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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

EPRINOMECTIN (modification)

SUMMARY REPORT (2)

1. Eprinomectin is a semi-synthetic compound of the avermectin family, intended for the treatment of internal and external parasites in cattle and in lactating cows. Eprinomectin is a mixture of two homologues, eprinomectin B1a (90%) and eprinomectin B1b (10%), which differ by a methylene group in the C25-position. The recommended dosage regimen is a single dose of 0.5 mg/kg bw (0.1 ml/10 kg bw) applied topically along the midline of the animal's back.

   An ADI of 5 µg/kg bw (300 µg/person) was established for eprinomectin by applying a safety factor of 200 to the NOEL of 1.0 mg/kg bw/day for mydriasis and focal neuronal degeneration on nervous system which was established in the 53-week toxicity study in dogs.

   Based on this ADI, the Committee for Veterinary Medicinal Products proposed MRLs which are currently entered in Annex I of the Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRL	Target tissues	Other provisions
Eprinomectin	Eprinomectin B1a	Cattle	30 µg/kg 30 µg/kg 600 µg/kg 100 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk	

   An application has now been submitted for the modification of the MRLs for bovine and requesting revision of the toxicological ADI.

2. At the 50th meeting of the Joint FAO/WHO Expert Committee on Food Additives, the experts considered also that the most relevant effect for the safety evaluation was the effect on the mammalian nervous system. An ADI of 10 µg/kg bw, i.e. 600 µg/person was established by applying a safety factor of 100 to the NOEL of 1 mg/kg bw/day for mydriasis and focal neuronal degeneration in the brain of the 53-week toxicity study in dogs.

3. Published data showed that the hypersensitivity of the CF-1 mouse strain compared with the CD-1 mouse strain for ivermectin was due to individuals with a mutation at the MDR1a locus which resulted in a deficiency of P-glycoprotein, a protein affecting drug transport. In this sensitive strain, the concentrations of ivermectin were 90 times higher in brain and 3 to 4 times higher in other tissues than those measured in CF-1 mice presenting no deficiency of P-glycoprotein.

   In addition, over ten million people world-wide had been treated with oral doses of ivermectin of up to 400 µg/kg bw. No major side effects had been reported in human, except those resulting from the effects of the parasite itself. For this compound, the ADI established is 1 µg/kg bw per day.

   Hypersensitivity of ivermectin in collie dogs has been demonstrated. Oral doses of 200 µgivermectin/kg bw and 600 µg ivermectin/kg bw induced clinical neurologic signs (ataxia, depression, tremors, mydriasis). With doses up to 50 µg ivermectin/kg bw no occurrence of clinical signs was noted. In beagle dogs, similar clinical signs were only observed from oral doses of 2500 µg ivermectin/kg bw on.

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4. Having considered that :

   - the NOEL of 1.0 mg/kg bw/day for mydriasis and focal neuronal degeneration on nervous system observed in the 53-week toxicity study in beagle dogs was retained to establish the ADI,
   - no specific data showing a potential hypersensitivity of beagle dogs to eprinomectin was available,
   - the ADI has not been established from specific data on the sensitivity of CF1 mice to eprinomectin as no information was available,
   - for all the compounds of the avermectin family, a safety factor of 200 was retained to set the toxicological ADI when based on the absence of mydriasis in dogs, this factor accounting for the uncertain sensitivity of the test system used to assess the neurotoxicity, in absence on data provided on the CF1 mouse strain;

   the Committee considered that there is no scientific basis to decrease the value of the safety factor to 100 and maintained the conclusion of its first assessment, i.e. an ADI of 5 µg/kg bw (300 µg/person).

5. After a single topical application of 0.5 mg/kg bw of eprinomectin to adult bovines, the concentrations of eprinomectin B1a in plasma peaked on days 2 and 3 after the application (11 to 12 µg/l). Then the plasma levels declined to reach 2 µg/l at 7 days post application.

   After a single topical application of 0.5 mg/kg bw of eprinomectin to young non-ruminating calves, the highest concentrations of eprinomectin B1a in plasma occurred between days 4 and 8 with mean values of 116 and 136 µg/l on those days. Then, the plasma levels declined to reach 77.2 µg/l on day 10 and 49.6 µg/l on day 14.

6. Two new depletion studies with unlabelled eprinomectin in edible tissues were provided, the first one in adult cattle, the second one in young non-ruminating calves.

   In the first depletion study, eprinomectin was applied topically to groups of 5 adult cattle at the therapeutic dosage of 0.5 mg/kg bw. The mean concentrations of eprinomectin B1a in muscle, fat, liver and kidney reached a maximum at three days post dosing with values of 5, 20, 710 and 93 µg/kg, respectively. Then they declined to reach 4, 323 and 23 µg/kg in fat, liver and kidney, respectively, seven days after treatment whereas no residues could be quantified in muscle (less than 2 µg/kg) at this time point.

   In the second depletion study, eprinomectin was applied topically to groups of 3 young non-ruminating calves at the therapeutic dosage of 0.5 mg/kg bw. Seven days after the application, muscle, fat, liver and kidney contained the highest concentrations of eprinomectin B1a: 48, 287, 1220 and 237 µg/kg, respectively. Then the levels of eprinomectin B1a declined to reach 22, 103, 803 and 120 µg/kg in muscle, fat, liver and kidney, respectively, 14 days post-dose. However, as the distribution of the concentrations according to the time is not normal, as the variance between groups is not homogeneous and in absence of log-linearity and in addition as the number of animals per slaughtering time did not follow the requirements of Volume VI of The Rules Governing Medicinal Products in the European Community, it will not be possible to apply the current guideline on the statistical determination of a withdrawal period in this case.

7. On re-evaluating the substance, the Committee considered that the MRLs already established did not reflect the pattern of distribution in non-ruminant animals and would lead to unrealistic long withdrawal period which are unlikely to accommodate possible future development of use in young non-ruminating bovine. In addition the percentage of the ADI which remained for further development of the substance was too high (approximately 50%). For these reasons, the Committee re-considered the establishment of MRLs for eprinomectin.

8. The Committee noted that the 50th meeting of the Joint FAO/WHO Expert Committee on Food Additives had proposed MRLs of 100 µg/kg for muscle, 250 µg/kg for fat, 2000 µg/kg for liver, 300 µg/kg for kidney and 20 µg/kg for milk. The Committee agreed that the MRLs allocated for fat, kidney and milk could be adopted, but not the other ones because they did not reflect the distribution of residues in non-ruminating animals at the 7 to 14 day-time point and because the toxicological ADI established by the Committee was twice-fold lower than the ADI established by JECFA.

Conclusions and recommendation

Having considering that:

- the toxicological ADI is 5 µg/kg bw, i.e. 300 µg per person,
- eprinomectin B1a is the marker residue,
- the tissue distribution is based on results obtained 7 to 14 days after application,
- the ratio of parent compound towards total residues is known for all edible tissues including milk: 75% for muscle, 100% for fat, 80 % for liver, 78% for kidney and 80% for milk,
- validated analytical methods are available for monitoring residues in edible tissues;

the Committee recommends the modification of the MRLs for eprinomectin in bovine in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRL	Target tissues	Other provisions
Eprinomectin	Eprinomectin B1a	Bovine	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	

Based on these MRL-values, the maximum daily intake was estimated to be 276.23 µg per day, representing about 92% of the ADI.