European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

TOLTRAZURIL
(Extension to cattle and extrapolation to all mammalian food-producing species and poultry)

SUMMARY REPORT (5)

1. Toltrazuril is a triazinetrione derivative used as anticoccidial agent. It is widely used in chicken, turkeys, pigs and cattle 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, turkey	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
		Porcine	100 µg/kg 150 µg/kg 500 µg/kg 250 µg/kg	Muscle Skin + fat Liver Kidney	

   Toltrazuril was also included in Annex III of Council Regulation (EEC) No 2377/90 for bovine species in accordance with the following table further to the consideration of an application for the extension to cattle:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	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

   Additional data concerning the validation of the analytical method for monitoring of residues, have now been provided in response to the list of questions further to the recommendation of provisional MRLs for toltrazuril in bovine species.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eu.int http://www.emea.eu.int

2. An absorption, distribution, metabolism and excretion study of ^{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 was extensive although absorption was slow 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.

   The highest concentration of radioactivity was observed in liver at all sampling times. 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 to total residues 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 following the treatment were 4290, 2247, 643, 1652 µg/kg at 28 days in liver, kidney, muscle and fat, respectively. At day 42 day following the treatment residue concentrations were the 848, 393, 99 and 260 µg/kg, in liver kidney, muscle and fat, respectively. After 70 days following 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 HPLC analytical method based on fluorescence detection to monitor residues of toltrazuril in edible tissues of cattle, described in an internationally recognised format, was provided. The analytical method was validated according to the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union. Limits of detection were 5 µg/kg in liver, 2 µg/kg in kidney, 3 µg/kg in muscle and 4 µg/kg in fat and the limits of quantification were 40 µg/kg in liver and 30 µg/kg in kidney, muscle and fat.

5. Taking into account the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) and considering that the existing MRLs in porcine and the recommended ones for bovine species are identical it was considered appropriate to recommend the extension of the MRLs in such a way that the same MRLs values would apply to all mammalian food producing species. Also, considering that the existing MRLs in chicken and turkey are identical it was considered appropiate to recommend the extension of the MRLs in such a way that the same MRLs values would apply to all poultry.

Conclusion and recommendation

Having considered that:

- a toxicological ADI of 2 µg/kg bw (*i.e.* 120 µg/person) was previously established,
- toltrazuril sulfone was retained as the marker residue,
- in cattle, 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,
- MRLs established in porcine and the recommended ones for bovine species are identical,
- MRLs established in chicken and turkey are identical,
- validated analytical methods are available for the residue determination of toltrazuril sulfone in edible tissues of bovine, porcine, chicken and turkey species which should be applicable to all mammalian and poultry food producing species;

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of toltrazuril 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 Tissues	Other provisions
Toltrazuril	Toltrazuril sulfone	All mammalian food producing species	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
		Poultry	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

* For porcine species this MRL relates to “skin and fat in natural proportions”

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