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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

1-METHYL-2-PYRROLIDONE

SUMMARY REPORT (1)

1. 1-Methyl-2-pyrrolidone (CAS No. 872-50-4; synonyms: N-Methylpyrrolidone, N-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidinone, M-pyrol) is the lactam of 4-methylamino-butyric acid.

   1-Methyl-2-pyrrolidone is included in an infusion solution containing guaifenesin as the active ingredient and used intravenously as a preanaesthetic in horses at dose levels of approximately 80 mg/kg bw.

   This MRL application relates to the use of 1-methyl-2-pyrrolidone in veterinary medicinal products for use in horses only.

   1-Methyl-2-pyrrolidone is also used as an excipient in topical pharmaceutical formulations in human medicine and in cosmetics.

2. No data on pharmacodynamics were submitted, therefore it was not possible to conclude whether the substance is devoid of pharmacological activity.

3. In a rat study using ^{14}C- and ^{3}H-labelled 1-methyl-2-pyrrolidone a plasma half-life of approximately 7 hours for the ^{14}C- and 10 hours for the ^{3}H-isotope was calculated following single intravenous administration at a dose of 45 mg/kg bw. 1-Methyl-2-pyrrolidone was rapidly and extensively distributed to all major organs with similar distribution profile for the two labelled compounds. Six hours following treatment, 2% and 1.5% of the total radioactivity were found in the liver and intestine, respectively, and 2% in the bile. About 1% and 3% of the label were eliminated via expired air and faeces, respectively. Urinary excretion of radioactivity accounted for approximately 70% of the administered dose within 12 hours and 80% within 24 hours, while excretion via faeces and expired air were reported to be 2 to 4% and less than 2%. Several urinary metabolites were observed in rats after intravenous and oral administration. The most abundant were reported to be 5-hydroxy-N-methylpyrrolidone and 3-hydroxy-N-methylpyrrolidone.

   Data on pharmacokinetics of 1-methyl-2-pyrrolidone after oral administration were limited. Rats were treated with a combination of ^{14}C-1-methyl-2-pyrrolidone and 2-pyrrolidone (3:2 on a w/w basis) at oral gavage dose levels of 112 mg/kg bw and 75 mg/kg bw, respectively. 1-Methyl-2-pyrrolidone was reported to be nearly completely absorbed. Maximum plasma levels of the parent compound for the dose of 112 mg/kg bw were 57.1 µg/ml in males and 70.6 µg/ml in females. A t_{max} of 2 hours was reported. Biotransformation appeared to be rapid: At 12 hours post application mainly unknown polar metabolites were found in the blood of treated animals. About 90% of the combined dose was excreted via urine within 5 days. Similar results were reported after dermal application of the same combination of ^{14}C- 1-methyl-2-pyrrolidone and 2-pyrrolidone (3:2 on a w/w basis).

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4. Reported LD_{50} values for rats, mice and rabbits are as follows; rat: 3914 mg/kg bw (orally), 2266 mg/kg bw (intravenously), and 2472 mg/kg bw (intraperitoneally), mouse: 5130 mg/kg bw (orally), 1980 mg/kg (intravenously), 3564 mg/kg bw (intraperitoneally), rabbit (dermal route): 8000 mg/kg bw (intact skin), 4000 mg/kg bw (abraded skin). No detailed information was provided.

5. Subchronic repeated dose toxicity studies were reported in literature for rats and mice. Rats (5 male and 5 female per dose group) were treated for 28 days with 0, 2 000, 6 000, 18 000, or 30 000 mg 1-methyl-2-pyrrolidone/kg feed. No significant haematological, clinico-chemical, or histological effects were seen up to dietary doses of 6 000 mg/kg feed, (429 and 493 mg/kg bw/day in males and females). Compound related alterations in lipid, protein and carbohydrate metabolism occurred in males at 18 000 mg/kg feed and above and in females at 30 000 mg/kg feed. Centrilobular hepatocellular hypertrophy was noted in 60% to 100% of animals at the two higher dose levels. At the highest dose depressed body weights, hypocellular bone-marrow, atrophy of testicular seminiferous tubules and thymic atrophy was noted. Mice (5 male and 5 female per dose group) were treated for 28 days with 0, 500, 2 500, 7 500 or 10 000 mg 1-methyl-2-pyrrolidone/kg feed. Stained urine was seen at 2 500 mg/kg feed and above. A compound related increase in the incidence of cloudy swelling in the epithelia of renal tubuli was noted at the two higher doses in males and the highest dose in females. Serum alkaline phosphatase was significantly decreased in females at the highest dose. Due to the low number of animals included into the repeated dose toxicity investigation and the lack of details no definite NOEL can be derived.

6. In several studies on reproductive toxicity including embryotoxicity/teratogenicity, toxicity studies using various routes of administration embryotoxic and, in some cases, teratogenic effects were reported in rats, mice or rabbits at high dose levels (approximately 300 to 1000 mg/kg bw, orally), which, however, did not always lead to overt maternotoxic effects. Mice appeared to be the most sensitive species: In one published study, following intraperitoneal administration of 1-methyl-2-pyrrolidone to AB Jena and C57B1 mice at dose levels between 37 to 166 mg/kg bw at various time points of gestation dose-dependently increased numbers of implantation losses/resorptions and malformed foetuses were observed. No NOEL could be derived due to the inadequate study reporting and design.

   In a two-generation reproduction study, in which rats were exposed to 1-methyl-2-pyrrolidone via inhaled air (0, 10, 51 or 116 ppm for 6 hours/day, 7 days/week) a decrease of response to sound in the parent generation and a slight decrease in foetal weight of the F1-offspring and in pups persisting till 21 days after birth was reported at the highest concentration. In a reported 3-generation feeding study (0, 50, 160 or 500 mg/kg bw *via* diet) at the highest dose number of stillborn pups increased in the F_{1a}, F_{2a}, F_{2b} generation and the survival at day 4 *post partum* was reduced. The fertility index of the F_{1b} males and females was decreased.

7. Reverse mutation assays (with/without metabolic activation), a mouse-lymphoma-test, micronucleus-test and a dominant-lethal-test were reported to be negative. Negative results were also reported for a gene mutation assay (HPRT locus) in Chinese Hamster ovary cells, a mouse lymphoma test and an unscheduled DNA synthesis test in primary rat hepatocytes.

   Several studies on the induction of aneuploidy in *Saccharomyces cerevisiae* were reported to give positive results at concentrations of 150 to 230 mM. A recent published study on the induction of micronuclei in the bone marrow of mice and on chromosomal aberrations in Chinese hamsters using oral doses of up to 3800 mg/kg bw with sampling times of 16, 24 and 48 hours after treatment in the mouse and 24 and 48 hours in karyotype analysis for chromosomal aberrations in hamsters showed negative results. The available information suggests that the substance is unlikely to be genotoxic.

8. A carcinogenicity study in rats (2 years, inhalation) gave negative results. The full study was not available.

9. No information on neurotoxic effects of 1-methyl-2-pyrrolidone was available, while signs of changes in neurologic parameters have been reported in reproductive studies.

10. 1-Methyl-2-pyrrolidone was reported to have considerable local irritating effects in dermally exposed humans at the working place, while studies in 50 test persons gave negative results.

11. No information on immunotoxicity was provided.

12. A case of embryotoxicity in a pregnant woman (stillbirth) after inhalation of and accidental high dermal exposure at the working place to 1-methyl-2-pyrrolidone has been discussed recently.

13. An ADI could not be established from the available information. However, overall the available information allows the conclusion that there is no concern for the consumer safety connected to the use of the substance in veterinary medicine.

14. Residue studies for 1-methyl-2-pyrrolidone in edible tissues of target animals were not available. However, the available information indicated rapid excretion of the compound; thus no further residue studies are deemed necessary.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- 1-methyl-2-pyrrolidone is only intended for use in horses,
- it is only used in individual animals and for a non-regular treatment,
- is rapidly absorbed and eliminated,
- the animals are unlikely to be sent for slaughter during or immediately after treatment;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for 1-methyl-2-pyrrolidone 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
1-Methyl-2-pyrrolidone	Equidae	