COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

IVERMECTIN

SUMMARY REPORT (1)

1. Ivermectin is a mixture of two components containing at least 80% 22,23-dihydro-avermectin B_{1a} and not more than 20% 22,23-dihydro-avermectin B_{1b}. It is obtained by chemical modification of avermectin B_{1a} fermentation production of the actinomycete *Streptomyces avermitilis* NRRL 8165.

2. Ivermectin is an important broad spectrum antiparasitic drug. In veterinary medicine it is extensively used in many countries in cattle, horses, sheep and pigs. In human medicine it is used for the treatment of onchocerciasis. Ivermectin's spectrum of activity covers nematodes and arthropodes. The mechanism of action in parasites has not yet been clearly established.

3. The individual components have very similar toxicological properties, and for the practical purpose of establishing a tolerance for the whole product, all other derivatives of the avermectins tested up to now can also be considered equivalent.

4. In mammals acute toxic effects are central-nervous disorders, such as tremor, depression, ataxia, paresis, paralysis, depending on the test species and the applied dose.

5. Great differences in sensitivities are observed amongst various species; rodents, especially mice, show an increased sensitivity to the acute toxicity of ivermectin, whereas primates including humans possess a relatively lower degree. Therapeutic doses are usually well tolerated in all species. Subpopulations with a particularly high sensitivity have been identified in dogs (eg collies), however the extensive and safe use in human medicine suggests that for the safety evaluation of residues with regard to the consumer this aspect is not relevant.

6. Teratogenic effects in laboratory animals occur only at maternotoxic doses. Studies on mutagenicity and carcinogenicity (with abamectin) are negative.

7. Based on a non-observed-effect level of 0.1 mg/kg bw taken from the mouse teratogenicity study (maternotoxic effects) and a safety factor of 500 results an ADI of 0-12 µg/60 kg/bw/day.

8. This would also cover the teratogenic potential of ivermectin, since the NOEL from the teratogenicity study (teratogenic effects) is 0.2 mg/kg bw to which a safety factor of 1000 has to be applied.

9. In studies with isotopically labelled ivermectin, the radioactive residue was essentially all extractable from tissues with solvents. Thus there is very little, if any, covalently bound residue. The parent H_2B_{1a} -component represents the major fraction of residue in all animal species and could be used as a suitable marker-residue.

10. The Committee for Veterinary Medicinal Products recommends establishing a single Community MRL of 15 µg/kg H_2B_{1a} for liver as the suitable target tissue. Such an MRL should serve as the basis for the calculation of withdrawal periods which could realistically be observed in practice. In cases where liver is not available (eg importation of meat from "third countries") fat should be used for analysing with an MRL of 20 µg/kg H_2B_{1a}.

11. Analytical methods for the determination of residues in plasma and/or tissues based on the detection of fluorescent derivatives following HPLC-separation have been published. A method with a lower limit of Reliable Measurement at a level of 10 µg/kg in tissues and a limit of detection close to 1 µg/kg has been developed by the sponsor.

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