European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

TOLTRAZURIL
(Extension to cattle)

SUMMARY REPORT (4)

1. Toltrazuril is a triazinetrione derivative used as anticoccidial agent. It is widely used in chicken, turkeys and pigs for the prevention and treatment of coccidiosis, by administration *via* drinking water.

   Toltrazuril was previously assessed by the CVMP and a toxicological ADI of 2 µg/kg bw, *i.e.* 120 µg/person was established based on the threshold dose of 1 mg/kg bw/day for pre-neoplastic lesions retained from a carcinogenicity study in rats and applying a safety factor of 500.

   Currently, toltrazuril is included in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Toltrazuril	Toltrazuril sulfone	Chicken	100 µg/kg 200 µg/kg 600 µg/kg 400 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption
		Turkey	100 µg/kg 200 µg/kg 600 µg/kg 400 µg/kg	Muscle Skin + fat Liver Kidney	
		Porcine	100 µg/kg 150 µg/kg 500 µg/kg 250 µg/kg	Muscle Skin + fat Liver Kidney	

   An application has now been submitted for an extension of the MRLs to calves. Toltrazuril is intended to be administered as an oral suspension containing 5 % toltrazuril at a single oral dose of 15 mg/kg bw in the calves which are approximately 5 weeks of age onward.

2. An absorption, distribution, metabolism and excretion study of the ^{14}C-toltrazuril was performed following oral administration of toltrazuril in calves at a dose of 15 mg/kg bw. The absorption and distribution of toltrazuril in calves is extensive following oral administration. Toltrazuril is slowly absorbed by calves following oral administration. The maximal plasma concentration (33.41 mg equivalent/l) was observed 120 hours following the oral administration. The area under the curve extrapolated to infinity was 15 290 mg equivalent·h/l. The half-life time of elimination was 154 hours. Toltrazuril is slowly eliminated in both urine and faeces. Up to 168 hours, the observed recoveries of radioactivity are 3.3, 5.3, 1.1 and 9.6 % of the administered dose in urine, faeces and cage wash, respectively.

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The highest concentration of radioactivity was observed in liver at all sampling time. Initially toltrazuril was the major component in plasma, excreta and tissues after dosing but at later times toltrazuril sulfone accounted for most of the radioactivity present. The toltrazuril sulfone levels were 8515 and 617 µg/kg in liver, 4251 and 319 µg/kg in kidney, 1296 and 71 µg/kg in muscle and 3920 and 261 µg/kg in fat at 28 and 56 days, respectively. Toltrazuril sulfone was considered the most suitable marker residue because it is the major metabolite and was detected in all tissues.

The ratios of marker/total residue observed 56 days following the treatment were 0.92, 0.94, 0.85 and 0.89 for liver, kidney, muscle and fat, respectively.

3. A depletion study of toltrazuril sulfone (*i.e.* marker residue) in calves was performed following a single oral administration of toltrazuril at 15 mg/kg bw.

   The highest levels of marker residues were observed in liver with a residue level of 4500 µg/kg being detected 28 days following the treatment. The mean toltrazuril sulfone levels in tissues were 4290, 2247, 643, 1652 µg/kg at 28 days following the treatment in liver, kidney, muscle and fat, respectively. Following the treatment for liver the concentrations were 848, 393, 99 and 260 µg/kg at 42 days, kidney, muscle and fat, respectively. After 70 days following the treatment, all samples were below the limits of quantification of the analytical method (40 µg/kg in liver and 30 µg/kg in other edible tissues).

4. An analytical method described in an internationally recognised format is provided. This HPLC analytical method based on fluorescence detection to monitor residues of toltrazuril in edible tissues of cattle was not fully validated according to the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union essentially in regards to the repeatability and the reproducibility.

Conclusion and recommendation

Having considered that:

- the toxicological ADI of 2 µg/kg bw (i.e. 120 µg/person) was previously established,
- the toltrazuril sulfone was retained as the marker residue,
- the ratio of marker residue to total residues is 92, 94, 85 and 89 % for liver, kidney, muscle and fat, respectively, 56 days following the single oral treatment,
- an analytical method for the routine determination of toltrazuril sulfone in edible tissues of bovine species is available, that can provisionally be used for monitoring purposes until the outstanding issues relating to validation have been completed;

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of toltrazuril in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target Tissues	Other provisions
Toltrazuril	Toltrazuril sulfone	Bovine	100 µg/kg 150 µg/kg 500 µg/kg 250 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption. Provisional MRLs expire on 1.7.2006

Based on these MRLs values, the daily intake will represent about 93 % of the ADI.

Before the Committee for Medicinal Products for Veterinary Use can consider the inclusion of toltrazuril in Annex I of Council Regulation (EEC) No 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The applicant should complete the validation of the analytical method for monitoring purposes, i.e. for measuring the marker residue (toltrazuril sulfone) in bovine edible tissues, according to the requirements of Volume 8: the reproducibility for the three requirement levels (½, 1 and 2x MRL) was not fully tested. It was tested only on 2 occasions for the values of ½ and 1x MRL. The intra- and inter-day accuracy and precision should be performed with a sufficient number of test portions in each run and the stability after the freeze/thaw cycle and the linearity in the matrix should be clarified. Moreover some parameters did not appear to be fully validated: stability after the freeze/thaw cycle and linearity in matrix, these points require further clarification.