



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

IVERMECTIN (deer)

SUMMARY REPORT (3)

1. Ivermectin belongs to the macrocyclic lactone class of endectocides and consists of a mixture of two homologous compounds, 22,23-dihydroavermectin B_{1a} (H₂B_{1a}, not less than 80%) and 22,23-dihydroavermectin B_{1b} (H₂B_{1b}, not more than 20%). Ivermectins are potent anthelmintic, insecticidal and acaricidal compounds which, by increasing the membrane permeability to chloride ions, mediate the paralysis of the nematodes and certain classes of ectoparasites. Ivermectin was included in Annex I of Council Regulation (EEC) No 2377/90 with MRLs for the bovine, porcine, ovine and equidae species. The ADI was established to 0-1 µg/kg bodyweight. The marker residue in all species was H₂B_{1a}, and liver and fat were chosen as marker tissues.

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	

2. Ivermectin has been proposed for use in the minor species deer, including reindeer. The recommended dose is 0.2 mg/kg bodyweight subcutaneously or 0.5 mg/kg bodyweight percutaneously. Both treatments are intended to be given only as a single dose. Additional data have been provided to support the extension of the established MRLs for ivermectin to include deer.
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 bodyweight. 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 or 0.4 mg/kg were approximately 4 days.
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-H₂B_{1a} and in swine the major liver metabolites were 3'-O-desmethyl-H₂B_{1a} and 3'-O-desmethyl-H₂B_{1b}. 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 39-78% of the faecal radioactivity in cattle, sheep and rat.
5. The toxicity studies evaluated by the 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 bodyweight for

maternal toxicity in pregnant CF1 mouse. A safety factor of 100 was used. On this basis, an ADI of 0-1 µg/kg bodyweight for ivermectin was established both by the CODEX 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 bodyweight and in one study cattle were dosed subcutaneously with 0.2 mg/kg bodyweight. 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 injection site muscle. JECFA has calculated the percentage of the marker residue (H_2B_{1a}) 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 recommended 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 H_2B_{1a} 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 mg H_2B_{1a} /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 H_2B_{1a} 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 H_2B_{1a} /kg were in back fat 362 µg/kg and 68 µg/kg respectively, in liver 71 µg/kg and 28 µg/kg respectively, in kidney 54 µg/kg and 13 µg/kg respectively, in muscle 40 µg/kg and 11 µg/kg respectively, and in the injection site muscle 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/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 tentatively assumed that the marker residue (H_2B_{1a}) in deer 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 reindeer after subcutaneous application and 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. The marker residue 22,23-dihydroaivermectin B_{1a} is proposed and provisional MRLs to deer, including reindeer are proposed for inclusion in Annex III.

9. A routine analytical method based on HPLC with fluorescence detection has been presented (USDA Method 5.035, June 1987). The method is stated to have a limit of quantification of 10 µg/kg or less. The method has been validated for cattle tissues. Acceptable recoveries from blank tissues spiked with the marker residue at a concentration of 20 µg/kg have been demonstrated in deer tissues. However, there is no formal method validation report for deer tissue analysis. The applicant should provide a fully validated method for deer tissues in accordance with Volume VI of the Rules Governing Medicinal Products. Furthermore, the method should be presented according to an internationally recognised format (e.g. ISO 78/2).

The European and the USA authorities have developed methods for monitoring of ivermectin in muscle, liver, kidney and fat for different species including cattle and reindeer.

Conclusions and recommendation

Having considered :

- Σ the toxicological ADI previously established of 1 µg/kg bw (60 µg/person);
- Σ the 22,23-dihydroavermectin B_{1a} as marker residue;
- Σ the lack of a validated analytical method for residues monitoring purposes;

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

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ivermectin	22,23-Dihydro-avermectin B _{1a}	Deer, including reindeer	20 µg/kg 50 µg/kg 20 µg/kg 100 µg/kg	Muscle Liver Kidney Fat	Provisional MRLs expire on 1 January 1999

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

LIST OF QUESTIONS

1. The routine analytical method should be fully validated for muscle, liver, kidney and fat applicable to deer tissues and presented in an internationally recognised format (e.g. ISO 78/2).