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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PYRANTEL EMBONATE

SUMMARY REPORT

1. Pyrantel embonate (synonym: pyrantel pamoate, 1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl pyrimidine) is a tetrahydropyrimidine anthelminthic differing from morantel by the absence of a methyl group on the thiophene ring. It is intended for use in horses as oral paste or granulates at a recommended therapeutic dosage equivalent to 6.6 to 13.2 mg base/kg bw of as a single administration to treat roundworms and tapeworms. Other pyrantel salts as citrate and tartrate are used in other species such as sheep, cattle, goats and pigs. However, this submission concerning the pamoate salt is restricted to horses.

2. Pyrantel acts as a potent agonist at the acetylcholine receptors on the muscle cells of nematodes. Activation of the acetylcholine receptors induces a prolonged, spastic paralysis of the worms and expulsion from the host. It also been reported to block neurotransmission in vertebrates, to possess nicotine-like properties and to mimic acethylcholine at receptors in autonomic ganglia, adrenal medullae and respiratory tissues.

3. In rats, after a single oral administration of ^{14}C-pyrantel embonate at a dose equivalent to 10 mg pyrantel base/kg bw, the highest concentration (0.2 µg equivalent pyrantel/ml) was measured in plasma 4 hours after dosing. At 24 hours, levels of 0.02 µg/ml were still measured and no radioactivity could be measured at later sampling times (0.01 µg/ml). The parent compound could only be detected at the 4 hours post-dosing and represented 10% of the total radioactivity. All the radioactivity administered was excreted within 48 hours, 6% via urine and the remainder radioactivity via faeces. The unchanged drug represented 5 to 10% and 50 to 70% of the urine and faeces radioactivity respectively.

4. In dogs, after a single oral administration of ^{14}C-pyrantel embonate at doses ranging from 8.7 to 10 mg pyrantel base/kg bw the highest concentrations in plasma were in the magnitude of 0.6 µg equivalent pyrantel/ml, 4 to 6 hours after dosing. Then, the levels decreased to reach 0.20 µg/ml at 24 hours post dosing. The parent compound represented 10% of the total radioactivity. All the radioactivity administered was excreted within 96 hours, 15% via urine and the remainder radioactivity via faeces. Seven polar metabolites accounting for 80% of the urinary radioactivity were detected. However, the name and their relative proportions were not given. The amount of parent compound was in the same magnitude as that indicated for rats.

5. In Welsh ponies, 24 hours after a single oral administration of pyrantel embonate at a dose equivalent to 13.2 mg pyrantel base/kg bw, no N-methyl-1,3-propanadiamine could be measured in plasma (limit of quantification: 50 µg/l). No information on the excretion balance was given.

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6. Pyrantel is extensively metabolised in dogs, rats, sheep and cattle by three metabolic pathways (oxidation of the thiophene ring, oxidation of the tetrapyrimidine ring and mercapturic acid conjugation). From the *in vivo* radiolabelled studies, it was shown that the thiophene ring underwent extensive degradation leading to acidic metabolites which are highly polar (4-ketohept-2-eneldioic acid, levulinic acid, 4-ketopimelic acid and α-ketoglutaric acid). This fraction acid represents 7 to 12% of the urinary radioactivity. Around 50 to 63% of the urinary radioactivity, convertible to N-methyl-1,3-propanediamine, was issued from the metabolites containing the tetrahydropyrimidine ring.

7. The oral LD_{50} values were above 2000 mg/kg bw in rat, mouse and dog for the pamoate pyrantel. It was of low acute oral toxicity when compared with the tartrate salt, for which the LD_{50} in mice was 175 mg/kg bw. Overt signs of toxicity following administration of the tartrate salt included respiratory effects, ataxia, prostration, tremors and convulsions.

8. Two oral 13-week toxicity studies were carried out in rats.

   In the first study, rats received in their diet the pamoate salt at doses equivalent to 35, 105 and 210 mg pyrantel base/kg bw/day. Significant reductions in plasma chloride and blood glucose concentrations were observed at 35 mg/kg bw/day, the lowest dose level tested, and at 105 mg/kg bw/day. These effects were not observed in the highest group. However as pyrantel could not be detected in the blood samples of the highest dose group, it is not possible to draw any conclusions from this study.

9. In the second study, rats received in their diet the tartrate salt at doses equivalent to 0.012, 0.12, 1.2 and 12 mg base/kg bw/day. Although variations in the biochemical parameters were seen (CO_2 content and alkaline phosphatase), there were without toxicological significance and no adverse effects were reported up to 12 mg/kg bw/day pyrantel base administered as its tartrate salt.

10. Two oral 13-week toxicity studies were carried out in dogs.

    In a first study, dogs (2 animals/sex/dose) received pamoate salt orally in gelatine capsules at doses equivalent to 35, 105 and 210 mg pyrantel base/kg bw, 5 days/week. A NOEL of 35 mg/kg bw/day was established as serum asparatate aminotransferase and serum alanin aminotransferase values were increased at higher dose levels.

    In a second study, pyrantel tartrate was administered oral to dogs (4 animals/sex) in gelatine capsules at doses equivalent to 0.012, 0.12, 1.2 and 12 mg pyrantel base/kg bw/day. Diarrhoea was reported in the high dose group. No changes attributable to the drug treatment were reported for doses up to 12 mg/kg bw/day pyrantel base administered as its tartrate salt.

12. In horses, after a single oral administration of a suspension or a paste formulation of pyrantel embonate at the recommended therapeutic dose or repeated dosing at 19.1 mg/kg bw at 2 to 4 week intervals, for a total of 5 treatments, no adverse effects were noted. Pyrantel was well tolerated in the target species.

13. In a 3-generation study, rats received in their diet pyrantel tartrate at doses equivalent to 0, 3 and 30 mg pyrantel base/kg bw/day. No compound-related effects on fertility, length of gestation and numbers of pups per litter and on malformations were noted up to the highest dose administered (30 mg/kg bw/day as pyrantel base).

14. In a reproduction and lactation study carried out in rats, animals were fed diets containing pyrantel embonate at doses equivalent to 0, 9 and 90 mg pyrantel base/kg bw/day from day 14 prior mating, throughout pregnancy until all the pups had been weaned. There were no significant differences between the treated and the control groups on fertility, gestation, viability or lactation indices up to the highest dose of 90 mg/kg bw/day base.

    The administration of the same doses to pregnant rats from day 14 of gestation to day 21 of lactation, did not induced adverse effects up to the highest dose tested.

15. Teratogenicity studies were carried out in rats and in rabbits.

    No evidence of teratogenicity, foetotoxicity or maternal toxicity was observed in rats after oral administration of pyrantel embonate at daily oral doses equivalent to 0, 9 and 90 mg pyrantel base/kg bw/day. No statistical and no dose-related incidence of malformations was seen when compared to the control group.

    In the rabbit study, pyrantel embonate was administered at doses equivalent to 0, 9 and 90 mg base/kg bw/day of from day 7 to day 17 of gestation. An increase in the incidence of resorptions (8.5 and 12.6% *versus* 2.5% for the controls) was noted. No conclusion can be drawn with regard to a NOEL for maternal toxicity. No adverse effects of toxicological significance were reported for foetuses up to a dose of 90 mg/kg bw/day.

16. Pyrantel tartrate gave negative results in the Salmonella microsomal assay (TA98, TA100, TA1535, TA1537, TA1538) for concentrations ranging from 0.75 to 7500 µg/ml in absence or presence of metabolic activation. Considering the metabolic justification provided for relying on the mutagenicity data provided for the related analogue morantel, it was concluded that pyrantel can not be considered as a mutagenic compound.

17. Two long-term feeding studies were carried out one in rats and the other one in dogs using the tartrate salt.

    Rats were given tartrate salt by oral route at doses equivalent to 0, 3, 30 and 115 mg base/kg bw/day for up to 93 weeks. A NOEL of 3 mg/kg bw/day was established based on reductions in bodyweight gain, changes in haematology values indicative of anaemia and changes in some organ weights. Although there was no evidence of dose-related increase in tumour incidence, the study was inadequate for the assessment of carcinogenicity due to the small group sizes (25/sex/dose), the short duration (93 weeks) and the inadequate survival rate of the animals.

    Groups of 6/sex/dose Beagle dogs were given daily oral doses of pyrantel tartrate (approximately 0, 3, 15, 30 mg base/kg bw/day), 5 days per week for up to 2 years. A NOEL of 3 mg/kg bw/day was established, based on increased liver weights and serum alanine aminotransferase values at higher doses.

    Because of the deficiencies noted in the rat study, and because carcinogenicity cannot be properly evaluated in 2-year studies in dogs, it was concluded that these studies were not acceptable to assess the carcinogen potential of pyrantel, in view of mutagenicity studies.

18. Pyrantel has been used in human medicines for over 20 years. It is normally administered as pamoate salt at oral doses of 10 to 20 mg/kg bw/day for 1 to 3 days. The reported adverse effects in humans in case of overdose include gastro-intestinal disturbances, central nervous system effects and skin reactions. serum asparatate aminotransferase and serum alanin aminotransferase values were elevated in 1.8% of patients.

19. A toxicological ADI of 30 µg/kg bw/day (i.e. 1800 µg/person) based on the NOEL of 3 mg/kg bw pyrantel base from the 2-year studies carried out in rats and dogs and applying a safety factor of 100, could be established. However, as pyrantel has the same metabolism pathway of its related analogue morantel leading to the same major metabolites, the toxicolgical ADI established for morantel, 12 µg/kg/day should be retained for this compound too.

20. In a depletion study, Welsh ponies (1 year old, 126 to 177 kg) received a single oral dose of pyrantel embonate equivalent to 13.2 mg/kg bw base. The animals (4 animals per point) were slaughtered 1, 3 and 5 days after treatment. One day after the administration, significant amounts of pyrantel-related expressed as N-methyl-1,3-propanediamine residues could be measured in liver (1050 µg/kg) and in kidney (175 µg/kg). In muscle, the concentrations were lower than the limit of quantification of the analytical method (100 µg/kg). At later sampling times, pyrantel-related residues could only be measured in liver: 465 and 445 µg/kg at 3 and 5 days, respectively. No information on concentration in fat was available.

In a second depletion study, four New Forest ponies (150 to 250 kg; 2 animals per slaughtering point) received a single oral dose of pyrantel embonate equivalent to 7.25 mg/kg bw base. One animal was untreated (control). No details on the analytical method were given. In liver, the mean concentrations of pyrantel-related residues were close to 320 and 45 µg/kg at 24 and 72 hours after treatment, respectively. In kidney and muscle no residues were found, whatever the sampling time. However, as levels in the magnitude of 40 to 60 µg/kg have been measured in control animals, the results of this study cannot be considered reliable.

21. Pyrantel is extensively metabolised *in vivo* to compounds having either the thiophene or the tetrapyrimidine ring. All the residues of pyrantel and its major metabolites can be converted following alkaline hydrolysis to N-methyl-1,3-propanediamine which is assayed by gas or liquid chromatographic methods. They can be also hydrolysed in presence of hydrochloric acid to 3-(3-2-thienyl) acrylic acid, which is assayed by a liquid chromatographic method. So, even in absence of radiometric studies, it can be assumed that the major fraction of pyrantel and of its residues has been measured by the analytical method used.

22. A gas liquid chromatography method for determining residues of pyrantel for the edible tissues of horses is available but its validation does not fulfil all the requirements of Volume VI of the Rules Governing Medicinal Products in the European. The limits of detection and of quantification for all edible tissues except fat were given as 100 µg/kg.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 12 µg/kg bw was established for pyrantel base,
- pyrantel embonate is intended for use in horses only,
- pyrantel embonate is extensively metabolised into polar metabolites which are rapidly excreted,
- one day after the administration of pyrantel embonate, the amount of residues likely to be ingested by the consumer represents about 20% of the toxicological acceptable daily intake;

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

Pharmacologically active substance(s)	Animal species	Other provisions
Pyrantel embonate	Equidae	