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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DORAMECTIN
(Modification for cattle)

SUMMARY REPORT (2)

1. Doramectin is an avermectin produced by fermentation of a selected strain of *Streptomyces avermitilis* in the presence of cyclohexanecarboxylic acid. It is administered by subcutaneous injection to cattle at a dose of 200 µg/kg bw for the treatment and control of gastrointestinal nematodes, lungworms, eyeworms, warbles, lice and mange mites in cattle. It is contraindicated for use in lactating cattle. EC MRLs for doramectin were agreed in Commission Regulation (EC) No 1430/94 as follows:

Substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doramectin	Doramectin	Bovine	15 µg/kg 25 µg/kg	Liver Fat	

2. The CVMP considered new data on the toxicity of doramectin and some related avermectins including ivermectin. In an acute toxicity study in female CD-1 mice, doramectin was shown to be less acutely toxic than moxidectin and abamectin. Its acute toxicity was similar to or possibly lower than that of ivermectin. A single oral dose of 75 mg/kg bw caused the death of all 5 mice given moxidectin or abamectin, only 1/5 mice given ivermectin, but no mice given doramectin.

3. Ivermectin was significantly more toxic to the CF-1 mouse compared with the CD-1 mouse. A study comparing plasma:brain concentrations in the 2 strains was inconclusive due to poor study design. However published work indicated that the increased sensitivity of the CF-1 strain was due to individuals with a mutation at the mdr1a locus which resulted in a deficiency of p-glycoprotein, a protein affecting drug transport. Brain concentrations of ivermectin were 90 times higher and concentrations in other tissues were 3-4 times higher in CF-1 mice which were homozygous for the mdr1a deletion, compared with mdr1a (+/+) mice. Similar data were not provided for doramectin; however there is no reason to suppose that the effects of doramectin would be different.

4. The results of a limited dose-escalation experiment in ivermectin-sensitive Collie dogs suggested that doramectin was less toxic than ivermectin. An oral dose of 0.125 mg/kg bw doramectin had no effect on the dogs but the same dose of ivermectin caused ataxia and tremors in one of the dogs.

5. No NOELs were established in new repeated dose studies in the CD-1 mouse and Long-Evans rats in which very high dose levels were employed. However satisfactory NOELs were established in previously-supplied repeated dose toxicity studies in rats and dogs; these were 2 mg/kg bw per day and 0.1 mg/kg bw per day respectively.

6. In new target species safety studies, administration of 3 times the therapeutic dose to breeding bulls, pregnant cattle, and neonatal calves did not affect fertility, gestation, parturition or post-natal development.

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7. A published report described a herd of Murray Grey cattle which had been "closed" for 15 years and which was particularly sensitive to the toxicity of ivermectin. To check the sensitivity of this breed to doramectin, 22 Murray Grey calves were given a single intramuscular injection of 600 µg/kg bw doramectin and a second group of 28 calves was given the same dose subcutaneously. No signs of toxicity were observed and all calves gained weight normally.

8. Doramectin had been developed for veterinary use and had never been administered to humans. In contrast, over 10 million people world-wide had been treated with oral doses of ivermectin of up to 200 µg/kg. No major side effects had been reported, except those resulting from the effect on the parasite itself (the Mazzotti reaction). No information was available concerning the incidence of mutations in the MDR1 human gene and consequent p-glycoprotein deficiency in humans. However there was no evidence from the extensive human use of ivermectin that a subset of atypically sensitive individuals existed.

9. For the reasons stated in the previous paragraphs, the CVMP concluded that a 500-fold safety factor was not necessary in calculating an ADI for doramectin. The most relevant effect for the safety evaluation was the effect on the mammalian nervous system. It was agreed that the NOEL of 0.1 mg/kg bw per day which was established in the 3-month repeated-dose toxicity study in dogs, based on mydriasis, was most relevant for calculating the ADI. A safety factor of 200 was applied because the test systems used to assess the neurotoxicity of doramectin were of uncertain sensitivity. The ADI was therefore 0-0.5 µg/kg bw.

10. The CVMP also considered new data on the depletion of total radio-labelled residues and residues of unmetabolised doramectin in cattle following intramuscular administration of 200 µg/kg bw. (Pharmacokinetic data previously submitted had shown that the intramuscular and subcutaneous routes were bioequivalent in cattle following administration at 200 µg/kg bw (10/sex/group).) 2 males and 2 females were slaughtered 7, 14, 21, 28, 35 and 42 days after treatment. The total residues were determined by combustion - liquid scintillation counting. Total residues in fat, liver, muscle and kidney declined from 551 ± 42 µg/kg, 470 ± 110 µg/kg, 40 ± 5 µg/kg and 108 ± 15 µg/kg, 7 days after treatment, to 23 ± 6 µg/kg, 24 ± 1 µg/kg, less than 3 µg/kg and 4 ± 1 µg/kg, 42 days after treatment.

11. In all tissues, most of the residues were present as unmetabolised doramectin. The ratio of marker to total residues was fairly constant over the time period 7-42 days post-treatment and varied between 84-75% in muscle, 68-60% in liver, 89-77% in kidney and 89-86% in fat, 7-28 days after treatment. The residues of doramectin were determined using the routine HPLC analytical method (limits of quantification 2.5 µg/kg for liver, kidney and muscle and 10 µg/kg for fat). Residues of doramectin in fat, liver, muscle and kidney declined from 493 ± 47 µg/kg, 319 ± 78 µg/kg, 33 ± 4.2 µg/kg and 96.2 ± 13 µg/kg, 7 days after treatment, to 16.7 ± 4.9 µg/kg, 13.2 ± 0.6 µg/kg, less than 2.13 µg/kg and 3.11 ± 0.8 µg/kg, 42 days after treatment. The highest residues were found at the injection site. Total residues at the injection site declined from 2530 ± 1500 µg/kg, 7 days after treatment, to less than 18 ± 17 µg/kg, 42 days after treatment.

12. The routine analytical method previously accepted by the CVMP was based on HPLC with fluorescence detection. Data provided previously indicated that the limits of quantification were 2.5 µg/kg for liver, kidney and muscle and 10 µg/kg for fat. Precision and accuracy of the method were satisfactory.

Conclusions and recommendation

Based on the pattern of distribution and residue depletion, the Committee agreed to adopt the JECFA MRLs and recommends that the maximum residue limits as established under Council Regulation (EEC) No 2377/90 for doramectin be amended in accordance with the following table :

Substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doramectin	Doramectin	Bovine	150 µg/kg 100 µg/kg 30 µg/kg 10 µg/kg	Fat Liver Kidney Muscle	

Based on these MRLs, the consumer intake of total doramectin-related residues was estimated to account for around 100% of the ADI calculated in paragraph 9.