European Medicines Agency
*Veterinary Medicines and Inspections*

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# COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

## DICLAZURIL
## (Extension to all ruminants and porcine species)

## SUMMARY REPORT (2)

1. Diclazuril (2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetonitrile) a benzeneacetonitrile derivative is an anticoccidial intended for oral use in lambs. The therapeutic dosage is either a single administration of 1 mg diclazuril/kg bw (most commonly at about 6-8 weeks of age) or two administrations (the first at 3 to 4 weeks of age and the second about 3 weeks later).

   Diclazuril has been registered as an anticoccidial feed additive for broilers with a withdrawal period of 5 days in the Council Directive 93/107/EC of 26 November 93 amending Council Directive 70/524/EEC.

   Diclazuril was previously assessed by the CVMP and an acceptable daily intake (ADI) of 0.030 mg/kg bw (i.e. 1.8 mg/person) was established. . The same ADI value of 0-0.03 mg/kg bw was established by Joint WHO/FAO Expert Committee on Food Additives (JECFA) at its 50th meeting in 1998. Both Committees based the ADI on a NOEL of 3 mg/kg bw/day retained from the 2-year chronic toxicity/carcinogenicity study in mice applying a safety factor of 100.

   Currently, diclazuril is included in Annex II of Council Regulation (EEC) No 2377/90 for diclazuril for ovine species in accordance with the following table:

| Pharmacalogically active substance(s) | Animal species | Other provisions |
|---|---|---|
| Diclazuril | Ovine | For oral use in lambs only |

   An application has now been submitted for the extension of the current Annex II entry for diclazuril to cattle and pigs. The proposed indication is the control of coccidiosis in calves and piglets with a recommended dose regimen of 5 mg/kg bw as a single oral administration.

2. In piglets after a single oral administration of 5 mg/kg bw of diclazuril, the maximum plasma concentration 0.035 mg/l was observed 24 hours post administration (first sampling time).

   In calves after a single oral administration of 5 mg/kg bw of diclazuril, the mean maximum plasma concentration 0.039 mg/l was observed 12 hours post administration. The very high value of the volume of distribution corrected by the bioavailability factor of 100 l/kg indicates that the bioavailability is low. Diclazuril is poorly absorbed in calves after oral administration.

3. The metabolism of diclazuril in pigs was investigated with suspension cultures and primary cell cultures of swine hepatocytes. The analyses of incubate samples revealed that the metabolism of diclazuril was limited. The parent compound represented more than 98 and 59% in suspension culture or in primary culture, respectively.

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An *in vitro* comparison of the metabolism of diclazuril was carried out in primary cell cultures and in suspension culture of hepatocytes of rats, rabbits, chickens, turkeys, sheep, goats and cattle. The pharmacokinetic profile and metabolism of diclazuril was similar in all these species. The parent compound represented more than 90% of the radioactivity in suspension cell culture of all species.

4. In pigs, a non-radiometric depletion study was carried out. Twenty-four hours after a single oral administration of diclazuril at 5 mg/kg bw to 4-5 days-old piglets, 33.8 µg of diclazuril/kg were measured in muscle, 162 µg/kg in fat + skin in natural proportions, 45.2 µg/kg in liver and 43.1 µg/kg in kidney. Residue levels of diclazuril were below the limit of quantification of 25 µg/kg at day 3 for muscle, liver and kidney and day 5 for fat + skin.

5. In cattle, a non-radiometric depletion studies was carried out. Twenty-four hours after a single oral administration of diclazuril at 5 mg/kg bw to 3-5 days old calves, 25.8 µg of diclazuril/kg were measured in muscle, 361 µg/kg in fat, 108 µg/kg in liver and 75.2 µg/kg in kidney. Residues of diclazuril were below the limit of quantification 25 µg/kg at day 3 for muscle and kidney, day 5 for liver and day 7 for fat.

6. Gas chromatographic methods with a micro-electron capture detection (GC-µECD) have been developed to measure residues of diclazuril in pigs and cattle edible tissues. The limits of quantification were 10, 25 and 25 µg/kg, respectively.

**Conclusions and recommendation**

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

- diclazuril is of low toxicity,
- the low bioavailability of diclazuril following oral administration,
- at 24 hours post-treatment, the consumer intake represents only 1.38 and 2.24% of the toxicological ADI of 0.030 mg/kg bw for piglets and calves, respectively;
- for bovine and ovine species, which are major ruminant species, 24 hours after treatment the consumer intake of residues represents less than 3% of the ADI; therefore it was considered appropriate that the entry could be extended to all ruminant species

the Committee recommends the modification of the current entry of for diclazuril for ovine species in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

| Pharmacalogically active substance(s) | Animal species | Other provisions |
|---|---|---|
| Diclazuril | All ruminants, porcine | For oral use only |