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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DORAMECTIN (extension to deer including reindeer)

SUMMARY REPORT (4)

1. Doramectin is an avermectin produced by fermentation of a selected strain of *Streptomyces avermitilis* in the presence of cyclohexanecarboxylic acid.

   An ADI of 0.5 µg/kg bw (i.e. 30 µg/person) was previously established by the Committee of Veterinary Medicinal Products, based on the NOEL of 0.1 mg/kg bw/day for mydriasis identified in a 3-month repeated dose toxicity study in dogs and a safety factor of 200.

   Currently, doramectin is included in Annex I to Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doramectin	Doramectin	Bovine	10 µg/kg 150 µg/kg 100 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	Not for use in bovines from which milk is produced for human consumption
		Porcine, ovine	20 µg/kg 100 µg/kg 50 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	Not for use in ovines from which milk is produced for human consumption

   An application for the extension of the MRLs to deer including reindeer has now been submitted. The anticipated use pattern is against nematodes and throat bot in reindeer. Doramectin is administered to reindeer as single treatment to the neck using subcutaneous injection at the dose of 200 µg/kg bw.

2. The pharmacokinetic behaviour of doramectin (200 µg/kg bw) was studied in 4 male reindeer after a single subcutaneous administration. Mean elimination half-life was 3.6 days. A maximum concentration of 44 ng/ml was reached in plasma at 2.7 days. At day 21, the mean doramectin concentration in plasma was 1.6 ng/ml.

3. Doramectin was well tolerated by reindeer when treated with the proposed dosing. No formal tolerance study in target species has been provided.

4. The residue depletion of doramectin in reindeer was investigated in 4 males. After single subcutaneous doramectin injections (200 µg/kg), reindeer were killed at day 35 (1 animal), 42 (2 animals) and 56 (1 animal). Residues of doramectin were determined using HPLC with fluorescence detection. The limit of quantification was 20 µg/kg for all tissues. Residue concentrations were below the limit of quantification in all samples analysed except in the injection site of 1 animal at day 35. The residue study does not allow to establish the presence of marker residue in tissues.

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5. A further residue depletion study was carried out using 8 red deer (15 to 17 months old, 66 to 105 kg), 2 of which served as non-treated controls. Doramectin was administered subcutaneously as a single dose (200 µg/kg bw). Groups of 3 animals were killed on days 10 and 21 post-administration. Residues of doramectin were determined using HPLC with fluorescence detection. The limit of quantification was 10, 15, 20 and 20 µg/kg for muscle, kidney, liver and fat, respectively. On day 10, doramectin concentrations ranged from below the limit of quantification to 12.8 µg/kg in muscle, from 18.2 to 30.6 µg/kg in kidney, from 26.4 to 65.5 µg/kg in liver and from 23.8 to 65.9 µg/kg in fat. Residues at site of injection were between 1410 and 4255 µg/kg. On day 21, no residues were detected in muscle and kidney. The liver and kidney of one animal had 17.8 and 25.3 µg/kg, respectively. Doramectin residues at the injection site varied extensively (40.4, 59.2 and 3816 µg/kg).

6. The proposed routine analytical method (HPLC with fluorescence detection) for determination of residues of doramectin in tissues of red deer and reindeer was based on the method developed for cattle tissues. The limit of quantification for liver and fat is 20 µg/kg. The method is not adequately validated for muscle and kidney. The method has been provided in ISO 78/2 format.

Conclusions and recommendation

Having considered the CVMP note for guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97/FINAL) and that:

- an ADI of 0.5 µg/kg bw (30 µg/person/day) was previously established for doramectin,
- doramectin was identified as marker residue in cattle, sheep and swine,
- the presence of doramectin in deer has been shown in a residue study,
- the MRLs set for deer including reindeer are identical to those for ovine tissues,
- an analytical method for the monitoring of residues is available but has not been fully validated for muscle and kidney;

the Committee recommends the inclusion of doramectin for deer including reindeer in Annex III of Council Regulation of (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doramectin	Doramectin	Deer, including reindeer	20 µg/kg 100 µg/kg 50 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.7.2001

The consumer intake of total doramectin-related residues from bovine tissues and milk was estimated to account for around 100% of the ADI. Lower MRLs than for bovine tissues have been now been set for deer including reindeer. The residue intake from deer tissues is therefore less than that from bovine tissues.

LIST OF QUESTIONS

1. The method should be validated for kidney and muscle tissues of deer taking to account the CVMP Position paper on requirements for LOQ/MRL ratio (EMEA/CVMP/274/96-FINAL and point 3.3.4 of the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL).