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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DECOQUINATE

SUMMARY REPORT (2)

1. Decoquinate [3-quinolinecarboxylic acid, 6-(decyloxy)-7-ethoxy-4-hydroxy-, ethyl ester. CAS 18507-89-6] is a quinolone coccidiostat which can be administered via the feeding stuff at levels up to 1 mg/kg bw/day for up to 28 days for the prevention and treatment of coccidiosis in calves and lambs. It is authorised as feed additive under Council Directive 70/524/EEC for use in chicken. The substance is used as an in-feed medication as well as a water-soluble medication.

   Decoquinate is currently entered into 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
Decoquinate	Decoquinate	Bovine, ovine	500 µg/kg 500 µg/kg 500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney	Provisionnal MRLs expire on 1.7.2000

   Further data have now been provided to support the establishment of final MRLs for decoquinate.

2. In a pharmacodynamic study, decoquinate is reported to act on the sporozoite stage of the coccidial life cycle and inhibits both respiration and sporulation of *Eimeria* spp.

3. Groups of 10 male and 10 female Carworth rats were given 20 g feed per day, for up to 11 days, containing radiolabelled decoquinate of specific activity 0.61 µCi/mg. Excretion in the urine reached a plateau after 2 days of treatment and corresponded to 12% of the administered dose in males and 6% in females. Groups of 2 rats per sex were killed after 3, 5, 7, 9 and 11 days of treatment. Tissue concentrations reached a plateau after 3 days. The highest residues were found in liver (690 and 450 µg equivalents in males and females, respectively) and kidney (mean residues of 540 and 370 µg equivalents in males and females, respectively). Decoquinate is reported to be incompletely absorbed after oral administration.

4. Decoquinate is of low acute toxicity by the oral route in a range of avian and mammalian species. It is also of low acute inhalational and contact toxicity. The acute oral LD_{50} was equal to or greater than 5000 mg/kg bw in all the species studied. In rats, a single oral dose of 5000 mg/kg bw caused no deaths and no overt signs of toxicity. Oral administration of 1000 mg/kg bw to anaesthetised cats had no effect on a range of parameters including blood pressure and heart rate.

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5. Repeated dose studies of orally administered decoquinate have been carried out in rats and dogs. These included a range-finding study in which Wistar rats were given daily oral doses of 2000 mg decoquinate/kg bw for 12 days, an 11-week study in which Wistar rats were administered daily oral (gavage) doses of 0, 4, 15, 62.5, 250 or 1000 mg/kg bw/day, and a 26-week study in which CFE rats were fed decoquinate in the diet equivalent to 0, 12, 120 or 1200 mg/kg bw/day in females and 0, 10, 100 or 1000 mg/kg bw/day in males. Decoquinate was shown to be a substance of low toxicity, the main findings being occasional minor changes in feed consumption, feed conversion, body weight and some organ weights in the highest dosage group. The overall NOELs in rats were 100 and 120 mg/kg bw/day in males and females, respectively.

6. Groups of 2 male and 2 female Beagle dogs were given daily oral (gavage) doses of 0, 4, 15, 62.5, 250 or 1000 mg/kg bw/day for 12 weeks. The main finding was subdued behaviour in dogs administered 62.5 mg/kg bw/day and above. The NOEL in this study was 15 mg/kg bw/day. In another study, groups of 3 male and 3 female dogs were fed diets containing decoquinate at concentrations equivalent to approximately 0, 5 or 25 mg/kg bw/day for 2 years. There were no effects attributable to treatment.

7. Reproductive toxicity has been studied in rats and teratology in rats and rabbits. No adverse effects were observed on any of the parameters in a 2-generation reproduction study in which groups of Sprague-Dawley rats were fed diets equivalent to approximately 0, 12 or 60 mg/kg bw/day. In a teratogenicity study, groups of 15 female Sprague-Dawley rats were given daily oral (gavage) doses of 0, 100 or 300 mg/kg bw/day from days 6 to 16 of presumed gestation. There was a slight reduction in foetal weight and a slight increase in the incidence of retarded skeletal development in foetuses in the high dose group. The NOEL was 100 mg/kg bw/day.

8. Groups of 15 female New Zealand White rabbits were given daily oral (gavage) doses of 0, 100 or 300 mg/kg bw/day from days 6 to 16 of gestation. There was a decrease in the number of live foetuses in both treated groups and a NOEL was not established. Therefore, the study was repeated using dose levels of 0, 30, 60 or 120 mg/kg bw/day. There was a decrease in the number of live foetuses in the high dose group administered 120 mg/kg bw. The NOEL for foetotoxicity was 60 mg/kg bw/day.

9. Negative results were obtained in 2 *in vitro* assays for gene mutation in *Salmonella typhimurium* starins TA98, TA100, TA1535, TA1537 and TA1538, in both presence and absence of metabolic activation. A published report using the same strains of *Salmonella typhimurium* and *Bacillus subtilis* H17 (Rec+), *Bacillus subtilis* M45 (Rec+) and *Escherichia coli* WP2 also claimed negative results. Concentrations in the range 50 to 5000 µg/ml of decoquinate were not mutagenic in an *in vitro* assay for gene mutation at the TK locus of L5178Y mouse lymphoma cells in the absence of metabolic activation. Concentrations in the range 50 to 4000 µg/ml were tested in the presence of metabolic activation; a significant increase in mutant frequency was observed at 2500 µg/ml but this concentration caused more than 98% cell death. An *in vitro* cytogenetics assay in Chinese Hamster Ovary cells gave negative results in both presence and absence of metabolic activation. It was concluded that decoquinate was not mutagenic.

10. In a combined chronic toxicity and carcinogenicity study, groups of Sprague-Dawley rats were fed diets containing decoquinate at concentrations equivalent to 0, 8 or 40 mg/kg bw/day in males and 0, 10 or 50 mg/kg bw/day in females, for 2 years. The study was deficient in a number of areas and so it was not possible to draw any conclusions regarding a NOEL. However there was no evidence of carcinogenicity.

11. Decoquinate has not been subjected to any specific tests for immunotoxicity but the findings of the repeated dose toxicity tests do not indicate that decoquinate is likely to be immunotoxic.

12. Decoquinate has not been tested specifically with regard to effects on human gut flora and organisms used in the food processing industry. However, it is reported in the open literature that it has no anti-bacterial action and no effect on protozoa other than coccidia. A study on environmental effects indicated no effects on soil bacteria.

13. An ADI of 75 µg/kg bw (i.e. or 4.5 mg/person) was established for decoquinate based on the of NOEL of 15 mg/kg bw/day based on subdued behaviour observed in the 12-week dog study and applying a safety factor of 200 to take into the methodological weaknesses in this study.

14. Sheep were fed medicated feed equivalent to 0.5 mg decoquinate/kg bw/day for 7 consecutive days then given an intravenous dose of 30 µg ^{14}C-decoquinate/kg bw. Treated sheep were sacrificed, in 3 groups of 4, on days 1, 7 and 14 after the intravenous dose. The total residue content of blood, urine, faeces and tissue samples were determined by liquid scintillation counting (LSC) with or without prior combustion. The average total residue eliminated in urine and faeces accounted for 32 and 77% of the administered dose. The elimination half-lives were 0.45 and 0.66 hours respectively. The average residue concentration in liver, kidney, muscle and fat were 7, 8, 2 and 5 µg equivalents/kg, respectively 1 day after the last dose. The respective residue concentrations depleted as follows: 1, 3, less than 1 and 1 µg equivalents/kg at 7 days and less than 1 µg equivalents/kg at 14 days after the last dose. The values given in this study were should be considered with caution as the methodology used was likely to result in an underestimation of the total residue content of tissues.

15. Three calves were orally dosed with 1 mg ^{14}C-decoquinate/kg bw/day for 6.5 consecutive days. Samples of blood, urine, faeces, and cage washings were collected during treatment and thereafter until the animals were sacrificed 7 days after the last dose. The total residue content of samples was determined by combustion/LSC. The average total residue content of urine, faeces and cage washings accounted for 2, 88 and 1% of the administered dose.

    In the same study, calves were dosed as above then sacrificed, in 2 groups of 4, at 12 and 24 hours after treatment respectively. The average residue concentration in liver, kidney, muscle and fat were 585, 356, 32 and 168 µg equivalents/kg, respectively 12 hours after the last dose. The respective residue concentrations depleted as follows: 541, 289, 39 and 197 µg equivalents/kg at 24 hours and 35, 16 less than 10 and less than 10 µg equivalents/kg at 7 days after the last dose.

    In another study, calves were fed medicated feed equivalent to 0.5 mg decoquinate/kg bw/day for 5 consecutive days then given an intravenous dose of 30 µg [^{14}C]-decoquinate/kg bw. Treated calves were sacrificed, in 3 groups of 4, on days 1, 7 and 14 after the intravenous dose. The total residue content of blood, urine, faeces and tissue samples were determined by combustion/LSC. The average total residue eliminated in urine and faeces accounted for 2 and 29% of the administered dose. The elimination half-lives were 0.76 and 0.28 hours respectively. The average residue concentration in liver, kidney, muscle and fat were 37, 31, 12 and 7 µg equivalents/kg, respectively 1 day after the last dose. The residue concentrations depleted as follows: 10, 9, 7 and less than 1 µg equivalents/kg at 7 days and 24, 8, less than 1 and 3 µg equivalents/kg at 14 days after the last dose. The values given in this study should be considered with caution as the methodology used was likely to result in an underestimation of the total residue content of tissues.

    When 2 calves were fed medicated feed equivalent to 5 mg ^{14}C-decoquinate/kg bw for 4 consecutive days then sacrificed 24 hours later decoquinate accounted for 85, 80, 100 and 100% of the total residue present in liver, kidney, muscle and fat samples, respectively.

16. Sheep were fed medicated feed equivalent to a dosage of 2 mg decoquinate/kg bw/day for 105 consecutive days. Groups of 4 treated animals were sacrificed on days 1, 2 and 3 after treatment. The decoquinate content of tissue samples was determined by high performance liquid chromatography (HPLC) with ultra violet (UV) detection. The average decoquinate concentration in liver, kidney, muscle and fat were less than 70, less than 35, less than 35 and less than 100 µg/kg on days 1, 2 and 3 after the last dose.

17. Two calves were fed medicated feed equivalent to 7 mg decoquinate/kg bw/day for 28 consecutive days. One cow was dosed for 39 days. All animals were sacrificed immediately after the last administered dose. The decoquinate content of tissue samples was determined by the Association of Official Analytical Chemists (AOAC) method based on fluorometry with a limit of quantification of approximately 100 µg/kg. The average decoquinate concentration in liver, kidney, muscle and fat were 160, 145, 115 and 160 µg/kg, after 28 days of dosing. The decoquinate concentrations in the cow dosed for 39 days were: 330, 210, 120 and 330 µg/kg after the last dose.

    In another study, calves were fed medicated feed equivalent to a dosage of 1 mg decoquinate/kg bw/day for 28 consecutive days. Groups of treated animals (2 per sex) were sacrificed at 1, 3 and 6 days after treatment. The decoquinate content of tissue samples was determined by HPLC with UV detection. The average decoquinate concentration in liver, kidney, muscle and fat were 104, 104, less than 35 and 238 µg/kg, respectively 1 day after the last dose. The residue concentrations depleted as follows: 123, 23, less than 35 and 71 µg/kg at 3 days and less than 70, 26, less than 35 and less than 100 µg/kg at 6 days after the last dose.

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:

- an ADI of 75 µg/kg bw (i.e. 4.5 mg/person) has been established,
- decoquinate has a low oral bioavailability,
- at 24 hours after treatment the amount of residues likely to be ingested by consumers represents only a low fraction (less than 5%) of the ADI,
- no information was available concerning residue depletion in milk;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish MRLs for decoquinate 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
Decoquinate	Bovine, ovine	For oral administration only. Not for use in animals from which milk is produced for human consumption.