The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DORAMECTIN
(Extension to deer)

SUMMARY REPORT (5)

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

   The Committee for Veterinary Medicinal Products previously established an ADI of 0.5 µg/kg bw (i.e. 30 µg/person) for doramectin, 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 aplying 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

   Doramectin is currently entered in Annex III of Council Regulation of (EEC) No 2377/90 as follows:

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

   Further data have now been provided to support the establishment of final MRLs for doramectin in deer, including reindeer.

   In reindeer doramectin is used against nematodes and throat bot as a 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.

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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 did not allow to establish the presence of marker residue in tissues.

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 after treatment. 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 residue concentrations 17.8 and 25.3 µg/kg, respectively. Doramectin residues at the injection site varied extensively (40.4, 59.2 and 3816 µg/kg).

   Doramectin was previously identified as marker residue in cattle, sheep and swine and was shown to be present in concentrations high enough to be used for the monitoring of residues of doramectin in deer, including reindeer, according to the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97/FINAL).

6. The 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 validated limit of quantification for liver and fat is 20 µg/kg and for muscle and kidney 10 µg/kg and 15 µg/kg, respectively. The method has been provided in ISO 78/2 format and validated in accordance with CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species.

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 previously identified as marker residue in cattle, sheep and swine and has been demonstrated to be acceptable as marker residue in deer, including reindeer,
- the MRLs set for deer, including reindeer are identical to those for ovine tissues,
- a validated analytical method for the monitoring of residues is available;

the Committee recommends the inclusion of doramectin for deer, including reindeer in Annex I 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	

It was previously estimated that consumer intake of residues from bovine tissues would result in the entire ADI being used up. Because lower MRLs were proposed for deer, including reindeer, it was considered that the intake of residues from these species would be lower than from bovine.