



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DORAMECTIN

SUMMARY REPORT (1)

SAFETY FILE

1. Doramectin is a new substance of the chemical class of the avermectins produced by submerged aerobic fermentation of the soil actinomycete *Streptomyces avermitilis*. Unlike the main components B1 and B1b of the closely related ivermectin, doramectin possesses a double bond between C-22 and C-23 and a cyclohexyl ring on C-25.
2. Doramectin displays a wide spectrum of antiparasitic activity. In nematodes and parasitic arthropodes, doramectin produces a rapid non-spastic paralysis.
3. Doramectin in an oily formulation is intended for use in cattle at a dose of 0.2 mg/kg bw administered as a single subcutaneous injection. The use of Doramectin in cows producing milk for human consumption (lactating dairy cows) is contra-indicated.
4. In cattle, doramectin is rapidly absorbed following subcutaneous administration. From studies using 3-H-doramectin in an oily formulation a plasma half-life of approximately 6 days for total drug related residues was calculated. Tissue levels were highest in liver and fat with significantly lower concentrations in kidney and muscle.

By day 14, 87% of the dose were excreted via bile and faeces and a very small amount was eliminated via urine (less than 1%). The proportion of unchanged drug in the faecal residues increased from 33% on day 7 to 80% on day 12.

Metabolic disposition of doramectin was studied in faeces and liver of cattle, rat, and dog. The faecal excretion of unchanged drug was 24% in cattle, 22% in rats, and 6% in dogs. In liver of cattle, rat and dog at three, two and two days after treatment respectively, the proportion of unchanged drug was 70%, 18% and 28%. 3"-O-desmethyldoramectin was observed as major metabolite in all of the liver and faecal samples (8-19%). Minor metabolites were 24-hydroxymethyldoramectin and 24-hydroxymethyl-3"-O-desmethyldoramectin. In cattle fat, an epimer of doramectin was detected at low levels.

5. Rats appear to be more sensitive than mice following acute oral (LD_{50} male rat : 50-100 mg/kg bw; male mouse : 250-500 mg/kg bw) or intraperitoneal (LD_{50} male rat : 50-100 mg/kg bw; male mouse : 100-200 mg/kg bw) administration of doramectin in oily formulation. Signs of intoxication observed in both species included decreased activity and respiration, tremor and ataxia. Administration of an aqueous formulation of doramectin produced less toxicity in rats and mice.
6. In the repeated dose toxicity studies performed in rats and dogs, doramectin was administered either as a homogeneous mixture of the pure compound in the diet or by gavage as sesame oil formulation. Treatment related effects observed were increased liver weights in rats at doses $\geq$ 5 mg/kg bw and mydriasis in dogs at 0.3 mg/kg bw. At doses $\geq$ 2 mg/kg bw, dogs showed anorexia, tremor and ataxia.

No attempt was made to elucidate in separate studies the potential toxicity of the doramectin metabolites 24-hydroxymethyl-3"-O-desmethyldoramectin, 24-hydroxymethyl-doramectin, 3"-O-desmethyldoramectin identified in liver and faeces of rats, dogs, or cattle.

7. In 3 two-generation studies in rats, continuous exposure to doramectin at doses of ≥ 1 mg/kg bw/day led to diminished neonatal viability and a decrease in pup weight gain possibly caused by the presence of drug derived residues in milk and the immaturity of the blood brain barrier in neonatal rats. These effects were not observed at a dose of 0.3 mg/kg bw/day and thus, this dose level can be taken as a NOEL based on neonatal toxicity. No drug related effects on fertility were noted.
8. Studies on maternal/embryotoxic and teratogenic effects of doramectin were performed in rats, mice and rabbits treated orally by gavage. In rat dams, an increase in body weights at doses ≥ 1.5 mg/kg bw/day was observed. Other effects were not observed and a NOEL of 6 mg/kg bw/day was derived.

In mice significantly lower fetal body weights at 1.6 mg/kg bw/day were registered and a NOEL of 0.8 mg/kg bw/day could be established.

Detection of doramectin in rat and mouse fetuses indicates that doramectin passes the placental barrier in these species.

In rabbits, effects observed were significantly lower maternal body weights or food intake at doses ≥ 1.5 mg/kg bw/day. Increased embryomortality was registered at doses of 1.6 mg/kg bw/day in one study and, in a second study, at 6 mg/kg bw/day but not at 3 mg/kg bw/day. Single external (cleft palate, phocomelia, syndactylia, coelosomia, encephalocoelia) and visceral anomalies (ventricular septal defects, diaphragmatic hernia) were found in fetuses of the 3 mg/kg bw/day dose group. These effects were valued to have been caused by maternal toxicity although it is not clear whether phocomelia (1/123 fetuses examined) was induced by a different mechanism. There is no evidence for teratogenicity at dose levels relevant for the establishment of an ADI. From these studies NOELs of 0.75 mg/kg bw/day can be concluded for maternotoxicity and of 1.5 mg/kg bw/day for embryotoxicity.

9. Tests for mutagenic activity of doramectin at gene (Ames test, Mouse lymphoma gene mutation assay) and chromosome level (mouse micronucleus test) and an unscheduled DNA synthesis assay did not reveal any evidence of genotoxicity.
10. There are no specific studies on the carcinogenic potential of doramectin. Their omission can be justified by i) the absence of mutagenic effects of doramectin and closely related substances demonstrated in a variety of bacterial and mammalian genotoxicity assays, ii) negative results in 3-months studies in rats and dogs with doramectin that indicate a potential to cause tumors by any recognized non-genotoxic mechanism, iii) lack of carcinogenic response in mice and rats reported for closely related compounds (e.g. abamectin).
11. In rabbits, doramectin showed slight eye irritating effects which disappeared by the end of day 2. In dermal irritation studies doramectin was without significant adverse effects on normal and abraded skin. Skin sensitization tests were not performed.
12. Doramectin was not specifically assessed for effects on the immune system or for possible allergenic potential. No evidence of any immunomodulatory activity was observed in the various toxicity studies.
13. The lowest NOEL of 0.1 mg/kg bw/day can be derived from the results of a 3 month gavage study in dogs on the basis of mydriasis observed at 0.3 mg/kg bw/day. A safety factor of 500 is applied because of the lack of studies with the CF-1 mouse strain which proved to be the most sensitive test system for other avermectins and because there are no complementary data from doramectin treated humans. The ADI is established at 0-0.012 mg/person.

RESIDUE FILE

1. Pharmacokinetics were investigated using cattle treated with a single subcutaneous injection of 3-H-doramectin in the projected commercial formulation (75 : 25 sesame oil : ethyl oleate) at a dose of 0.2 mg/kg bw.

The drug was well dispersed from the injection site, with less than 1% of the dose remaining at 21 days. Excretion was almost entirely into the faeces (87% of the dose by day 14). Urinary excretion was only about 1% of total radioactivity by day 14.

The mean plasma half-life was found to be 6.2 days for the parent compound doramectin and 5.9 days for total drug-related residues.

2. The metabolic disposition of 3-H-doramectin was analyzed in liver and faeces of rat, dog, and target species cattle. The major component found in the liver of all three species was unchanged doramectin. Three metabolites, 3"-O-desmethyl-doramectin, 24-hydroxymethyl-doramectin and 24-hydroxymethyl-3"-O-desmethyl-doramectin, were detected in rat and bovine liver while in dog liver only 3"-O-desmethyl-doramectin was present. All three metabolites and doramectin were found in the faeces of all species investigated. Analysis of cattle fat indicated a further metabolite identified as the 2-epimer of doramectin.
3. Residue depletion was studied in cattle following subcutaneous treatment with 3-H-doramectin in the projected commercial formulation at a dose level of 0.2 mg/kg bw. Samples were assayed for total radioactivity and for unchanged doramectin using a HPLC method.

Concentrations of residues were highest at the injection site, in liver, and fat; much lower concentrations were detected in muscle and kidney. In all samples unchanged doramectin represented a major fraction of the total residues. From the results of this study liver and fat were determined as target tissues and the parent substance doramectin as the marker residue. The marker residue doramectin represented approximately 40% of the total residues in liver, 55% in fat, 35% in kidney, and 45% in muscle at 28 days post dose, the time point when total residues had depleted to below the ADI in the standard food package.

4. MRLs for the marker residue doramectin in the target tissues liver and fat were assigned on the basis of the ratios of total/marker residues and on the relative distribution of the marker in tissues at day 28 post dose. The establishment of an MRL for doramectin residues in milk was not applied for. Since measurable residues of doramectin were found in milk when dry cows had been treated before calving, doramectin may not be used in lactating dairy cows or in dairy cows in the interlactational dry period.

The following MRLs for cattle are recommended for inclusion into Annex I.

Liver	15 µg doramectin/kg
Fat	25 µg doramectin/kg

5. A routine analytical method for the determination of doramectin in liver and fat was developed based on a HPLC-method with fluorescence detection. Precision and accuracy of the method were satisfactory. The limits of quantitation of the method were approximately 2.5 µg/kg for liver and 10 µg/kg for fat.