEC of 31 March 1992 and Article 12 of Directive 75/319/EEC of 20 May 1975 regulates through the Committee for Proprietary Medicinal Products (CPMP) the suspensions, withdrawal or variations to the terms of the marketing authorisation, in particular to take account of the information collected in accordance with Pharmacovigilance.
(b) Knowledge and Perception of ketamine Among Users

There is apparently low awareness of and experimentation with ketamine in Europe compared with drugs such as cannabis, MDMA, amphetamine and cocaine. Lack of information about the dose content of the ketamine on the market may be an important factor. Anecdotal reports from France and the UK indicate growing awareness among consumers about how to manage doses to achieve sought after effects and to avoid negative ones. A survey in a dance setting in Austria found that the respondents, using regularly MDMA and amphetamines, considered the psychological risks attached to ketamine as very high.

At low doses, ketamine is sometimes reported to have a stimulant effect: this could be the result of stimulant effect of other drugs or active cutting agents (like caffeine) because ketamine is often snorted with amphetamines and/or cocaine or taken with other drugs in the illicit drug scene. There is some indication that ketamine has an up-market image as an esoteric drug for experienced drug users.

(c) Prevalence and Patterns of Use

Surveys of selected groups of drug users in dance settings have shown that a significant number of people experiment with ketamine but the level varies between sub-populations and geographical areas. A London club survey in 1997 found that up to 40% of the 200 respondents had experimented with ketamine and were to use it the same evening. A large French survey conducted the same year found that 15% of the 900 respondents in techno party settings had experimented with ketamine. Recently, a large school survey conducted in the North East of England found that 1% of 13/14 years old children and 2% of 15/16 years old had ever tried ketamine compared to 2% and 5% respectively who had tried cocaine.

The most popular route of administration is to snort ketamine as a powder and to inject liquid preparations, and there have been reports of it being swallowed, smoked or inserted rectally.

(d) Characteristics and Behaviours of Users

Although there is evidence of use by younger people, targeted surveys and anecdotal reports indicate that prevalence may be higher in older, highly educated, experienced, MDMA users, particularly in the free party/new age travellers scene, in the gay club scene, and among small groups of self-exploratory individuals. Among ‘closed’ groups in Europe, initiation into ketamine use is often ritualised.

The most vulnerable groups are those who take ketamine under the illusion they are taking MDMA or some other stimulant drug. The volume of seizures of ketamine in tablet form with ecstasy-type logos reflects the scope for this scenario and the need for better information about drug contents and harm reduction. Ketamine does not react with commonly used field tests (e.g., Marquis reagent) although other drugs present in the tablet may produce a positive reaction.
(e) Indicators of Health Consequences

In the EU since 1996, there have been four deaths reported to the EMCDDA in which ketamine was found by laboratory analysis, of which two occurred in 1996 in Ireland. In neither of the Irish cases, ketamine was considered to be the main cause of death. One death of a 19 year-old-male has been reported in France where ketamine, LSD and ecstasy were implicated. The fourth death, also reported from France, was a polydrug user.

There has been a notable lack of reporting about hospital emergencies in Europe. A recent report in France presents some data on 17 cases of intoxication associated with ketamine.

An important factor of health risk is the lack of reliable indications of dose accompanying sales of ketamine at street level. In the absence of advice, first time users of ketamine will tend to follow similar consumption patterns as those previously adopted for other drugs. This uninformed use of ketamine increases the risk of both physical and psychological problems. The existence of tolerance may increase a tendency to move from snorting to injecting ketamine, with the risks associated with injection.

(f) Context of Use

The implications for the non-ketamine using population appears to be phenomenon of ketamine entering the recreational drug market in the guise of ecstasy, or other stimulant drugs. This means that someone expecting to take MDMA, cocaine or amphetamine may find themselves taking ketamine inadvertently, without warning, knowledge or support.

Compared with the effects of stimulants, the rapid physical incapacity rendered by ketamine consumption has serious implications for driving.

4 SOCIAL RISKS: sociological/criminological aspects
   (Documents III and IV)

4.1 Sociological aspects

4.1.1 Social Consequences

Social consequences for the user stem firstly from its anaesthetic properties and loss of physical control if too high a dose is taken, and secondly from reported psychological effects of regular, or heavy, use which include dependency. In addition to the loss of physical control it may cause tension due to the introspective quality of effects, other psychological symptoms, and compulsive use by a small minority

4.1.2 Consequences for the Social Behaviour of the User

Main consequences on social behaviour stem directly from ketamine’s effects and a tendency towards compulsive use by some users.
4.1.3 Other Social Consequences

In dance settings ketamine often appears in the form of well-made tablets, which are visually similar to MDMA and usually mixed with a stimulant ranging from caffeine to amphetamine. It is also found as liquid, powder and capsules. Ketamine has also been used as a cutting agent for drugs such as cocaine, amphetamines and heroin and may be taken by problem opiate users. The chosen route of administration for a small minority is by injection which raises a value conflict in a drug using culture which is strongly against injecting.

A range of social factors increase the probability of use, such as the existence of a large market of long term ecstasy users seeking new drug experiences, a rather intellectual trend-setting image and low price. However, other factors mitigate against widespread diffusion, such as the anaesthetic effects, marked discomfort with intranasal use, the short action, acute psychological reactions when taken without due knowledge about dose or effects, psychological dependence, and negative effects on social relationships.

In view of potential anaesthetic and numbing effects, psychological disturbances and compulsive use there are implications for: drug services, research institutes, hospital emergency departments and the press.

4.2 Criminological aspects

The seizure of considerable amounts in Belgium, Ireland, the Netherlands and the UK could suggest an involvement of organised crime. In the UK, it is believed that ketamine raw material is imported in bulk from legitimate suppliers in Europe. A number of sources, close to the user, suggest that there may be diversion from licit sources or foreign purchase, particularly from Asia.

5. POSSIBLE CONSEQUENCES OF PROHIBITION

5.1 Legal Status

Ketamine is subject to control in five Member States: Belgium, France, Greece, Ireland (to be scheduled in the Misuse of Drugs Act) and Luxembourg. It is controlled through general medicines legislation in all Member States. Due to the fact that ketamine preparations, as medical and veterinary products, have marketing authorisation in most Member States and have a recognised unique therapeutic value, the major concern appears to be the diversion from legitimate supply to the black market.

The complex routes of synthesis for manufacturing illegally ketamine reduce the potential impact on the illegal market for ketamine of targeted measures to control ketamine precursors. Illegal production of ketamine is unlikely to develop due to these conditions. However, the implication of organised crime in the production and supply of ketamine in tablet form, with the possible health risks due to sales of ketamine tablets with ecstasy logos, represents a particular matter of concern.
5.2 Possible Consequences of Prohibition

The possible consequences of prohibition discussed at the meeting included the following:

- The EMEA highlighted the fact that changes in the conditions of marketing authorisations for ketamine containing medicinal products proposed by the meeting should be dealt with at national level or referred to the CPMP and CVMP.
- Introducing penalties for use would be unlikely to deter use in groups where illegal drugs are already well-established.
- Concern was expressed about the effects of prohibition and control measures on informal information and harm-reduction networks.
- One opinion was that control measures might draw unnecessary attention to the drug thus increasing its attractiveness to potential users.
- In discussions on possible mechanisms of control, differences between control of the bulk drug and of medicinal products containing ketamine were mentioned. In this regard, there was a strong support that the view of the chemical and pharmaceutical industry about possible measures of control be sought.
- The view that as a common minimum approach, medicines legislation should be used as a control measure received strong support.
- Another opinion expressed at the meeting was that, in addition to the medicines legislation, stronger measures of control to deal with diversion, trafficking and inadvertent exposure (i.e. through fake ‘ecstasy’-tablets) were necessary. It was also stated that control of import and export of ketamine requires such measures.
- The meeting noted the concern of the Federation of Veterinarians of Europe that placing ketamine under the same stringent restrictions as opioids could be detrimental to good veterinary medicine. It was noted that the same concern could apply to the use of ketamine in human medicine.

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6. CONCLUSIONS

The Scientific Committee of the EMCDDA enlarged with experts from the Member States and representatives of the Commission, Europol and EMEA have considered the health and social risks as well as the possible consequences of prohibition of ketamine and in accordance with Article 4 of the Joint Action submit the following conclusions:

6.1 Ketamine is not a new synthetic drug. While it has a significant therapeutic use, it is also being used in recreational settings.

6.2 The meeting noted the main risks of the recreational use of the drug, such as the psychological dependence, loss of self-control, and the risk of acute intoxications. To date, the use of ketamine has been reported as associated with mortality or morbidity in a small number of cases.

6.3 An opinion, which received strong support at the meeting, was that as a common minimum ketamine should be subject to control under the medicines legislation in Member States.

6.4 Another opinion firmly expressed at the meeting was that, in addition to the medicines legislation, stronger measures of control to deal with diversion, trafficking and inadvertent exposure to the drug were necessary.

6.5 The meeting recommends that both the EMCDDA and Europol should further monitor the manufacture, trafficking, distribution, patterns of use and health consequences of ketamine, particularly the fatalities and non-fatal emergencies.

6.6 The meeting recommends that a study on possible neurotoxicity of ketamine in primates should be considered in the context of the 5th Framework Research Programme of the European Commission.

6.7 The possibility for improving control of diversion should be discussed with the chemical and pharmaceutical industry in order to ensure the continued availability of ketamine for medical and veterinary use.

6.8 The meeting recommends that consideration should be given to how appropriate information be disseminated to the most vulnerable risk groups.

Lisbon, 25 September 2000