

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DECOQUINATE

SUMMARY REPORT (1)

1. Decoquinat is a quinolone coccidiostat which can be administered via the feeding stuff at levels up to 1 mg/kg bodyweight/day for up to 28 days for the prevention and treatment of coccidiosis in calves and lambs. It has a long history of use and is an approved feed additive as defined by Directive 70/524/EEC. The substance is used as an in-feed medication as well as a water-soluble medication. Its mode of action is not understood.
2. Decoquinat 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.
3. Repeat dose studies of orally administered decoquinat have been carried out in rats and dogs. Decoquinat was shown to be a substance of low toxicity, the most severe findings being occasional minor changes in feed consumption, feed conversion, body weight and some organ weights; subdued behaviour was noted in some animals in the 12 week dog study.
4. Decoquinat is well tolerated by a range of possible target species (cattle, lambs).
5. Reproductive toxicity has been studied in rats and teratology in rats and rabbits. No adverse effects were observed on any of the parameters in the reproductive toxicity study in which the highest dose level was 60 mg/kg bw/day. In the rat teratogenicity studies, there was a slight reduction in foetal weight and a slight increase in the incidence of skeletally retarded foetuses in the high dose group (no effect level 100 mg/kg bw/day), and in the rabbit study there was a decrease in the number of live foetuses in the high dose group (no effect level 60 mg/kg bw/day).
6. Decoquinat has been tested for mutagenic potential and chromosome aberrations in a variety of bacterial and mammalian cells. It was concluded that decoquinat was not mutagenic.
7. The 2-year rat study indicates that there was no change in the incidence or type of tumours which developed at the highest dose level of 1000 ppm (roughly 40 mg/kg bw/day).
8. Decoquinat has not been subjected to any specific tests for immunotoxicity but the findings of the routine toxicity tests do not indicate that decoquinat is likely to be immunotoxic.
9. Decoquinat 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.
10. The lowest no observed effect level is the 15 mg/kg bw/day based on the subdued behaviour observed in the 12-week dog study and this has been selected for the calculation of the ADI. In recognition of the fact that this study is rather old, a safety factor of 200 has been applied to give an ADI of 75 µg/kg bw/day or 4.5 mg/day for a 60 kg person.

11. Little is known about the absorption of orally administered decoquinatate except that some must be absorbed since residues are found in the tissues. Little is excreted via the urine in all species examined (rat, chicken, cow and sheep). The highest levels of decoquinatate are found in liver and kidney with variable amounts in fat. Only low levels occur in muscle. Of the residue, most appears to be in the form of parent compound with 3 other components occurring in rats; some of these non-decoquinatate compounds also occur in liver and kidney in the target species. The pharmacokinetic studies show that residues have very little tendency to accumulate in the tissues after repeated dosing but no formal residues studies have been carried out using the recommended dosage regime.
12. In the absence of residues studies, but taking into consideration the low toxicity of decoquinatate, the following provisional MRLs (based on decoquinatate as marker residue) have been set for cattle and sheep:

Substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Decoquinatate	Decoquinatate	Cattle, sheep	500 µg/kg 500 µg/kg 500 µg/kg 500 µg/kg	Liver Kidney Muscle Fat	Provisional MRLs expire on 1.7.2000

Since there is some evidence that the decoquinatate residues account for at least 50% of the total residue, these MRLs would account for less than 10% of the ADI and the limited residues data which are available indicate that these levels would be reached within hours of drug withdrawal.

13. Several analytical methods are available for the determination of decoquinatate in the tissues of various species. However, most of these are not validated and validation data, preferably for a method which can be used with only minor modifications for different species, are required before the MRLs can be finalised.

LIST OF QUESTIONS

1. The applicant should provide further information on absorption of orally-administered decoquinatate.
2. The applicant should provide further information on the relationship between the marker residue and total residues.
3. The applicant should conduct residues studies in each species for which an MRL is required as specified in Volume VI of the Rules Governing Medicinal Products in the European Community. If a milk MRL is to be set, these studies should include a milk residues study.
4. The applicant should provide a fully validated method for the analysis of decoquinatate in the tissues of those species for which MRLs are required and this method should be presented in an internationally accepted format.

This information should be provided to the CVMP by 1 July 1999.