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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

IVERMECTIN (extension to deer)

SUMMARY REPORT (4)

1. Ivermectin belongs to the macrocyclic lactone class of endectocides and consists of a mixture of two homologous compounds, 22,23-dihydroavermectin B1a (H_2B1a, not less than 80%) and 22,23-dihydroavermectin B1b (H_2B1b, not more than 20%). Avermectins are potent anthelmintic, insecticidal and acaracidal compounds which, by increasing the membrane permeability to chloride ions, mediate the paralysis of the nematodes and certain classes of ectoparasites.

   Ivermectin was previously assessed by CVMP and an ADI of 1 µg/kg bw was established. The marker residue in all species was 22,23-dihydroavermectin B1a, and liver and fat were chosen as marker tissues. Ivermectin is currently included in Annex I of Council Regulation (EEC) No 2377/90 with MRLs for bovine, porcine, ovine and equidae species as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ivermectin	22,23-Dihydro-avermectin B1a	Bovine	100 µg/kg 40 µg/kg	Liver Fat	
		Porcine, ovine, equidae	15 µg/kg 20 µg/kg	Liver Fat	

   Ivermectin has been proposed for use in the minor species deer, including reindeer. The recommended dose is 0.2 mg/kg bw subcutaneously or 0.5 mg/kg bw percutaneously. Both treatments are intended to be given only as a single dose. Provisional MRLs are currently set for ivermectin in deer, including reindeer.

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ivermectin	22,23-Dihydro-avermectin B1a	Deer, including reindeer	20 µg/kg 100 µg/kg 50 µg/kg 20 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.1.1999

2. Additional analytical data have now been provided to support an inclusion in Annex for deer, including reindeer.

3. The plasma concentration profile in deer treated subcutaneously with ivermectin showed that maximum plasma concentration was reached approximately 28 hours after treatment with 0.2 and 0.4 mg/kg bw. The peak plasma concentrations were 15.3 µg/l and 28.3 µg/l, respectively. The plasma half-lives of ivermectin in deer treated with 0.2 mg/kg bw or 0.4 mg/kg bw were approximately 4 days.

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4. In animal tissues the ivermectin residues are essentially found as non bound residues. Similar tissue residue distribution patterns exist in cattle, sheep, swine and rats. However, the residue depletion half-lives in liver and fat are approximately 4 to 5 times shorter in sheep and rats than in cattle and swine, reflecting a more rapid metabolism in sheep and rats. In cattle and rats the major liver metabolite was 24-hydroxymethyl-H_2B1a and in swine the major liver metabolites were 3'-O-desmethyl-H_2B1a and 3'-O-desmethyl-H_2B1b. The parent drug accounted for at least 50% of the total residues in tissues from cattle up to 14 days, in sheep up to 5 days, in swine up to 7 days and in rats up to 3 days after treatment. Seven days after subcutaneous treatment 1.5% and 62% of the dose were recovered in urine and faeces, respectively. The parent drug has been found to account for 39 to 78% of the faecal radioactivity in cattle, sheep and rat.

5. The toxicity studies evaluated by Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1991 and 1993 showed that the CF1 strain of mouse was the most sensitive species to treatment with ivermectin. The ADI is based on a NOEL of 0.1 mg/kg bw for maternal toxicity in pregnant CF1 mouse. A safety factor of 100 was used. On this basis, an ADI of 1 µg/kg body weight for ivermectin was established both by the Codex Alimentarius and the CVMP.

6. Residue studies have been performed in red deer, reindeer and cattle.

   Four residue studies in cattle were presented. In three studies cattle were dosed percutaneously with 0.5 or 1.0 mg ivermectin/kg bw and in one study cattle were dosed subcutaneously with 0.2 mg/kg bw. These studies show that the highest concentrations of residues in tissues of cattle were found in liver followed by fat, kidney and muscle except for the injectionsite muscle. Joint FAO/WHO Expert Committee on Food Additives has calculated the percentage of the marker residue (22,23-dihydroavermectin B1a) of the total residues in cattle 28 days post treatment. The marker accounted for 67% in muscle, 37% in liver, 54% in kidney and 18% in fat of total residues and the distribution of residues between tissues was 1:2:11:27 for muscle, kidney, fat and liver, respectively.

   Following a single percutaneously administered dose of 1 mg/kg (twice the recomended dose) to red deer, the tissue residues decreased progressively with time with highest concentrations found in fat followed by liver, muscle and kidney. The ratio of 22,23-dihydroavermectin B1a in tissues at 28 days withdrawal, were in this study 6.8:2.5:1.3:1 for fat, liver, kidney and muscle. At 7 and 28 days post treatment the mean concentrations in µg 22,23-dihydroavermectin B1a/kg of residues in fat were 292 µg/kg and 13.2 µg/kg, respectively, in liver 180 µg/kg and 9.3 µg/kg, respectively, in muscle 78 µg/kg and 1.4 µg/kg respectively and in kidney 78 µg/kg and 3.6 µg/kg, respectively.

   A single subcutaneous dose of 0.2 mg ivermectin/kg bw was given to reindeer. The ratio of 22,23-dihydroavermectin B1a in tissues at 17 days withdrawal, were in this study 9.5:6.6:2.6:1 for fat, liver, kidney and muscle, respectively. Ten and 17 days after treatment, the highest residue concentrations in µg 22,23-dihydroavermectin B1a/kg were in back fat at 362 µg/kg and 68 µg/kg respectively, in liver at 71 µg/kg and 28 µg/kg, respectively, in kidney at 54 µg/kg and 13 µg/kg, respectively, in muscle at 40 µg/kg and 11 µg/kg, respectively, and in the injection site muscle at 44 µg/kg and 9 µg/kg, respectively. The half-lives in the tissues after a single subcutaneous treatment were 7.1 days in back fat, 2.9 days for the injection site, 4.9 days for muscle, 5.8 days for liver and 5.7 days for kidney.

7. Ivermectin was well tolerated by the target species, red deer, when treated with the proposed dosing schedule.

8. The metabolism of ivermectin has not been investigated in deer or reindeer. Furthermore, studies on the relationship between total residues and the marker residue were not performed in deer which precludes a proper comparison between cattle and deer. In the studies provided, it appears that fat contains the highest concentration of ivermectin in deer, contrary to cattle where liver contains the highest concentration of residues. Ivermectin also appears to be eliminated faster in deer than in cattle. However, the limited number of animals and the sampling times chosen in the residue studies makes it difficult to draw any definite conclusions. Since deer is regarded as a minor species, and since there were no major differences in the metabolism and residue profiles in the other investigated species (sheep, cattle, rats and swine), it is assumed that 22,23-dihydroavermectin B1a is also the marker residue in deer and accounts for approximately the same percent of the total residues as in cattle. Since residues in muscle and kidney as well as in liver and fat can be found up to at least 17 days in reindeers after subcutaneous application and up to 28 days in red deer after percutaneous application, it is suggested that MRLs for all major target tissues (liver, fat, kidney and muscle) should be established for ivermectin in deer, including reindeer.

9. A routine analytical method based on HPLC with fluorescence detection has been presented. The limit of quantification was 2 µg/kg and the limit of detection was less than 1 µg/kg for liver, kidney, muscle and fat. The method is fully validated according to Volume VI of the Rules Governing Medicinal Products in the European Community for muscle, fat, liver and kidney.

   In addition the European and the USA authorities have developed methods for monitoring of ivermectin that are more practicable than the proposed method.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 1 µg/kg bw (60 µg/person) was previously established for ivermectin,
- the marker residue is 22,23-dihydroavermectin B1a,
- there is a validated analytical method for residues monitoring purposes;

the Committee recommends the inclusion of ivermectin into Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substances(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ivermectin	22,23-Dihydro-avermectin B1a	Deer, including reindeer	20 µg/kg 100 µg/kg 50 µg/kg 20 µg/kg	Muscle Fat Liver Kidney	

Based on these MRL values, the daily intake will represent about 87% of the ADI.