The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/MRL/892/03-FINAL
December 2003

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXOLINIC ACID
(Extension to bovine)

SUMMARY REPORT (4)

1. Oxolinic acid is a synthetic quinolone antibiotic. Oxolinic acid is used in veterinary medicine for treatment of fin fish, pigs and poultry. It is administered by the oral route, in the feed, the drinking water or as a bolus. The recommended doses are for fin fish: 12 mg/kg bw/day for up to 7 days; for pigs and poultry: 20 mg/kg bw/day for up to 5 days.

   Oxolinic acid was previously assessed by the CVMP and a microbiological acceptable daily intake (ADI) of 2.5 µg/kg, i.e. 150 µg/person was established.

   Currently oxolinic acid 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 tissues	Other provisions
Oxolinic acid	Oxolinic acid	Porcine	100 µg/kg 50 µg/kg 150 µg/kg 150 µg/kg	Muscle Skin + fat Liver Kidney	
		Chicken	100 µg/kg 50 µg/kg 150 µg/kg 150 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption
		Fin fish	100 µg/kg	Muscle and skin in natural proportions	

   An application has now been submitted for the extension of the MRLs for oxolinic acid to cattle. The proposed indication is treatment of gastro-enteritis due to *E.coli* with a recommended dose regimen of 10 to 20 mg/kg bw/day, administered orally for up to 5 days.

2. Calves were given an oral bolus of 22 mg/kg bw oxolinic acid followed by a second oral bolus of 11 mg/kg bw, 24 hours later. The calves were killed (3 per time point), 3 hours or 9 hours after the second dose. Residues of oxolinic acid in tissues were determined using HLPC. At 3 and 9 hours, mean residues in liver were 12 500 µg/kg and 13 300 µg/kg, in kidney were 14 600 µg/kg and 17 500 µg/kg and in muscle were 8 000 µg/kg and 8 600 µg/kg respectively. No fat samples were analysed.

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A new cold residue depletion study was provided in which 4 male calves were administered oxolinic acid in water (using a drench gun) at a dose of 20 mg/kg bw/day for 5 consecutive days. All 4 calves were killed 6 hours after administration of the last dose. The oxolinic acid concentration in tissues was determined by HPLC with diode array detection with a limit of quantification of 50 µg/kg in all tissues. The concentration of total residue with antimicrobiological activity was determined in tissues by a microbiological assay based on a *Bacillus subtilis* sensor with a limit of quantification of 25 µg/kg in muscle and kidney and 50 µg/kg in fat and liver. The average residue concentration of oxolinic acid was 9100, 7800, 12900 and 10700 µg/kg in muscle, fat, kidney and liver respectively. The oxolinic acid concentration, as a percentage of the total residue with antimicrobiological activity, was 81, 85, 80, 84% in muscle, fat, kidney and liver, respectively.

3. The proposed routine analytical method was presented in the ISO 78/2 format and was based on HPLC with ultra violet-diode array detection. The limits of quantification were 25 µg/kg in fat and 50 µg/kg in all other edible tissues of cattle. Data demonstrating the specificity of the proposed routine analytical method against other quinolones derivatives commonly used in veterinary medicines such as enrofloxacin, marbofloxacin, difloxacin, flumequine and ciprofloxacin were presented. With respect to danofloxacin, specificity was demonstrated for (similar) analytical methods for chicken and pig tissues but not for the proposed routine analytical method for cattle tissues.

Conclusions and recommendation

Having considered that:

- a microbiological ADI of 2.5 µg/kg bw (i.e. 150 µg/person) was previously established for oxolinic acid,
- oxolinic acid was identified as the marker residue,
- after oral treatment the percentage of marker to total residues with antimicrobiological activity in cattle muscle, fat, liver and kidney was 81, 85, 84 and 80%,
- a validated analytical method was available for cattle tissues, however specificity relative to danofloxacin could not be demonstrated;

the Committee for Veterinary Medicinal Products recommends the inclusion of oxolinic acid for bovine species 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
Oxolinic acid	Oxolinic acid	Bovine	100 µg/kg 50 µg/kg 150 µg/kg 150 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption. Provisional MRLs expire on 1.1.2006

Based on the newly provided data on ratio marker/total residues, the daily intake of residues with antimicrobial activity will represent about 45% of the ADI.

Before the Committee for Veterinary Medicinal Products can consider the inclusion of oxolinic acid for cattle in Annex I of Council Regulation (EEC) 2377/990, the point included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The applicant should further improve specificity of the routine analytical method with respect to separation of oxolinic acid and danofloxacin.