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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

TRICLABENDAZOLE

SUMMARY REPORT (1)

1. Triclabendazole is a benzimidazole anthelmintic used in food animals, where it is mainly employed in the control of the liver fluke, *Fasciola hepatica* in sheep and cattle. Typically, an oral dose of 10 mg/kg bw is administered.

2.i Studies in the rat, sheep, goat and rabbit demonstrated that the vast majority of an oral dose of triclabendazole was eliminated in the faeces after six to ten days. About half was unabsorbed drug and the rest was due to binary excretion. Urinary excretion was minimal in all species tested (about 6% in rats). Tissue residues were measured in rats after six days and sheep and goat after ten days, and were generally below 1%-2%. The highest concentrations were found in the heart and brain of rats, and in the liver and thyroid of sheep and goats.

In all species tested (sheep, cattle, goats and rats) the same metabolites of triclabendazole were found in the faeces but in different proportions. These were the sulphone, sulphoxide, ketone and the 4-hydroxy-derivatives of triclabendazole.

Preliminary studies in man indicate that triclabendazole is well absorbed from the gut. The sulphoxide and sulphone metabolites were identified in plasma, although lower sulphone levels were found than those occurring in sheep, and the sulphoxide had a shorter plasma half-life.

2.ii Triclabendazole had low acute toxicity when administered by the oral, intraperitoneal, dermal and inhalation routes. The sulphoxide and sulphone metabolites of triclabendazole also had low acute oral toxicity. Triclabendazole produced minimal skin irritation, no eye irritation and had limited potential for skin sensitisation.

2.iii Repeat dose toxicity studies (13 weeks) in rats revealed minor transient haematological effects, decreased food intake and growth retardation at high doses (≥100 mg/kg in diet). A 13-week feeding study in dogs revealed slight hepatotoxicity, growth retardation, delayed onset of sexual maturity, reversible electrocardiogram changes and haemolysis at high doses (≥100 mg/kg in diet).

2.iv There was no evidence of teratogenicity in rats or in chinchilla rabbits, although foetal development was retarded (low foetal bodyweight and delayed ossification) at doses which caused maternal toxicity (100 mg/kg bw and above in rats and 10 mg/kg bw in rabbits). Oral administration to sheep of doses up to 50 mg/kg bw had no adverse effects on reproductive parameters in both males and females. However, oral administration to pregnant ewes in combination with fenbendazole at high doses (150 mg/kg bw of a 1:1 mixture) caused kidney and skeletal abnormalities in the offspring.

In a two-generation study in rats, pup survival and bodyweight were decreased in the F2 generation but not in the F1 generation. Post-mortem examinations of weanlings revealed decreased lung/brain-weight, test/brain-weight and adrenal/bodyweight ratios in Fl males in the top dose group. Histology revealed minimal fatty changes in perilobular hepatocytes in a few top dose F1 animals of each sex and in two mid-dose F2 females. There was a dose-related decrease in liver-weight in F2 females. These effects were considered to be treatment-related, however, and a NOEL was determined at 0.15 mg/kg bw/day.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

2.v Triclabendazole was clearly negative in numerous *in vitro* and *in vivo* mutagenicity tests, including the Ames test (with 5 strains of *Salmonella typhimurium*); V79 Chinese hamster cells with and without metabolic activation; an autoradiographic DNA repair test in rat hepatocytes and human fibroblasts; a micronucleus test *in vivo* in Chinese hamster bone-marrow; and in an SCE test.

2.vi A carcinogenicity study was conducted in mice where the only pathological findings were increased serum levels of hepatic enzymes, increased liver-weight and benign hepatomas in females in the top dose group only (300 mg/kg in the diet).

A well conducted carcinogenicity study in rats demonstrated no statistically significant effects on tumor incidences at any dose, or on any other parameter, at doses up to 30 mg/kg in diet (equivalent to about 1.5 mg/kg bw/day).

2.vii Triclabendazole has been used in clinical trials for the treatment of parasitic infestations in humans. Single and double doses of 10 mg/kg bw were well tolerated. Transient epigastric pain was attributed to the death of the parasites.

3. Triclabendazole has no significant antimicrobial activity.

4. *Acceplable Daily Intake (ADI)*

The ADI was set on the basis of the increased postpartum mortality of the F2 generation in the two-generation rat reproduction study (NOEL = 0.15 mg/kg bw/day) using a safety factor of 100:

ADI = 0-0.0015 mg/kg bw.

5. The Working Group agreed the following MRLs for triclabendazole :

muscle, liver, kidney: 0.15 mg/kg;

fat : 0.05 mg/kg.

based on the sum of extractable residues that may be oxidised to ketotriclabendazole. The estimated total intake of residues is within the ADI calculated in paragraph 4.

6. The Working Group is aware of the differences in the interpretation made by JECFA of the toxicological data. The JECFA report concludes that the reported increase in mortality and lower bodyweights of pups in the F2 generation of the 15 ppm group (0.75 mg/kg bw/day) of the 2-generation rat study were not treatment-related and an ADI of 0-0.003 mg/kg bw was proposed based on a chronic mouse study. As stated in paragraph 2.iv, the Working Party considered that the possibility of these effects being treatment-related had not been disproved. However, given the fact that further data on the total residues in edible tissues in sheep might still lead JECFA or the Working Group to reconsider the MRLs assigned to these target tissues, the Working Group agreed to recommend the MRLs set out in paragraph 5 as provisional.

7. Analytical methods with the appropriate sensitivity are available based on HPLC.