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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MOXIDECTIN

SUMMARY REPORT (2)

1. Moxidectin is an antiparasitic drug which is intended for the treatment of endo- and ecto-parasites in cattle and sheep at the recommended dose of 0.2 mg/kg bw administered by oral or subcutaneous routes. It is produced by a chemical modification of nemadectin, a natural fermentation product produced by the microorganism *Streptomyces cyaneogriseus subsp. noncyanogenus*. It is a semisynthetic macrocyclic lactone, structurally similar to abamectin, ivermectin and milbemycin.

2. Moxidectin has already been assessed by the CVMP in 1993. At that time, the most appropriate end-point for setting an ADI was identified as the reduced pup survival which was observed in the two-generation rat study. Based on a NOEL of 0.4 mg/kg bw and using a safety factor of 500 to compensate for the absence of data on the mice CF1 strain, an ADI of 0-0.0008 mg/kg was established, providing an adequate margin of safety for the effects seen in the repeat dose toxicity studies (NOEL = 0.3 mg/kg bw).

3. Recently, new scientific data showed that the hypersensitivity of the CF1 mouse compared with the CD1 mouse 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 3-4 times higher in other tissues than those measured in CF1 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 0.2 mg/kg bw. No major side effects had been reported in humans, except those resulting from the effects of the parasite itself (the Mazzotti reaction).

4. It is reasonable to suppose that the same conclusions could be drawn with moxidectin, which had been developed for veterinary use; the value of the safety factor and the animal species retained for the first assessment should therefore be reconsidered. The NOEL of 0.3 mg/kg bw established from the 90-day toxicity study performed in dogs could be retained.

5. Based on this NOEL of 0.3 mg/kg bw/day and applying a safety factor of 200 to account for the uncertain sensitivity of the test system used to assess the neurotoxicity of moxidectin, a toxicological ADI of 0-0.0015 mg/kg bw was established. This value is in accordance with that established on the 45th Joint Experts Committee for Food Additives (JECFA) meeting.

6. A new non-radiometric residue study in sheep was provided.

   In this assay it was shown that 10 days after a single subcutaneous administration of moxidectin at the recommended rate of 0.2 mg/kg bw, only large amounts of moxidectin residues could be measured in fat (222 µg/kg) when compared to other tissues : 40.8 µg/kg in muscle, 21.1 µg/kg in liver and 12.8 µg/kg in kidney. The concentrations at the injection site were close to 1600 µg/kg.

   In sheep receiving two injections of 0.2 mg/kg bw moxidectin by subcutaneous route ten days apart, the following concentrations of moxidectin were measured after a 10-day withdrawal period: 324 µg/kg in fat, 29 µg/kg in muscle and liver and 21 µg/kg in kidney. The concentrations decreased to 230 µg/kg in fat, 550 µg/kg at the injection site and values below 20 µg/kg in muscle, liver and kidney, at 20-days withdrawal period.

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7. As the applicant has provided data on the specificity with regard to other compounds of the same family, a routine analytical HPLC method with fluorescence detection has now been validated according to the recommendations of Volume VI of the Rules Governing Medicinal Products in the European Community and is available to ensure the monitoring of moxidectin residues in all the edible tissues of sheep and cattle. The limit of quantification was 10 µg/kg.

Conclusions and recommendation

Having considered that :

- the toxicological ADI is 0.0015 mg/kg bw (i.e. 90 µg per person),
- moxidectin is the marker residue,
- the ratio of parental compound to total residues is known for all edible tissue: 50 % for muscle, 90 % for fat, 40 % for liver and 60-75 % for kidney,
- the tissue distribution observed at 21 days for cattle and 20 days for sheep showed that the concentrations of moxidectin in fat are 10-fold higher than those observed in all other edible tissues except at the injection site,
- MRLs have been elaborated for moxidectin at the 45th JECFA meeting,
- validated analytical methods are available for monitoring residues in all edible tissues;

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

Pharmacalogically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Moxidectin	Moxidectin	Bovine, ovine	500 µg/kg 100 µg/kg 50 µg/kg	Fat Liver Muscle, kidney	

Based on these MRLs values, the daily intake will represent about 89% of the toxicological ADI.