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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PRAZIQUANTEL

SUMMARY REPORT (1)

1. **Praziquantel is an anthelmintic used in both human and veterinary medicine. It is indicated for use in non-lactating sheep as a single oral dose of 3.75 mg/kg bw. Praziquantel is a racemate derivative of pyrazinoisoquinoline and is effective against many species of cestodes and trematodes. Praziquantel affects the integumental membrane of the parasite, disrupting the regulatory processes and inducing spastic paralysis of the parasite's musculature.**

2. **After oral administration to the rat, dog and monkey between 75 and 100% of the praziquantel is absorbed. Maximum serum concentrations are reached within 30 minutes to 2 hours in rats, dogs, monkeys and sheep. All species excrete the parent compound and its metabolites rapidly; within 24 hours after administration of radiolabelled compound the radioactivity in the serum was of the same order of magnitude as the detection limit.**

3. **After both oral and intravenous administration of radiolabelled compound to rats, the highest concentrations of radioactivity were found in the liver and kidneys. None of the other organs and tissues showed specific accumulation. Praziquantel is subject to a marked first pass effect in the liver where it is rapidly and extensively metabolised. Rapid elimination of the ^{14}C-radioactivity from serum correlates with rapid elimination from the organs. Twenty four hours after administration of ^{14}C-praziquantel either by the intravenous route at 2 mg/kg or orally at 10 mg/kg bw, elimination of ^{14}C-praziquantel and its metabolites from the organs and tissues of rats is almost complete.**

   Radiolabel studies with ^{14}C-praziquantel in rats, dogs and monkeys following oral or intravenous dosing show that the kidney is the predominant elimination path for praziquantel. Eight hours after oral administration of 10 mg ^{14}C-praziquantel/kg bw, renal excretion amounted to 40%, 66% and 38% in the rat, dog, and monkey respectively. Elimination by the liver is somewhat lower. In rats, 37% of the dose following intravenous injection and 15% of the dose following oral administration were recovered in the bile within 7 hours. A third elimination pathway in rats is by secretion into the gastrointestinal tract, with more than 10% secreted within 1 hour of post intravenous dosing.

4. **Praziquantel is 80% bound to serum proteins in rats, 71% in dogs, 77 % in sheep and 74% in monkeys.**

5. **Radiolabel studies with ^{14}C-praziquantel in rats, dogs and monkeys dosed either intravenously or orally confirm extensive metabolism of the compound in these species. No unmetabolised compound was found in any of the excretion products. Metabolism is rapid; 15 minutes after dosing the proportion of metabolites in serum was:**

rat :	**oral 99 %,**	**intravenous 54%;**
dog:	**oral 84%,**	**intravenous 59%;**
monkey:	**oral 99 %,**	**intravenous 50%**

   All major metabolites investigated consisted of hydroxylated derivatives of the parent compound. Praziquantel is excreted as a variety of different metabolites, a fraction of them representing conjugates with glucuronic acid and/or sulphuric acid.

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6. **The acute oral and parenteral toxicity of praziquantel to mice and rats is low:**

   Rat LD_{50} : oral 2249 mg/kg bw;

   Mouse LD_{50} : oral 2454 mg/kg bw.

7. **Subacute oral toxicity studies of 4 weeks duration were conducted in rats and dogs, while a subchronic oral toxicity study was conducted in dogs. Studies were conducted in the mid 1970s and were not therefore GLP approved. The NOEL for the 4 week study in rats is 33 mg/kg bw and for the 4 week dog study is 60 mg/kg bw.**

8. **Only one 90 day subchronic toxicity study has been performed. In the study in dogs, transient signs of vomiting and depressed appetite as well as an increase in liver weight of high dose (180 mg/kg bw) animals was seen. No treatment related changes were seen in dogs dosed with 60 mg/kg bw and this is established as the NOEL for the study.**

9. **Praziquantel was well tolerated in the target species when given at the recommended therapeutic dose, 5 times this dose and the recommended dose for 5 consecutive days as evidenced by clinical haematological, clinico-chemical and post mortem examinations. Indeed, field trial data indicate good tolerance at doses of 50 times higher than the recommended therapeutic dose in sheep.**

10. **Segment I (reproductive toxicity) studies were conducted in rats treated with 0, 30, 100 or 300 mg praziquantel/kg bw for 3-10 weeks premating, throughout the mating period and up to the 7th day of pregnancy. No embryotoxic effects were seen and fertility and reproduction performance were unaffected by treatment.**

11. **Segment II (teratogenicity) studies were conducted in rats and rabbits dosed orally with praziquantel at doses between 0-300 mg/kg bw during the organogenesis phase of pregnancy. No foetotoxic or teratogenic effects were observed in any of the studies presented.**

12. **Segment III (perinatal and post natal toxicity) studies were conducted to examine perinatal and postnatal toxicity in rats treated orally with 0, 30, 100 or 300 mg praziquantel/kg bw/day. However, the study design involved treatment of pregnant rats on day 15 to 21 of gestation. The offspring of these rats were raised without treatment, paired and their progeny (F_2) raised for 28 days. No treatment-related effects on perinatal or postnatal toxicity were seen.**

13. **A comprehensive battery of mutagenicity studies (including *in vitro* tests for point mutation assays, chromosome aberration assays, tests for DNA damage as well as *in vivo* point mutation assays and chromosome aberration assays) have been conducted. The conclusion from the studies conducted is that praziquantel is not a mutagenic substance. The International Commission for Protection against Environmental Mutagenes and Carcinogens (ICPEMC) in 1990 concluded that praziquantel is virtually devoid of genotoxic potential.**

14. **Published oral toxicity studies in rats and hamsters given praziquantel orally at doses of 0, 100 and 250 mg/kg bw once weekly for 104 or 80 weeks revealed no treatment-related effects in tumour incidence, latency and multiplicity.**

15. **Pharmacokinetic data in man show that radiolabelled praziquantel is rapidly and almost completely metabolised. Following oral administration of ^{14}C-praziquantel at doses of 14-46 mg/kg bw the radioactivity was eliminated from serum with a half life of approximately 4 hours; the half life of the unmetabolised parent compound was approximately 1.5 hours. The major metabolites in serum and urine were isolated and identified as predominantly hydroxylation derivatives of praziquantel, containing one or two hydroxy groups. Doses up to 50 mg/kg bw in man are well tolerated with no clinically relevant changes in the medico-neurological or clinico-physiological examinations nor in haematological, clinical chemistry or urinological parameters. Therapeutic doses in man range from single oral dose of 5 mg/kg bw to 60 mg/kg bw, multiple oral doses of 3 x 25 mg/kg bw for up to 3 days, to 50-60 mg/kg bw for 15 days. Up to 25,000 humans have been treated with praziquantel with single dose schemes. The drug was well tolerated in the studies reported.**

16. **While a 90-day subchronic toxicity study in a second species was not provided, two oral subacute studies of four weeks duration were conducted in rats. When taken together with the other toxicity studies and in view of the history of use of the compound in humans (over 5 million humans treated between 1984 and 1989 with no untoward side effects of importance) an ADI can be determined. Taking the NOEL of 33 mg/kg bw from the 4-week rat study and using a safety factor of 200 (100 x 2 ; the factor of 2 being retained as the NOEL is based on the results of a subchronic toxicity study of only one month's duration), an ADI of 0.17 mg/kg bw (10 mg/person) can be established.**

17. **The metabolism of praziquantel was investigated in two sheep given a single oral dose of radiolabelled ^{14}C-praziquantel at 10 mg/kg bw and sacrified 8 hours post treatment. Thirty-five to 50% of the dose was excreted in urine in the 8 hour period: faeces accounted for only approximately 1% of the dose. At sacrifice, the highest radioactivity concentrations were measured in kidney (5.46-8.15 µg/g), liver (5.35-7.58 µg/g), with low concentrations in muscle (0.45-0.52 µg/g) and fat (0.16-0.21 µg/g). Unchanged parent compound was a minor component (less than 10%) of the extractable radioactivity in the edible tissues present only in liver and fat. Besides the parent compound seven metabolites were identified. The percentage ratio of these metabolites one to the other varied between 3% and 13% in the different tissues.**

18. **A residue study using ^{14}C-praziquantel was conducted in sheep given an oral dose of 3.75 mg/kg bw. The study confirmed the rapid absorption of praziquantel, peak plasma concentration being reached within 2 hours of dosing. A half life of 4.2 hours was determined and excretion from plasma was rapid. Eighty-eight percent of the total dose administered was excreted within 24 hours; 98 % within 72 hours. At 8 hours post treatment, the maximum levels present in tissues of 4 sheep were as follows : liver, 2.87 µg equivalent/g; kidneys, 2.55 µg equivalent/g; muscle 0.19 µg equivalent/g; and fat, 0.13 µg equivalent/g. Ingestion of total residues from edible tissues at this time amounts to 0.48 mg. This is some 20 times lower than the ADI. After 24 hours post treatment, levels in muscle and fat were 0.02 µg equivalent/g. At this time mean levels of 0.56 µg equivalent/g and 0.3 µg equivalent/g were present in the liver and kidney.**

19. **Metabolism studies in the rat, dog, monkey and humans indicate a rapid biotransformation in the liver in all species. As in sheep all the important metabolites are hydroxylation products and it is concluded that the metabolism of praziquantel is comparable in all species, including sheep and humans.**

20. **No information on the depletion of residues in milk of treated sheep has been provided.**

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- **animals are unlikely to be sent for slaughter immediately after treatment,**
- **praziquantel is rapidly and extensively detoxified and excreted in sheep,**
- **at 8 hours post treatment total residues in edible tissues of treated sheep represent 4.8% of the ADI,**

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

Pharmacologically active substance(s)	Target species	Other provisions
Praziquantel	**Ovine**	**For use in non-lactating sheep only**