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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

IVERMECTIN

SUMMARY REPORT (2)

1. At the 36th JECFA meeting in 1990, MRLs for ivermectin were adopted: 0.015 mg/kg liver and 0.02 mg/kg fat (H_2B_{1a}). The same MRLs were established under Council Regulation (EEC) No 2377/90 amended by Commission Regulation (EEC) No 675/92.

2. In the meantime, the company created an extensive data base on observations in ivermectin treated humans with emphasis on treatment related adverse effects. The majority of the adverse effects noted were due to the so-called Mazzotti reaction (immunological reactions caused by death of the parasites) characterized by fever, pruritus, adenitis, arthralgia, hypotension and tachycardia. Mild headache noted in healthy volunteers following repeated administrations was also recorded for placebo treated control persons. Among a wide variety of populations with different ethnic origin, including children and pregnant women, no subset of individuals atypically sensitive to ivermectin was noticed. In contrast to these observations in humans, there are publications on increased susceptibility of certain dog and cattle breeds towards ivermectin or avermectin B_{1a} toxicity.

3. On the basis of the new human data, ivermectin was reevaluated by the 40th JECFA in 1992. Results from embryotoxiclty studies in the CF-1 mouse strain were used as most sensitive parameter for the risk assessment. The study results suggest that ivermectin is a developmental toxicant but not a genuine teratogenic agent and a NOEL of 0.1 mg/kg bw/day based on maternotoxicity was established. In the light of the new human data, the previous safety factor of 500 was lowered to 100 resulting in a new ADI of 0-1 µg/kg bw/day for ivermectin residues (total drug-related residue) in edible tissues of treated animals.

   On the basis of an updated residue study in market weight cattle (300-400 kg bw) using ivermectin injectable formulation the 40th JECFA also recommended revised MRLs of 0.1 mg/kg for bovine liver and 0.04 mg/kg for bovine fat.

4. The Working group for the Safety of Residues recommends to adopt this revised ADI value of 0-1 µg/kg bw/day corresponding to 0-60 µg/person/day. For bovine liver and fat it is proposed to adopt MRLs of 0.1 mg/kg and 0.04 mg/kg, repectively, as recommended by JECFA, H_2B_{la} being the marker residue.

   The existing MRLs for ovine, porcine and equine tissues were not the subject of this reevaluation and should remain unchanged.

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