



## COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

### OXOLINIC ACID (Extension to all food producing species)

#### SUMMARY REPORT (5)

- Oxolinic acid is a synthetic quinolone antibiotic, used in veterinary medicine for the treatment of cattle, pigs, poultry and fin fish. It is administered by the oral route, in the feed, the drinking water or as a bolus. The recommended doses are 20 mg/kg bw/day for up to 5 days in pigs and poultry and 12 mg/kg bw/day for up to 7 days in fin fish. In cattle the substance is used for the treatment of gastro-enteritis due to *Escherichia coli* with a recommended dose regimen of 10 to 20 mg/kg bw/day, administered orally 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	

and in Annex III as follows:

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

Additional data have now been submitted concerning further validation of the analytical method for the monitoring of residues in cattle tissues, with regard to specificity.

2. Calves were given an oral bolus of 22 mg oxolinic acid /kg bw followed by a second oral bolus of 11 mg oxolinic acid/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 HPLC. At 3 and 9 hours, mean residues were 12 500 µg/kg and 13 300 µg/kg in liver, 14 600 µg/kg and 17 500 µg/kg in kidney and 8 000 µg/kg and 8 600 µg/kg in muscle, respectively. No fat samples were analysed.

A 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, 84 and 80% in muscle, fat, liver and kidney, respectively.

3. The 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, ciprofloxacin and danofloxacin were presented.

The validated analytical methods available for residue determination of edible tissues of porcine, chicken, bovine and fin fish species should be applicable to all food producing species.

4. 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, chicken and fin fish 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 food producing species.

## 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%, respectively,
- a validated analytical method was available for cattle tissues,
- final MRLs in bovine species can be recommended with the same values as the previously established provisional MRLs;

and that

- final MRLs have previously been established in porcine, chicken and fin fish,
- MRLs established in porcine, chicken and fin fish and the recommended ones for bovine species are identical,
- validated analytical methods are available for residue determination of edible tissues of bovine, porcine and chicken species and fin fish, which should be applicable to other food producing species;

the Committee for Medicinal Products for Veterinary Use recommends the extension of the existing MRLs for oxolinic acid in Annex I of Council Regulation (EEC) No 2377/90 to all food producing species in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Oxolinic acid	Oxolinic acid	All food producing species	100 µg/kg 50 µg/kg 150 µg/kg 150 µg/kg	Muscle* Fat** Liver Kidney	Not for use in animals producing milk or eggs for human consumption

\* For fin fish this MRL relates to “muscle and skin in natural proportions”; MRLs for fat, liver and kidney do not apply to fin fish

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

The daily intake of residues with antimicrobial activity will represent about 45 % of the ADI.