European Medicines Agency
Veterinary Medicines and Inspection

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MORANTEL

SUMMARY REPORT (1)

1. Morantel (1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)ethenyl pyrimidine) is a tetrahydro-pyrimidine anthelmintic, differing from the related analogue pyrantel by the presence of a methyl group on the thiophene ring. It is intended to treat roundworms and tapeworms. It is administered in lactating and non lactating cattle as morantel tartrate as a slow-release bolus (11.8 g morantel base per animal) or as a single oral dose of 6 to 7.5 mg morantel base/kg bw and in pigs at a single dose equivalent to 7.5 mg base/kg bw. In sheep, the citrate salt is administered at a single dose equivalent to 5 to 6 mg morantel base/kg bw.

   Morantel and its salts are not used in human medicines.

2. Morantel 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 acetylcholine at receptors in autonomic ganglia, adrenal medullae and respiratory tissues.

3. In mice, after single oral administrations of ^{3}H- or non-radiolabelled morantel citrate at doses equivalent to 50 mg morantel base/kg bw or of ^{3}H-morantel tartrate at doses equivalent to 6 mg morantel base/kg bw, approximately 27% of the administered dose were excreted in urine within 24 hours. A large number of metabolites was detected but non identified. The parent compound represented only 2.6% of the dose administered in urine. After a single oral administrations of radiolabelled morantel citrate at doses equivalent to 50 mg morantel base/kg bw, the mean plasma concentrations of morantel were 4.8 and 3.7 µg equivalents/ml, 1 and 2 hours after the administration. No parent compound was detected in plasma after 24 hours. After the last of 3 oral administrations of morantel citrate at doses equivalent to 50 mg morantel base/kg bw, the highest plasma concentration of the parent compound (1.06 µg/ml) was observed 1 hour after administration and its elimination half-life was 1.7 hours.

   After single oral administrations of morantel tartrate at doses equivalent to 6 and 30 mg morantel base/kg bw in rats and in dogs, 8% and 43% of the administered dose were excreted in urine within 24 hours, respectively.

   In bovine, after a single oral administration ^{3}H- or ^{14}C-morantel tartrate at a dose equivalent to 6 mg morantel base/kg bw, less than 20% of the administered dose was recovered in urine over 96 hours, the remaining part being excreted via faeces.

   In pigs after single oral administrations of ^{14}C-labelled morantel tartrate at doses equivalent to 8 to 15 mg base/kg bw, about 90% of radioactivity were excreted within 24 hours (half in urine and half in faeces).

   In sheep, after single oral administrations of ^{14}C-labelled morantel tartrate at a dose equivalent to 5 to 9 mg morantel base/kg bw, 17% and 65% of the radioactivity administered was excreted in urine and faeces within 4 days.

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In all species, a substantial proportion of the administered dose was excreted in the faeces as unmetabolised morantel. Morantel is metabolised by three metabolic pathways (oxidation of the thiophene ring, oxidation of the tetrapyrimidine ring and conjugation with glutathione). The oxidative metabolism of the thiophene ring of the urinary radioactivity leads to acidic metabolites which are highly polar (4-ketohept-2-eneldioic acid, levulinic acid, 4-ketopimelic acid and α-ketoglutaric acid). This acid fraction represents 3% (sheep) to 25.7% (dogs) of the urinary radioactivity. Around 57% (dog and pigs) to 86% (rats) of the urinary radioactivity, convertible to N-methyl-1,3-propanediamine, were issued from the metabolites containing the tetrahydropyrimidine ring.

In vitro data, on liver microsomes of rat, dog and cow confirmed these biotransformations leading to the formation of the same 8 metabolites already identified in *in vivo* studies.

4. The oral LD_{50} values for morantel tartrate, were equivalent to 179 to 260 and 551 to 586 mg morantel base/kg bw in mice and rats, respectively. For the citrate salt, the oral LD_{50} values were in the magnitude of 125 mg morantel base/kg bw in mice. The main symptoms of intoxication were respiratory effects, hypothermia, ataxia, tremors and convulsions.

5. Two oral 3-month toxicity studies were conducted in rats.

   In the first study, animals received morantel tartrate in their diet at doses approximately equivalent to 0, 30, 90 or 270 mg morantel base/kg bw/day. In males, mortality was noted in the 270 and 90 mg/kg bw dose groups (40 and 30%, respectively) and histopathological findings (renal tubular necrosis and testicular atrophy) were recorded in the highest dose group. Haematological and biochemical changes were noted in the two highest dose groups and signs of haemorrhages were observed at doses equal to and higher than 30 mg/kg bw/day.

   In the second study, rats received morantel tartrate in their diet at doses equivalent to 0, 6, 12 and 30 mg morantel base/kg bw/day. No adverse effects were reported in this study.

   From these two studies, an overall NOEL of 12 mg/kg bw/day morantel base was retained.

6. In a 2-year toxicity study carried out in dogs, groups of 8 to 10 animals received morantel tartrate in gelatine capsules at doses equivalent to 0, 1.2, 6 and 12 mg morantel base/kg bw/day. Vomiting was frequently noted in the two highest dose groups. In the highest dose group, the absolute and relative liver and adrenal weights were significantly increased. A NOEL of 1.2 mg/kg bw/day morantel base was retained.

7. Morantel tartrate was well tolerated by oral route in swine, sheep and bovine at doses of up to 6.5, 28 and 28 times the recommended doses, respectively .

8. No effects on male or female fertility were reported in the 3-generation study carried out in rats after oral administration of morantel tartrate at doses equivalent to 0, 0.6, 1.5 and 3 mg morantel base/kg bw/day. No statistically significant effects and no dose-related pup mortality were seen when compared to the control group. However, the conclusion regarding *peri*- or *post*-natal effects should be taken with caution due to the very high pup mortality (approximately 50%) in all dose groups including the controls.

9. Teratogenicity studies were carried out in rats, in rabbits and in mice.

   No evidence of teratogenicity, foetotoxicity or maternal toxicity was observed in rats after oral administration of morantel citrate or tartrate salts, up to doses equivalent to 50 to 60 mg base/kg bw/day. No statistically significant effects and no dose-related incidence of malformations were seen when compared to the control group.

   No evidence of teratogenicity, foetotoxicity or maternal toxicity was observed in a teratology study in the rabbit after oral administration of morantel tartrate up to a dose equivalent to 60 mg morantel base/kg bw/day.

   No evidence of teratogenicity, foetotoxicity or maternal toxicity was observed in mice after oral administration of morantel tartrate up to a dose equivalent to 60 mg morantel base/kg bw/day.

10. Five *in vitro* and one *in vivo* mutagenic assays were carried out with morantel citrate or tartrate. Although the results did not give any cause for concern, four of the *in vitro* studies were inadequate due to the lack of replication, absence of information on the storage of the test materials and omission of positive controls in some of the studies. Only the *in vitro* mouse lymphoma assay (7 concentrations in the range of 390 to 2205 µg morantel base/ml as tartrate) and the *in vivo* cytogenetics assay (mouse micronucleus test) after oral administrations of morantel citrate at doses equivalent to 2.8, 25.5 and 50 mg base/kg bw were regarded as adequate and giving negative results. Morantel can be considered as a non mutagenic compound.

11. In a carcinogenicity study carried out in the rat, the animals received morantel tartrate in their diet at doses of 0, 1.2, 12 and 30 mg morantel base/kg bw/day for 104 weeks. The group sizes were inadequate for the proper evaluation of the carcinogenicity. A dose-related decrease in the absolute heart weights was noted in the females of the two highest dose groups. No significant dose-related trend in tumour incidence was noted and the absence of any structural alerts in the chemical structure of morantel and the lack of a mutagenic response indicated that further carcinogenicity studies were not warranted.

12. A toxicological ADI of 12 µg/kg bw (i.e. 720 µg/person) was established, based on the NOEL of 1.2 mg morantel base/kg bw from the 2-year study carried out in dogs and applying a safety factor of 100.

13. Morantel is extensively metabolised *in vivo* to compounds having either the thiophene or the tetrapyrimidine ring. All the residues of morantel 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-(3-3-methyl-2-thienyl) acrylic acid, which is assayed by a liquid chromatographic method.

14. In bovine, two radiometric studies after single administrations and two non-radiometric studies after intraruminal administration of boluses were provided.

    In a first radiometric study, calves (6 to 8 weeks, 50 to 60 kg) received a single oral dose of ^{14}C-morantel tartrate at a dose of 5.9 mg morantel base/kg bw. Groups of 1 to 3 animals were slaughtered at 7, 14 and 28 days post dose. Seven days after the administration, only levels of radioactivity (morantel equivalents) were measured: 60 µg/kg for kidney, 20 µg/kg for fat , and concentrations below 10 µg/kg (limit of quantification) for muscle. For liver, the amounts of radioactivity measured were 495, 250 and 140 µg/kg, at 7, 14 and 28 days post-dose, respectively.

    After hydrolysis, residues in liver related to morantel were converted into N-methyl-1,3-propane diamine and the ratios of this compound towards total residues were as follows: 59% (n=2), 54% (n=1) and 40% (n=2) at 7, 14 and 28 days post-administration, respectively. No information was provided for the other edible tissues.

    In a second radiometric study, 5 Holstein dairy cows (weight not stated) received a single oral dose of ^{3}H-morantel citrate at a dose equivalent to 5 mg morantel base/kg bw, in gelatine capsule. Four days after dosing, total drug-related residues in liver averaged 1150 µg/kg. About half of the radioactivity was unextractable. However, in absence of information on the comparison of this value to the amounts of morantel related residues convertible to N-methyl-1,3-propanediamine or to 3-(3-3-methyl-2-thienyl) acrylic acid, no further consideration can be given to this information.

    In one non radiometric depletion study of morantel in edible tissues of bovine, morantel tartrate as sustained release formulation over a period of 90 days (12 g morantel base/bolus/animal) was administered by intraruminal route to calves. Five animals were slaughtered at each time point, i.e. 1, 15, 30, 45, 60, 75, 90 and 120 days following the administration. The residues of morantel were analysed after being converted to N-methyl-1,3-propanediamine (method not clearly indicated). For the complete time range the concentrations calculated as morantel base equivalents ranged from 150 to 300 µg/kg in liver. On days 45 and 90 the concentrations in muscle were close to 100 µg/kg whereas for kidney, they were 200 µg/kg.

Ruminating calves received an intraruminal bolus of morantel tartrate (corresponding to 12 g morantel base/bolus/animal). The concentrations of morantel residues, convertible into 3-(3-3-methyl-2-thienyl) acrylic acid were determined by an HPLC method in edible tissues collected on animals slaughtered (n=2 per time point) at 1, 2, 3, 5 and 7 days after the administration. At one day post application, the concentrations of morantel related residues, expressed as morantel base equivalents were close to 15, 90 and 390 µg/kg in muscle, kidney and liver. Then, they declined slowly to reach 15, 40 and 150 µg/kg at 7 days after dosing. No information is available for the other edible tissue.

15. Two radiometric depletion studies were conducted in pigs.

    Groups of 3 or 2 pigs received a single oral administration of ^{14}C-morantel tartrate at a dose equivalent to 8 mg morantel base/kg bw. At 14 days after dosing, the total radioactivity levels in edible tissues were 70, 40, 80, 405, 160 µg morantel equivalent/kg in muscle, fat, skin liver and kidney respectively. Then, they declined to reach the magnitude of 40 µg/kg in all edible tissue except liver (70 µg/kg), 21 days after treatment . The ratio of N-methyl-1,3-propanediamine to total residue was only estimated for liver (34 to 43%, 36 to 50% and 55% at 14, 21 and 28 days, respectively). No information on this ratio for the other edible tissues was available.

    In a second radiometric study, 3 pigs received a single oral administration of ^{14}C-morantel tartrate at a dose equivalent to 15 mg morantel base/kg. Fourteen days after administration, the amounts of radioactivity were 50, 100, 50, 826, 150 µg morantel equivalents/kg in muscle, skin, fat, liver and kidney, respectively. In liver, the ratio of N-methyl-1,3-propanediamine to total residue averaged 50%.

    Several non-radiometric studies were carried out with morantel. Due to inadequacies of these studies (the incorrect dosing regimen, the too small number of animals slaughtered at each point, absence of information on the analytical method), the results could not be taken into account.

16. One-radiometric and one non-radiometric depletion studies were conducted on sheep. Results from an old non radiometric study were reported due to the inadequacy of the analytical method (colorimetric method) and the low number of animal per slaughtering point.

    Two animals received a single oral administration of ^{14}C-morantel tartrate at a dose equivalent to 9 mg morantel base/kg bw. At 7 days after dosing, the total radioactivity levels 20, 1130, 190, 20 µg morantel equivalents/kg in muscle, liver, kidney and fat, respectively. At 14 days, radioactivity levels were still high in liver (1050 µg/kg) and in kidney (80 µg/kg). In liver, the ratio of N-methyl-1,3-propanediamine/total residues was close to 60% at 7 and 4 days. No information on this ratio for the other edible tissue was available.

    In a non radiometric depletion study in edible tissues of sheep, groups of 5 or 8 animals received a single oral administration of morantel citrate at a dose equivalent to 5 mg morantel base/kg bw. Residues in tissues were determined by gas chromatography after conversion of residues to N-methyl-1,3-propadiamine. At 3 days after dosing, the concentrations calculated as morantel base equivalent were less than 100, 985, 200 µg/kg in muscle, liver and kidney, respectively. After 7 and 14 days, no morantel (below 100 µg/kg) could be detected in muscle and kidney. However, for liver they declined to reach 402 and 240 µg/kg at 7 and 14 days post-dosing. No data for fat were available.

17. Milk residues studies were conducted on cattle.

    In a radiometric study, 5 Holstein dairy cows received a single oral administration dose of ^{3}H morantel citrate at a dose equivalent to 5 mg morantel base/kg bw. In milk, the total radioactivity milk peaked at 84 µg/kg by the 2nd milking, then declined to reach 49 and 19 µg/kg by the 4th and the 6th milking, respectively. Morantel related residues convertible into N-methyl-1,3-propanediamine showed a parallel decline. The ratio of N-methyl-1,3-propanediamine/total residues averaged approximately 35% for all milkings.

Four non-radiometric depletion studies of morantel in milk were carried out in lactating cows.

In the first study, 11 lactating dairy cows received a single oral administration of morantel tartrate at a dose equivalent to 5.5 mg morantel base. The concentrations of morantel related residues were calculated either as N-methyl-1,3-propanediamine or as 3-[3-methyl-2-thienyl] acrylic acid. The peak time occurred at the second milking post-dose with levels averaging 17 and 2.7 µg/kg for residues convertible to N-methyl-1,3-propanediamine and 3-[3-methyl-2-thienyl] acrylic acid, respectively. From the fourth milking, the mean levels were 10 and 1.6 µg/kg, respectively. This study showed that the fraction of morantel of residues converted into 3-[3-methyl-2-thienyl] acrylic acid is about ten times lower that the fraction converted into N-methyl-1,3-propanediamine.

For the three other studies, when morantel was administered as intraruminal boluses at the therapeutic regimen, it was shown that the concentrations of morantel related residues calculated either as N-methyl-1,3-propanediamine or as 3-[3-methyl-2-thienyl] acrylic acid were always below 100 µg/kg.

18. In a depletion study of morantel in milk conducted in sheep, residues of morantel related residues calculated as N-methyl-1,3-propanediamine were always below 60 µg/kg after the administration of morantel tartrate at a single oral dose equivalent to 6 mg morantel base/kg bw.

19. According to the available data 3-(3-3-methyl-2-thienyl) acrylic acid obtained after acid digestion did not seem a suitable marker residue as this compound results for the thiophene ring which is extensively metabolised. In one study carried out in milk, it was shown that its concentrations were about ten-fold lower than those corresponding to the drug-related metabolites obtained after alkaline hydrolysis, the N-methyl-1,3-propanediamine compound. Although there is no information available on its conversion percentage in edible tissues of the target species and its ratio towards total residue in edible tissues of the target species, it was assumed that the major fraction of morantel and of its residues has been measured. Therefore, N-methyl-1,3-propanediamine was retained as the marker residue.

20. A gas liquid chromatography method for monitoring residues of morantel for some edible tissues of the different target species and milk was available but it was not fully validated according to the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community. Validation data were provided only for muscle, liver and kidney of sheep, for liver of cattle and pigs and for milk of cattle and sheep. The limit of quantification for liver of cattle and pigs and for edible tissues of sheep except fat is 100 µg/kg. For milk, the limits of quantification are 12.5 and 63 µg/kg for bovine and ovine milk respectively.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 12 µg/kg bw (i.e. 720 µg/person) was established,
- the N-methyl-1,3-propanediamine was retained as the marker residue,
- the ratios of the marker residue to total residues in liver and in milk were estimated at 50 % and 35 % respectively. For the other edible tissue, due to the low concentrations measured it was provisionally adopted that the marker residue represents the totality of the morantel residues,
- although the tissue distribution varied according to the formulation administered, the distribution at 14 days after treatment was considered to establish provisional MRLs,
- the routine analytical method proposed was not fully validated;

the Committee for Veterinary Medicinal Products recommends the inclusion of morantel in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Morantel	Sum of residues which may be hydrolysed to N-methyl-1,3-propanediamine and expressed as morantel equivalents	Bovine, ovine	100 µg/kg 100 µg/kg 800 µg/kg 200 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	Provisional MRLs expire on 1.7.2001
		Porcine	100 µg/kg 100 µg/kg 800 µg/kg 200 µg/kg	Muscle Skin + Fat Liver Kidney	

Based on these MRL values, the maximum daily intake of residues will be about 634 µg/person/day equivalent to 88 % of the toxicological ADI.

LIST OF QUESTIONS

1. The applicant should provide additional data in order to establish the ratio of the residue marker towards total residue in all edible tissues of all target species.

2. The appplicant should provide a fully validated analytical method for the determination of residues of morantel in all edible tissues of the target species and milk of bovine and ovine. The method should be presented according to a international recognised format (e.g. ISO 78/2).