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

EMEA/MRL/465/98-FINAL
July 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

METHYL NICOTINATE

SUMMARY REPORT

1. Methyl nicotinate is the methyl ester of nicotinic acid. It is an active ingredient of a number of veterinary preparations intended for topical application as a rubefacient for the treatment of a variety of diseases, such as respiratory diseases, vascular disorders (oedema, haematoma), and rheumatoid disorders in cattle and horses (doses not stated; the concentration in the formulated veterinary medicinal product is 2%).

2. No data on the pharmacodynamic activity of methyl nicotinate were presented. The ester hydrolysis product nicotinic acid is a vitamin of the B complex required by the body for the formation of the coenzymes NAD and NADP. The daily requirement of nicotinic acid as a supplement in humans is in the range of 10 to 20 mg. Nicotinic acid alone also leads to vascular dilatation and hyperaemia. Based on the assumption that the close structural relationship between methyl nicotinate and nicotinic acid (niacin) and nicotinamide (niacinamide) can be taken as evidence of close similarities with respect to the pharmacology, data concerning the activity of the latter compounds were submitted. Both niacin and niacinamide are used in the prevention of niacin deficiency in humans.

3. Only data on nicotinic acid and nicotinamide have been submitted. The acute subcutaneous LD_{50} of nicotinamide and nicotinic acid in rats were 1.68 and 5.0 g/kg bw, respectively. Doses of 500 mg nicotinamide administered intraperitoneally to rats at 12-hour intervals for 21 days caused histologic changes (hyperplasia) of liver cells, which remained throughout the 5-week follow-up period.

4. No data on the mutagenic or carcinogenic potential of methyl nicotinate were presented. However life-time studies in mice employing doses of 2 to 3 mg nicotinamide/kg bw/day gave no indication of carcinogenic potential.

5. In humans, consumption of 3 to 9 g nicotinic acid per day (intended for reducing the risk of vascular disease) may lead to "niacin hepatitis", gout, and impaired glucose tolerance within a relative short period, reportedly in less than one week in some cases.

6. Only little information on the pharmacokinetics of methyl nicotinate was presented. Approximately 15% of the activity contained in a small radio-labelled dose (a few microgram) administered epicutaneously to human volunteers was recovered from the urine within 108 hours after treatment. No data on the pharmacokinetics of methyl nicotinate in the target species were available. A few data on the pharmacokinetics of nicotinic acid and nicotinamide were presented. Both substances are readily absorbed from the gastrointestinal tract; they follow the same metabolic pathways ending up as the 6-hydroxy analogues, nicotinamide-N-oxide and various N-methyl-carboxamide-pyridones. Excretion takes place mainly via the kidney. In rats the proportion excreted as unchanged nicotinic acid is dose-dependent: almost nil at 5 mg/kg bw; around 80% at 500 mg/kg. At the low dose the main metabolites were derivatives of N-methyl-nicotineamide and nicotinuric acid, each accounting for about 20% of the administered dose.

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Conclusions and recommendation

Having considered that:

- methyl nicotinate is intended for topical use only,
- methyl nicotinate is used infrequently in a small number of individual animals
- animals are unlikely to be sent for slaughter immediately after treatment,
- methyl nicotinate is expected to be readily hydrolised to the vitamin moiety nicotinic acid,
- potential residues of methyl nicotinate in edible tissues in connection with topical administration of the compound are unlikely to be of toxicological concern to the consumer;

the Committee concludes that there is no need to establish MRLs for methyl nicotinate and recommends its inclusion into Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Methyl nicotinate	Bovine, equidae	For topical use only