The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ABAMECTIN

SUMMARY REPORT (1)[1] Updated

1. Abamectin is isolated from a fermentation broth of the soil actinomycete, *Streptomyces avermitilis*. There are 4 major homologues and 4 minor homologues of the lactones. Abamectin is comprised of not less than 80% of the component avermectin B1a and not more than 20% of the Avermectin B1b-component. Abamectin has a broad spectrum activity against nematode and arthropod parasites of animals and plants.

2. Following a single oral administration of tritium labelled avermectin B1a to rats (0.14 mg/kw bw or 1.4 mg/kg bw), highest tissue levels of radioactivity were found in fat and kidney followed by liver and muscle. Depletion rates were independent of dose and tissue ($t_{1/2}$: 1.2 +/- 0.3 days). Up to 77 % (females) and 82 % (males) of the administered dose were excreted via faeces and 0.3-1.1 % via urine.

   In addition to the parent compound, two metabolites were found in muscle, liver, kidney, and fat identified as 24-hydroxymethyl avermectin B1a and 3"-desmethyl avermectin B1a.

3. At day 1 and 2 following a subcutaenous application of 0.3 mg tritium labelled abamectin/kg bw to cattle, mean peak plasma levels of radioactivity corresponding to approximately 0.09 mg/l were found. Depletion rates ($t_{1/2}$) for liver, kidney, muscle, fat and plasma were 4.6, 5.7, 5.6, 8.1, and 4.7 days, respectively. About 50% of radioactivity was detected in feces within 7 days and 1% - 2% in urine.

   In liver, the main parent drug component avermectin B1a accounted for 34% - 61% of total residues independent of time of sacrifice; in fat, concentration of avermectin B1a decreased from 52 % on day 7 to 25 % on day 21. Avermectin B1b represented in liver 1% - 5% and in fat 0.5% - 5% of the total residue. In addition to the parent drug components, metabolite 24-hydroxymethylavermectin B1a was identified in liver and, following treatment of a major nonpolar metabolite fraction with cholesterol esterase, in fat.

4. Following oral administration of abamectin, mean LD_{50}-values of 9.2 mg/kg bw and 19.7 mg/kg bw were found in male and female mice, respectively. In rats, the LD_{50}-values were reported to be 8.7 mg/kg bw in males and 12.8 mg/kb bw in females.

   There is no difference in toxicity between component avermectin B1b and abamectin in mice.

5. An oral acute toxicity study was conducted in rhesus monkeys using a dose range of 0.2-24 mg/kg bw. Early sign of toxicity was emesis observed at 2 mg/kg bw. Mydriasis and a slight to moderate reversible sedation was noted at 24 mg/kg bw. Based on the results of this study, it was concluded that monkeys can tolerate abamectin doses which produce severe forms of toxicity or death in other species.

6. The acute dermal toxicity of abamectin was studied in rats (330 mg/kg bw) and rabbits (up to 2000 mg/kg bw). Clinical signs of intoxication observed at these high doses were reversible and comprised ataxia, tremor, bradypnea, decreased activity and bodyweight loss. There was only a slight dermal reaction with focal hemorrhage, erythema, edema and cellular infiltration. In Guinea pigs, abamectin had no skin sensitizing potential. Ocular irritation studies in rabbits yielded slightly positive results.

[1] The initial Summary Report was adopted on 21-22.09.1993. It was updated following revision of the ADI on 15.05.2002.

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7. Repeated dose oral toxicity studies were conducted in mice (2-8 mg/kg bw), rats (0.75-2.0 mg/kg bw) and dogs (0.25-8.0 mg/kg bw). The highest dose without effect observed in the rat and dog study was 0.25 mg/kg bw and 1.5 mg/kw/bw, respectively. In the mouse study, tremor was observed as an irregular treatment related effect in females of all dose groups.

   Signs of drug effect observed frequently in toxicity studies were tremor, ataxia, mydriasis, emesis and coma.

8. Reproductive studies (including teratogenicity studies) have been carried out in rats, rabbits and mice. A slight increase in fetal malformation was observed in rabbits whereas in rats developmental retardation was noted (beginning at doses of 1.0 mg/kg bw and 0.2 mg/kg bw, respectively). In mice, abamectin caused fetal malformations only at maternotoxic doses (0.4 mg/kg bw). Maternotoxicity in mice (tremor, coma) was the most sensitive parameter for toxicity observed and was taken as basis for the establishment of the ADI (NOEL 0.05 mg/kg bw).

9. Studies on genotoxicity (Ames tests; *in vitro* and *in vivo* alkaline elution assay; *in vitro* genotoxicity test in hamster lung cells and ovary cells, *in vivo* mouse bone marrow cell tests) were negative.

10. Cancerogenicity studies (combined with chronic toxicity studies) in mice and rats gave no evidence for an oncogenic potential of abamectin.

11. Initially, the ADI was set on the basis of a maternotoxicity study in the CF-1 mouse (NOEL : 0.05 mg/kg/bw/day). A safety factor of 200 was used to compensate for incomplete data of the maternotoxicity study and for the lack of observations in humans : ADI : 0.25 µg/kg bw/day, corresponding to 0-15 µg/adult/day. Following an assessment of additional data, including data indicating that the effects observed in the CF-1 mice were not relevant to the safety assessment, the CVMP established a revised ADI of 2.5 µg/kg bw (150 µg/person), by applying a safety factor of 100 to the NOEL of 0.25 mg/kg bw/day which was established in a one-year repeated-dose study in dogs.

12. Depletion of radiolabelled total residues and abamectin was investigated following subcutaneous treatment of cattle with a single dose of 3-H-abamectin at 0.3 mg/kg bw. At any time after dosing, the total residues in liver and fat were significantly higher than those in kidney and muscle. Avermectin B1a represented a major fraction of the total residues in all tissues examined. Liver and fat were determined as the target tissues and avermectin B1a as the marker residue. Between days 7 to 21, the ratios of marker/total residues ranged from 0.55-0.36 for liver, 0.65-0.20 for fat, 0.74-0.51 for muscle, and 0.48-0.24 for kidney.

13. These ratios of marker/total residues were used to estimate the MRLs. The MRLs were calculated from the total residue concentrations at the time point, when the daily residue intake had depleted below the ADI of 15 µg (day 21 post dose).

    The following MRLs for cattle were recommended :

    liver : 0.02 mg avermectin B1a/kg
    fat : 0.01 mg avermectin B1a/kg

14. Two residue depletion studies are available for the marker residue avermectin B1a in edible tissues of cattle treated with a single subcutaneous dose at 0.3 mg abamectin/kg bw. The residues at the injection site were found to be significantly higher than those observed in the other tissues. Appropriate withdrawal periods should be set in consideration of the injection site.

15. A routine analytical method for the determination of avermectin B1a was developed based on HPLC with fluorescense detection. The limit of quantitation was 5 µg/kg for each tissue. The average recoveries for the different tissues were in the range of 70-90% . The coefficients of variation were below 15%. The method was shown to be specific relative to ivermectin, doramectin and moxidectin.

16. Based on the above MRLs, it was estimated that consumer intake from the consumption of bovine meat would represent approximately 7% of the revised ADI of 2.5 µg/kg bw (150 µg/person). This would permit the pesticidal uses of abamectin (which were not expected to exceed 5 µg/person) to be accommodated.

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