The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

KETAMINE

SUMMARY REPORT

1. Ketamine [(±)-2-(2-Chlorophenyl)-2-methylamino-cyclohexanone hydrochloride] belongs to the group of the dissociative anaesthetics, which induce a state of sedation, immobility, amnesia and marked analgesia.

   In veterinary medicine ketamine can be administered by intramuscular, intravenous or subcutaneous routes and can even be sprayed into the mouth of fractious small animals for oral administration. It is used in nearly all kinds of animals even non-domesticated, birds and primates. The dosages depend not only on the route of application and on the animal species treated, but also on whether the animal is pre-medicated with other central nervous system depressants. In the horse the dose used is 2.2 mg/kg bw. Ketamine is used together with guaifenesin and xylazine as a method of restraint for casting the horse.

   For other target species the following doses and routes of administration are recommended: bovine: 2 mg/kg bw by intravenous or, in calves only, 10 mg/kg bw intramuscular injection; sheep and goats: 10-20 mg/kg bw by intravenous or intramuscular injection, swine: 5-10 mg/kg bw by intravenous or intramuscular injection, rabbits: 25-60 mg/kg bw by intramuscular or subcutaneous injection; birds (depending on species): 15-40 mg/kg bw by intramuscular injection, non-domesticated species (depending on species): 5-100 mg/kg bw by intramuscular injection.

   In human medicine ketamine is used for the induction of dissociative anaesthesia in adults in a dose of 1-2 mg/kg bw over a period of about 1 minute by intravenous route. In the case of intramuscular administration the dose is 6-13 mg/kg bw. It is especially useful in children for the management of minor surgical or diagnostic procedures.

2. Studies indicate that ketamine may have anticonvulsant activity, notwithstanding this literature refers to ketamine as an "epileptogenic anaesthetic". Several *in vivo* studies have been conducted in laboratory animals. In dogs, repeated administrations of doses of 40 mg/kg bw intramuscularly for each of 4 successive days, or 5 injections at 30 minute intervals on the same day induced pharmacological effects including incoordination followed by prostration, prolonged state of anaesthesia. When increasing daily injections over a 29-day period, starting with doses of 1 mg/kg bw reaching a final level of 160 mg/kg bw, clinical signs were related to pharmacological activity of the drug (excitement, tremors, incoordination and prostration). In monkeys, anaesthesia was induced by an intravenous administration of 20 mg/kg bw, at the rate of 5 mg every 15 seconds. Thereafter the anaesthesia was maintained by intravenous injections of 12 mg/kg bw every 15 minutes. Anaesthesia was maintained for either 1, 3 or 6 hours at twice weekly intervals. Insufficient data were provided to derive a pharmacological NOEL.

3. Ketamine as its hydrochloride can only be administered by the parenteral route. Absorption from the injection site is rapid with peak plasma concentrations after 10 minutes. Plasma protein binding in the horse averages 50% over a concentration range of 0.3-20 μg/ml, dependent upon the pH. In all species studied the pattern of decline in blood concentration is biexponential. The initial α-phase is very rapid

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and results from the wide distribution of the drug to body tissues. The half-life for distribution ($t_{1/2\alpha}$ for the horse is less than 3 minutes).

Also the very intensive and rapid metabolism is responsible for the short half-life. In rats and monkeys four metabolites were identified, of which norketamine was the major one. In sheep norketamine is already detectable in the plasma within 1 minute, reaching maximum levels at 6 minutes. In calves norketamine is detectable within 2 minutes and concentrations peak at 5-10 minutes. The minor pathway is by hydroxylation. The hydroxylated metabolites are unstable and dehydrated to dehydronorketamine and further conjugated to glucuronides. Percentages of these metabolites in the target animal species are not mentioned.

The half-life of elimination ($t_{1/2ß}$) in the horse is between 40 and 60 minutes. It is assumed that at the time when anaesthesia has disappeared 40-60% of the drug still remains in the body in active form and maintains blood levels well below anaesthetic ones. Pre-medicating with xylazine reduced volumes of distribution and the clearance rate of the drug by approximately 50%. Excretion is mainly in the urine but also, for a minor part, in bile. The very quick absorption, tissue distribution, metabolism and elimination mean that ketamine in all animal species tested is not a problem substance concerning residue levels. It is estimated that after 10 half-lives (approximately 7 hours) the percentage still present in the body is lower than 0.1%.

4. Single dose acute toxicity shows an LD_{50} between 140 (intraperitoneally in the neonatal rat) and 616 mg/kg bw orally in the mouse.

5. In a toxicological repeated toxicity study, carried out in dogs, 3 groups of 4 animals were given daily intramuscular doses of 4, 20 or 40 mg/kg bw during 6 weeks. At all dose levels there was some degree of weight loss and anorexia. Some blood parameters also were dose-related elevated. Histological changes in the liver were minor.

   In rats daily intravenous doses of 2.5, 5 or 10 mg/kg bw for 6 weeks provoked a slight but not significant decrease of food intake and moderate weight gain depression.

6. Reproduction studies in nine female dogs, injected with 25 mg/kg bw intramuscularly six times during one trimester of pregnancy (twice a week over a three weeks period) did not show apparent adverse effects on the bitch or the pups. Rats and rabbits were injected during the three fundamental periods of the reproduction process: premating period (rats 10 mg/kg bw intravenously on days 9, 10 and 11 prior to mating); period of organogenesis (rats and rabbits 20 mg/kg bw intramuscularly on days 6-10 and days 11-15); perinatal period (rats 20 mg/kg bw intramuscularly on days 18-21 of gestation). For all these groups there were no significant differences in litter size and delivered pups. Ketamine seems not to have a negative effect on reproduction.

7. A teratology study in six treatment groups of five female rats given intraperitoneal doses of 25, 50 and 100 mg/kg bw during days 1-15 or 5-15 of gestation showed-pathological degenerative changes in the foetuses at histological examination (e.g. focal nuclear hypochromatosis and interfibrillary oedema of the heart, degeneration of parenchymal liver cells, degeneration of the proximal convoluted tubuli in the kidney). The degenerative effects were observed at all dose levels tested and dependent upon dose and duration of treatment. It is not possible to derive NOELs for embryotoxic and teratogenic effects of ketamine from the reports provided.

8. In horses, elevated doses, three times the routine dose of 2.2 mg/kg bw intravenously, following sedation with intravenously administered xylazine provoke muscular tremor and rigidity, oculogyric movements, mydriasis, sweating, arterial hypertension, tachycardia and elevated body temperature during recovery from anaesthesia.

9. In an Ames test ketamine did not show a mutagenic effect in plate concentrations up to 10 mg. However the results of a sister chromatid exchange assay (SCE) in Chinese Hamster Ovary (CHO) cells at concentrations of 5, 10 and 15 µM in 50 cells indicated a dose dependent SCE induction.

10. Carcinogenicity studies have not been provided.

11. Studies on other effects such as immunotoxicity, effects on human gut flora and food-processing procedures were not mentioned and have not been provided.

12. In humans ketamine is reported to have a very strong analgesic and a neuroleptic effects. Within 30-60 seconds after intravenous administration total analgesia is noted, which continues after the anaesthetic effect has worn off, lasting for some 40 minutes. Loss of conscience occurs after 10 minutes, lasting for 10-15 minutes after a single dose. Amnesia is also observed and may be evident for 1-2 hours. Muscular reflexes remain unchanged or are increased. Blood pressure and heart rate increase initially, the respiration rate remains unchanged. Side effects of ketamine anaesthesia are hallucinations ('bad trips'), which are not observed in children or elderly patients. Ketamine is contraindicated in patients with high blood pressure or cardiac insufficiency. Ketamine interferes with psychomotoric functions for several hours after a single injection - driving is not allowed for 24 hours after ketamine narcosis.

    For humans the following information on ketamine was reported in a pharmacological textbook: Its pharmacokinetics are characterised by a distribution half-life of 11-16 minutes and an elimination half life of 2-2.5 hours. The plasma clearance is reported as 17.7ml/min · kg. The main products of hepatic metabolism are norketamine and dehydronorketamine (no percentages given). After 72 hours approximately 20% of an intravenous dose are recovered in urine; only 2.3% are the unchanged parent compound.

13. In absence of oral toxicity studies and considering the inadequacy of the mutagenicity data provided no ADI could be established. However, due to its rapid elimination, the Committee did not consider necessary to establish an ADI for ketamine

14. Tissue residues of ketamine were studied in 4 horses and 2 cows after intravenous injection of 2 mg/kg bw, in 2 further cows after intramuscular injection of 2 mg/kg bw and in 4 pigs after intramuscular injection of 10 mg/kg bw. All animals were slaughtered 24 hours later. Milk was collected 1, 2, 3, 6, 12 and 24 hours after intravenous treatment of 4 cows with ketamine at a dose of 2 mg/kg bw. In horse, ketamine residues could be detected in liver, kidney and in one muscle sample. In one cow (intramuscular treatment), ketamine residues could be detected in liver and kidney and in pigs in one fat sample. No residues could be detected at the injection site and in milk. The limit of detection of the analytical method was given as 8 µg/kg.

15. A description of a GC-MS method for the determination of ketamine was provided. The validation parameters accuracy, precision, limit of detection and limit of quantification are not supported by raw data.

Conclusions and recommendation

In spite of the fact that an ADI for ketamine was not set, nevertheless, having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- ketamine is used only infrequently for treatment of individual animals;
- the animals are unlikely to be sent for slaughter during or immediately after treatment;
- ketamine is rapidly absorbed and rapidly and extensively excreted;

the Committee concludes that there is no need to establish an MRL for ketamine and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Ketamine	All food producing species	