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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PARCONAZOLE

SUMMARY REPORT

1. Parconazole (IUPAC name: ±-cis-1-[2-(2,4-dichlorophenyl)-4-[(2-propynyloxy)methyl]-1,3-dioxolan-2-yl]-1 H-imidazole monohydrochloride) is a broad spectrum antimycotic, belonging to the imidazole group that, in contrast to the nitro-imidazole molecules, lacks the nitro group. Other members of this group include enilconazole, ketoconazole and propiconazole. It is used in veterinary medicine as an oral fungicide against candidiasis in guinea fowl (*Numida meleagris*) as a medicated feed at a concentration of 30 mg/kg (prophylactively) or 60 mg/kg feed (therapeutically), around the age of 3 to 4 weeks for 7 to 10 days. Guinea fowls are usually slaughtered between 10 to 12 weeks.

2. Parconazole is an oral fungicide with a broad-spectrum activity against dermatophytes, yeasts, and other fungi. It has no antibacterial effect. Its mode of action involves inhibition of the fungal cytochrome P_{450} dependent 14α–dimethylation of lanosterol to ergosterol, a specific component of the membranes for fungi and yeasts.

3. The pharmacokinetics of parconazole was only studied in one dog and one guinea fowl (the target animal species) study. As there are no adequate data concerning the pharmacokinetic profile of the parconazole it is not possible to make definite conclusions about its absorption, excretion and metabolism.

   In a radiolabelled ^{14}C study in the guinea-fowl treated with a single oral dose of 20 mg parconazole/animal corresponding to 13 mg/kg bw, a blood peak level (C_{max}) of 2.28 µg/ml was reached at 2 hours (t_{max}).

4. After oral administration of radiolabelled parconazole (13 mg/kg bw) to 55 guinea fowls, an overall limited absorption was seen with an initial rapid absorption phase followed by a peak plasma concentration at 2 hours of 2.28 mg/l. The concentration decreased monoexponentially up to 10 hours after administration. The plasma half-life of the parent substance was estimated as 74 minutes, while the half-life of the total of metabolites was estimated to be 108 minutes.

5. The limited data suggests that biotransformation is very extensive and that the unchanged parconazole represents only 0.6% of the total residue.

6. The metabolites formed from parconazole were not identified nor quantified.

7. In a guinea fowl study (55 animals) using orally administered radiolabelled parconazole at a dose of 20 mg parconazole/animal corresponding to 13 mg/kg bw, the tissue levels were, in general, lower than 50 µg/kg. The concentrations expressed in total radioactivity mostly dropped below the detection limit within 48 hours. This indicates that there was no accumulation of parconazole or its metabolites in tissues.

8. Parconazole is of low acute toxicity. The oral LD_{50} varied between 200 and 550 mg/kg bw dependent on the animal species tested (species not specified).

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9. Repeated-dose toxicity studies were carried out in rats (13 weeks) and dogs (12 months).

   The rat study was poorly reported and dose rates were only given as mg drug/kg feed. An approximate NOEL of 40 mg/kg bw/day was estimated.

   In the dog study, signs of toxicity included reductions in bodyweight, cholestasis and hepatocellular pigmentation. A NOEL of 10 mg/kg bw/day was identified.

10. Adequate reproduction and teratology studies were carried out in rats (fertility and general reproductive performance, embryotoxicity, peri- and postnatal toxicity studies) and rabbits (embryotoxicity studies).

    In the rabbit studies the animals were dosed at 0, 10 and 40 mg/kg bw orally by gavage during 12 days after insemination. Bodyweights were not affected at any dose. Deaths due to pneumonia and enteritis were recorded at all doses. Pregnancy rates were decreased at 40 mg/kg bw/day, but no teratogenic or embryotoxic effects were observed.

    In rats, the substance was administered in the diet at 100, 400 and 1600 mg/kg feed. The average feed intake was 80 g/feed per kg bw, the average dosage is 8, 32 and 128 mg/kg bw. Bodyweight gain was lower than normal for 1600 mg/kg feed group and feed consumption was lower than normal for 400 and 1600 mg/kg feed groups. There was a significant decrease of pregnancy at 1600 mg/kg feed but the gestation period was not changed. The litter size decreased at 400 and 1600 mg/kg feed with a higher percentage of pups born dead. No teratogenic nor embryotoxic effects were observed. Birth weight was normal in all groups but bodyweight gain was lower in pups born to 1600 mg/kg feed dosed females. The survival rate at 3 weeks also was adversely affected at 1600 mg/kg feed. Multigeneration studies were not carried out.

    A NOEL of 8 mg/kg bw/day was identified.

11. The mutagenic effects of parconazole were investigated in three *in vivo* mammalian tests. The results of a micronucleus test in rats and dominant lethal tests in male and female mice indicated that parconazole is not mutagenic.

    Imidazoles, to which parconazole belongs, have a different mode of action than nitro-imidazoles. Due to reduction of the nitro group, nitro-imidazole molecules induce short-live intermediates or free radicals that produce DNA damage by interacting with DNA and possibly other molecules. This mechanism is thought to have a role in the mutagenic and carcinogenic effect, which are characteristic for the nitro-imidazoles. This mechanism however, does not occur for the imidazole molecules, for which the mode of action involves inhibition of the fungal cytochrome P_{450} dependant 14α-dimethylation of lanosterol to ergosterol, a specific component of the membranes for fungi and yeasts.

12. Carcinogenicity studies were not carried out because of the negative results in mutagenicity studies, as there were no structural relationships with known carcinogenic substances, and because structurally parconazole is very similar to enilconazole, which has been shown to be without carcinogenic effects.

13. Immunotoxicity studies have not been carried out with parconazole as other fungicides from the same imidazole group, such as ketoconazole, have not shown any hypersensitivity effects when used in humans.

14. Microbiological endpoint studies on the human gut flora have not been carried out as parconazole lacks any antibacterial effect.

15. Based on the NOEL of 8 mg/kg bw/day from the embryotoxicity study in rats and a safety factor of 100, a toxicological ADI of 0.08 mg/kg bw, i.e. 4.8 mg/person was established.

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16. A kinetic study in guinea fowl with a single oral administration (capsule) of 20 mg ^{14}C-parconazole/animal (about 13 mg/kg bw) showed that the elimination of the total radioactivity is slightly slower in comparison to the elimination of the parent compound ($t_{1/2}$ 108 minutes versus 74 minutes). The concentration of the total radioactivity was always lower than 1 µg equivalents/g (1 mg/kg) except in the liver and the kidney. Based on the standard consumption figures a maximum daily intake of total residues of 0.86 mg/person is calculated, which is below the ADI.

17. Depletion studies carried out in guinea fowl with doses of 30, 60, 120 and 240 mg/kg feed over a 91 day-period using unlabelled parconazole show that the highest residue concentrations were found in liver. No parconazole could be detected in tissues from 72 hours after cessation of treatment.

18. The depletion curve of total radioactivity follows a curve parallel to that of unchanged parconazole. However, parent parconazole represented a very low fraction of the total radioactivity measured.

19. A fully validated GC-ECD analytical method described in the ISO/78/2 format was provided.

Conclusions and recommendation

Having considered that:

- absorption of parconazole from the gastro-intestinal tract is limited;
- parconazole is extensively and rapidly metabolised;
- parconazole is of low toxicity, the maximum daily intake of residues is below the ADI, even 24 hours after treatment,
- guinea fowl are unlikely to be sent for slaughter immediately after treatment,

the Committee concludes that there is no need to establish an MRL for parconazole and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance (s)	Animal species	Other provisions
Parconazole	Guinea fowl	

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