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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FENPIPRAMIDE HYDROCHLORIDE

SUMMARY REPORT

1. Fenpipramide hydrochloride (2,2-diphenylpropyl-4-piperidino-butyramid hydrochloride) is a parasympatholytic and is an active ingredient of some veterinary medicinal products. One of these, an injectable product, also contains levomethadone (2.5mg/ml) and is used as an analgesic, e.g. in the treatment of colic in horses. Other indications include treatment of poisoning in dogs and horses with *Taxus baccata* and parasympathomimetic substances e.g. areocoline, pilocarpine and physiostigmine. The rationale for the inclusion of fenpipramide (0.125mg/ml) in the product is to counteract the vagus effect of levomethadone. In the horse the recommended dose is 2 to 3 ml of the drug per 50 kg body weight intravenenously corresponding to 5 to 7.5 µg fenpipramide/kg bw.

2. Intravenous administration of 7.5 µg ^{14}C-fenpipramide/kg bw to 3 horses revealed that the C_{max} was 0.018 µg/ml in blood and 0.025 µg/ml in plasma. The t_{max} was 0.112 hours after administration. The concentration decreased in a biphasic process with a $t_{1/2phase\ I}$ of 0.82 hours and a $t_{1/2phase\ II}$ of 13.33 hours. The $AUC_{(\mu g\ equivalent/g\ x\ h)}$ is 0.036. Within 24 hours after intravenous administration the radioactivity in blood and plasma decreased to very low levels (mean concentration of 0.0003 µg/ml), and was eliminated in the urine and via the faeces (mean levels at 0 to 24 hours were 0.077 µg/ml in urine and 0.112 µg/g in faeces).

3. Following oral administration to rats fenpipramide showed moderate acute toxicity. Single doses of 250 and 500 mg/kg bw led to clinical symptoms such as irregular respiration, stupor, squatting posture, stilted gait and palpebral fissure narrow. Death occurred between 3 and 24 hours after administration. Thus the oral LD_{50} lies between 250 and 500 mg/kg bw in rats. The acute intravenous LD_{50} in mice was established as 30 mg/kg bw.

4. In rats, a 30-day repeated-dose study was carried out using oral dosing (0, 0.2, 2, 20 or 200 mg/kg bw) of both sexes. Ten males and 10 females were allocated to each group. Reduced body weight gain was observed in both sexes of the 20 and 200 mg/kg bw groups, and food consumption was decreased in the 200 mg/kg bw group. Increased salivation was observed in all animals of the 20 and 200 mg/kg bw groups. Further clinical symptoms (swollen abdomen, stilted gait, decreased spontaneous activity, mydriasis) were observed in all animals of the 200 mg/kg bw group. In females relative liver weights were increased dose dependently in the 20 and 200 mg/kg bw groups, associated with a marked increase in alkaline phosphatase activity in the 200 mg/kg bw group. In all males of the 200 mg/kg bw group a slight increase in fatty changes of the liver was observed. At 200 mg/kg bw 3 males (30%) and two females (20%) died during the study. Atrophy of the genital organs and accessory glands occurred in males only at 200 mg/kg bw, whereas atrophy of the uterus and ovaries was observed in all groups except the 0.2 mg/kg bw group. No compound-related effects were observed after repeated oral administration of 2 mg/kg bw in males and 0.2 mg/kg bw in females. The NOEL was 2 mg/kg bw in male rats and 0.2 mg/kg bw in female rats.

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5. In an oral developmental toxicity study groups of 23 mated female Sprague Dawley rats received fenpipramide by oral gavage once daily at dose levels of 0, 0.2, 2 or 20 mg/kg bw on days 7 to 18 of pregnancy (day 0: day of mating, day 1: day of sperm detection) and were euthanized on day 21 of pregnancy. No clinical signs were recorded in animals treated with fenpipramide. Body weights were not affected but food consumption was slightly decreased in animals of the high dose group. No compound-related effects were observed at necropsy. Gravid uterus weights, crown-rump lengths, litter size, sex ratios, foetal and placental weights remained unaffected. Additionally, no increase in the number of early or late resorptions was observed. Slightly increased incidences of distended renal pelvis and extra lumbar rib were observed in foetuses of the 20 mg/kg bw group. No signs of toxicity were observed in the 0.2 or 2 mg/kg bw groups. A NOEL of 2 mg/kg bw/day for both maternal toxicity and embryotoxicity was established.

6. Fenpipramide was tested for mutagenicity in bacterial reverse mutation tests (*Salmonella typhimurium* and *Escherichia coli* WP2uvA) in absence and presence of metabolic activation in concentrations ranging from 4 to 5000 µg/plate. No positive results were seen. The potential of inducing chromosome aberrations in V79 Chinese hamster lung cells with and without metabolic activation was negative at test concentrations ranging from 50 to 500 µg/ml without metabolic activation and 500 to 2500 µg/ml with metabolic activation. No mutagenic potential was observed in the performed studies.

7. Fenpipramide hydrochloride has formerly been used in humans as a spasmolytic for obstetric purposes to accelerate the process of birth. The product contained 0.25 mg fenpipramide/ml and 10 mg fenpiprane/ml and the recommended dose was 2 to 4 ml subcutaneously corresponding to 0.5 to 1.0 fenpipramide hydrochloride or 8.4 to 16.7 µg/kg bw (assuming a body weight of 60 kg). According to literature this dose was necessary in order to induce a pharmacological effect e.g. uterine spasmolysis in humans.

8. Based on the toxicological NOEL of 0.2 mg/kg bw in rats and applying a safety factor of 200, an ADI of 0.001 mg/kg bw, i.e. 0.06 mg per person, was established for fenpipramide hydrochloride.

9. Residue studies were conducted using radiolabelled ^{14}C-fenpipramide injected intravenously at the maximum recommended dose (7.5 µg/kg bw) in horses. At 24 hours after administration the horses were euthanised, and the radioactivity was measured. The highest level was detected in the liver (mean 43 µg/kg) indicating its central role for biotransformation of fenpipramide. The level in the kidneys (mean 3 µg/kg) points to the contribution of the renal excretion in the elimination of fenpipramide and/or its metabolites. The levels in the skeletal muscle and subcutaneous and retroperitoneal fat were below the limit of quantification (0.47 µg/kg), except for one horse revealing 0.49 µg/kg in the retroperitoneal fat.

10. Though the liver and kidney hold small amounts of residues 24 hours after administration of fenpipramide, the daily intake of fenpipramide is only 7.5% of the ADI.

Conclusions and recommendation

Having considered that:

- an ADI of 0.001 mg/kg bw, i.e. 0.06 mg/person was established for fenpipramide,
- fenpipramide is used in an small number of animals, which are treated once or twice only,
- the animals are unlikely to be sent for slaughter immediately after treatment,
- the tissue residue concentration at 24 hours after administration of the maximum recommended dose represents approximately 7.5% of the ADI;

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

Pharmacologically active substance(s)	Animal species	Other provisions
Fenpipramide hydrochloride	Equidae	For intravenous use only