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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MOXIDECTIN (extension to horses)

SUMMARY REPORT (1)

1. Moxidectin is intended for the treatment of endo- and ecto-parasites in cattle and sheep at the recommended dosage of 0.2 mg/kg bw administered by oral or subcutaneous routes. It has already been assessed by the CVMP. Considering a NOEL of 0.3 mg/kg bw/day and applying a safety factor of 200 to take the account of the uncertain sensitivity of the test system used to assess the neurotoxicity of moxidectin, a toxicological ADI of 1.5 µg/kg bw was established.

   In accordance with the requirements of Council Regulation (EEC) 2377/90, an Annex I entry for sheep and cattle was published in Commission Regulation (EC) No 748/97 of 25 April 97 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Moxidectin	Moxidectin	Bovine, ovine	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	

2. An application for extension of the annex entry to include horses has now been submitted. The recommended dosage is a single oral administration of 0.4 mg/kg bw.

3. After a single intravenous administration of ^{14}C-moxidectin at a dose of 0.4 mg/kg bw to 3 horses, the mean serum concentration of radioactivity at 2 minutes post dose was 3.3 µg moxidectin equivalents/g. Thereafter, the levels declined to reach 0.03 µg moxidectin equivalents/g at 168 hours post dose. Moxidectin had a serum clearance of 0.036 l/h x kg bw and its mean volume of distribution was 4.14 l/kg bw. The values of these two parameters explain the prolonged elimination half-life of 79.09 hours calculated for moxidectin.

   After a single oral administration of ^{14}C-moxidectin to 3 horses at the recommended therapeutic dose of 0.4 mg/kg bw, the mean peak serum concentration of total radioactivity (0.134 µg moxidectin equivalents/g) was attained at 6 hours post dose.

   The oral availability was 40.05%. The terminal elimination half-life for moxidectin was in the same range as that found after intravenous administration.

   Within 168 hours, 77.3% of the total radioactivity were excreted, 77% by the faecal route and 0.3% via the urine. In faeces, the parent compound represented approximately 70% of the faecal radioactivity. Four minor hydroxylated metabolites were detected in faeces (A; C; D; E - percentages ranging from 0.28 to 3.45% of the faecal radioactivity). These metabolites resulted from oxidation mainly on C14, C24 and/or C28. Due to the complexity of the chemical names of the metabolites, the chemical name of the metabolites will not be given in this summary.

   At 168 hours post-administration, the radioactivity was measured in all the edible tissues: 10, 690, 112 and 40 µg moxidectin equivalents/kg in muscle, fat, liver and kidney, respectively.

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At this sampling time, the ratios of the parent compound to the total radioactive residues were 48%, 87%, 61% and 78% in muscle, fat, liver and kidney, respectively. In tissues, up to six metabolites could be separated, five of them being identified. The main identified metabolite, E, did not exceed 10% of the total radioactivity in liver, 14% in muscle, 3% in kidneys but was not seen in fat.

Most of the radioactivity could be extracted from edible tissues (96-100%).

4. In a non-radiometric study, groups of 5 horses received a single oral dose of 0.4 mg/kg bw moxidectin formulated in a 2% gel and were slaughtered at 28, 35, 42 and 49 days post dosing. Moxidectin was only measurable in fat: 221 µg/kg at 28 days, 165 µg/kg at 35 days, 130 µg/kg at 42 days and 131µg/kg at 49 days after the administration. In all other edible tissues, the concentrations were below the limit of quantification (10 µg/kg). As the first slaughtering point chosen was 28 days post dose, this depletion study cannot be considered relevant for the establishment of MRLs.

5. The same analytical method as that retained for monitoring residues of moxidectin in bovine and ovine edible tissues was proposed: a high performance chromatographic liquid method with fluorescence detection. The limit of quantification is 10 µg/kg for all edible tissues. The limits of detection, determined as being the signal equivalent to three times the background noise, are 1 µg/kg for liver, kidney and muscle and 5 µg/kg for fat.

6. Having considered :

   - the toxicological ADI of 1.5 µg/kg bw, i.e. 90 µg per person,
   - the tissue distribution of moxidectin in muscle, fat, liver and kidney based on results obtained in the radiolabelled study (10 µg moxidectin/kg in muscle, 690 µg moxidectin/kg in fat, 112 µg moxidectin/kg in liver and 40 µg moxidectin/kg in kidney) at 168 hours post treatment,
   - the ratio of the marker residue to total residues determined at this slaughtering time: 48% for muscle, 87% for fat, 60% for liver and 78% for kidney,
   - the horse as a minor animal species,
   - the routine analytical method proposed is adequate as already having been accepted for monitoring moxidectin residues in ovine and bovine edible tissues, but not fully validated;

   the Committee recommends the inclusion of moxidectin in 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
Moxidectin	Moxidectin	Equidae	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on the 1.1.2000

In cattle and sheep, the ratios of the marker residue to total residues were as follows: 50% in muscle, 90 % in fat, 40 % in liver and 60 % in kidney. For an overall estimation of the amount of residues susceptible to be ingested by the consumer, these data being taken into account lead to a residue consumption of about 88 µg, representing about 98% of the total daily intake.

LIST OF QUESTIONS

1. The specificity/selectivity and the limits of detection of the analytical method proposed for monitoring purposes should be validated in accordance with the recommendations of the Volume VI of "The rules governing medicinal products in the European Union". The analytical method should be presented according to an internationally recognised format (e.g. ISO 78/2).