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

EMEA/MRL/692/99-FINAL
August 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ABAMECTIN
(extension to sheep)

SUMMARY REPORT (2)

1. Abamectin is a fermentation product produced by the soil actinomycete, *Streptomyces avermitilis*. Abamectin consists of a mixture of avermectin B1a (at least 80%) and avermectin B1b (not more than 20%). It is an endectocide with a broad spectrum of activity against nematode and arthropod parasites of animals and plants. In veterinary medicine it is administered to cattle as a single subcutaneous injection of 0.2 mg/kg bw. Abamectin is not used in human medicine.

   A toxicological ADI of 0.00025 mg/kg bw (i.e. 0.015 mg/person) was previously established by the Committee for Veterinary Medicinal Products (CVMP). This was was calculated by applying a safety factor of 200 to the NOEL of 0.05 mg/kg bw per day in a study in CF-1 mice, based on maternotoxicity.

   Currently, abamectin is included in Annex I of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Abamectin	Avermectin B1a	Bovine	20 µg/kg 10 µg/kg	Liver Fat	

   An application has now been made for the extension of the MRLs to sheep. Abamectin would be administered to sheep as a single oral dose of 0.2 mg/kg bw abamectin, for the treatment of gastro-intestinal nematodes, lungworms and nasal bots.

2. One male and one female sheep were given a single oral dose of 286 µg/kg bw of ^{3}H-avermectin B1a and samples of blood, urine and faeces were collected for up to 14 days. C_{max} values of 34 and 28 µg equivalents/kg were attained in 24 and 12 hours after dosing the male and female respectively. The half-life for plasma elimination was 53 hours in the male and 57 hours in the female. Two further sheep (one male, one female) were given a single oral dose of 286 µg/kg bw ^{3}H-abamectin (i.e. avermectin B1a + avermectin B1b) and samples of blood, urine and faeces were collected for up to 7 days. C_{max} values of 47 and 67 µg equivalents/kg were attained in 36 and 24 hours after dosing the male and female respectively. The half-life for plasma elimination was 88 hours in the male and 49 hours in the female. In both experiments, excretion was almost entirely *via* the faeces and less than 0.5% of the dose was recovered from urine.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard (44-20-7) 418 8400 Fax (44-20-7) 418 8447
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

3. Male and female sheep were given a single oral dose of 286 µg/kg bw ^{3}H-abamectin. The sheep were killed (5 per time point) at 3, 7, 10 or 14 days after dosing. Total residues in tissues were determined after combustion by liquid scintillation counting. The mean total residues in liver were 374 µg equivalents/kg at 3 days after dosing and depleted to 116, 33 and 19 µg equivalents/kg at 7, 10 and 14 days after dosing. The mean total residues in fat were 354 µg equivalents/kg at 3 days after dosing and depleted to 141, 41 and 35 µg equivalents/kg at 7, 10 and 14 days after dosing. The mean total residues in muscle were 42 µg equivalents/kg at 3 days after dosing and depleted to 14 µg equivalents/kg at 7 days after dosing. Residues were undetectable in most samples of muscle at later time points. In kidney, mean total residues were 105 µg equivalents/kg at 3 days after dosing and depleted to 41, 11 and 7 µg equivalents/kg at 7, 10 and 14 days after dosing.

4. In the same study, the residues in tissues were characterised using radio-HPLC profiling. In muscle and fat, almost all of the residues were present as avermectin B_{1a} and there was no evidence for the presence of any metabolites in these tissues. However the radio-HPLC profile of liver and kidney samples indicated the presence of a polar metabolite which was not identified. Radio-HPLC indicated that the major component of the residues in liver and kidney was avermectin B_{1a}, 3 days and 7 days after dosing.

5. In the same study, samples were also analysed for residues of avermectin B1a, using the proposed routine analytical method based on HPLC with fluorescence detection. The limits of quantification were 10 µg/kg for ovine muscle, liver and kidney and 5 µg/kg for ovine fat. Mean residues of avermectin B1a in liver were 226 µg/kg, 3 days after dosing and depleted to to 56 µg/kg, 7 days after dosing. 10 days after dosing, residues in liver ranged from below the limit of quantification to 31 µg/kg. Mean residues of avermectin B1a in fat were 307 µg/kg, 3 days after dosing and depleted to 116 µg/kg and 27 µg/kg, 7 and 10 days after dosing, respectively. Mean residues of avermectin B1a in muscle were 37 µg/kg, 3 days after dosing and were in the range from below the limit of quantification to 21 µg/kg, 7 days after dosing. Mean residues of avermectin B1a in kidney were 74 µg/kg 3 days after dosing and were in the range from below the limit of quantification to 50 µg/kg, 7 days after dosing. The results indicated that avermectin B1a accounted for 60%, approximately 50% and 58% of the total residues in liver 3, 7 and 10 days after dosing. Avermectin B1a accounted for 88% and 93% of the total residues in muscle, 88% and 93% of the total residues in fat and 71% and 75% of the total residues in kidney, 3 and 7 days after dosing. Avermectin B1a was retained as the marker residue.

6. The proposed routine analytical method for determining the residues of avermectin B1a (the marker residue) in the edible tissues and milk of sheep was based on HPLC with fluorescence detection and was described in the ISO 78/2 format. Specificity was satisfactory and residues of avermectin B1b and ivermectin did not interfere in the assay. The limits of quantification were 10 µg/kg for ovine muscle, liver and kidney and 5 µg/kg for ovine fat. The analytical method was not fully validated in that the full raw data to establish linearity were not provided, the values quoted for accuracy were actually those for recovery, and there was no information concerning intermediate precision (inter-day within laboratory variations).

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 0.00025 mg/kg bw, i.e. 15 µg/person, was established for abamectin,
- avermectin B1a was identified as the marker residue in ovine tissues and accounted for approximately 50% and 75% of the total residues in ovine liver and kidney, 7 days after dosing and almost all of the total residues in ovine muscle and fat,
- at 7 days after dosing, residues of avermectin B1a in fat were approximately twice those found in liver; at the same time point residues of avermectin B1a in kidney and muscle were low and MRLs for these tissues could be set at values corresponding to twice the limit of quantification,
- the routine analytical method was available, however not fully validated;

the Committee recommends the inclusion of abamectin for sheep in Annex III of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Abamectin	Avermectin B1a	Ovine	20 µg/kg 50 µg/kg 25 µg/kg 20 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.1.2001. Not for use in animals from which milk is produced for human consumption.

Based on these MRLs, it was calculated that the consumer intake of total residues from the consumption of ovine meat would account for approximately 99% of the ADI.

Before the Committee for Veterinary Medicinal Products can consider the inclusion of abamectin for sheep in Annex I of Council Regulation (EEC) No 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The proposed routine analytical method should be fully validated in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community, in particular, the full raw data to establish linearity should be provided, the values for accuracy should be shown correctly and not confused with recovery, and information concerning intermediate precision (inter-day within laboratory variations) should be provided.