The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ENROFLOXACIN (extension to sheep)

SUMMARY REPORT (4)

1. Enrofloxacin (CAS No 93106-60-6) is a synthetic fluoroquinolone antimicrobial agent. In veterinary medicine it is administered by subcutaneous injection to cattle, by intramuscular injection to pigs and orally to cattle, pigs, turkeys and chickens, for the treatment of infections of the respiratory and alimentary tract. The recommended doses are 2.5 to 5 mg enrofloxacin/kg bw/day for 3 to 5 days (cattle and pigs) or 10 mg enrofloxacin/kg bw/day for 3 to 10 days (chicken and turkeys). In some Member States, enrofloxacin is authorised for use in sheep, goats and rabbits. The dosage regime for sheep is 2.5 mg/kg bw/day for 5 days, administered parenterally. For treatment of watery mouth disease in neonatal lambs, a single oral dose of 5 to 7 mg/kg bw is administered. Rabbits may be dosed at 2.5 to 5 mg/kg bw/day for 3 to 5 days, by oral administration (drinking water or gavage) or by intramuscular injection.

   Ciprofloxacin, a major metabolite of enrofloxacin, is widely used in human medicine.

   A microbiological ADI of 6.2 µg/kg bw (i.e. 372 µg/person) has previously been established by the Committee for Veterinary Medicinal Products. This is lower than the toxicological ADI of 30 µg/kg bw, calculated by applying a safety factor of 100 to the NOEL of 3 mg/kg bw/day of a dietary 90-day repeated dose study in 3-month old Beagle dogs, based on arthropathy.

   Currently, enrofloxacin is included in Annexes I and III of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Bovine	100 µg/kg 100 µg/kg 300 µg/kg 200 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	
		Rabbits	100 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg	Muscle Fat Liver Kidney	
		Porcine	100 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	
		Poultry	100 µg/kg 100 µg/kg 200 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

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Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Ovine	100 µg/kg 100 µg/kg 300 µg/kg 200 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1 July 1999

Further information relating to the use in sheep has now been provided.

2. No adverse effects were observed in neonatal lambs treated orally with 5 to 7 mg enrofloxacin/kg bw and the lambs grew normally over the first 3 months of life.

3. No radiometric studies were provided for sheep. In cattle, the sum of the residues of enrofloxacin plus ciprofloxacin accounted for around 65% of the residues in liver, 80% of the residues in kidney, 88% of the residues in muscle and 50% of the residues in fat. Radiometric studies in pigs and chicken had confirmed that the sum of enrofloxacin and ciprofloxacin was the appropriate marker residue for these animal species. It was considered reasonable to assume that the same marker residue would be appropriate for sheep, therefore radiometric studies were not needed for sheep. In neo-natal sheep given a single oral dose of 7.5 mg enrofloxacin/kg bw, residues of enrofloxacin and ciprofloxacin (determined by HPLC) in liver, kidney, muscle and fat were each less than or equal to 10 µg/kg in all tissues, 16 days after dosing. Two days after dosing, mean residues of enrofloxacin in liver, kidney, muscle and fat were 520, 1370, 993 and 1370 µg/kg and declined to 48, 13, 13 and 13 µg/kg respectively, 4 days after dosing. Over the same time period, mean residues of ciprofloxacin in these tissues declined from 483, 175, 265 and 175 µg/kg in liver, kidney, muscle and fat, to 53, 13, 13 and 13 µg/kg.

4. A proposed routine analytical method was presented in the ISO 78/2 format for determining the combined residues of enrofloxacin and ciprofloxacin (the marker residue) in tissues of sheep. In the method, enrofloxacin and ciprofloxacin (the marker residue) are simultaneously extracted into a mixture of ethanol and glacial acetic acid. The extracts of fat are evaporated to dryness and re-suspended in HPLC mobile phase. Extracts of the other tissues are evaporated to a reduced volume then solid phase extracted on a column of Amberlite XAD-4 resin. Residues are eluted from the column in methanol, then evaporated to dryness and dissolved in HPLC mobile phase. Residue extracts were quantified against external standards by HPLC with fluorescence detection. The limits of quantification were 25 µg/kg for enrofloxacin and for ciprofloxacin for ovine muscle and fat, and 50 µg/kg for ovine liver and kidney.

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Conclusions and recommendation

Having considered that:

- a microbiological ADI of 6.2 µg/kg bw (i.e. 372 µg/person) was established for enrofloxacin,
- in cattle, the sum of the residues of enrofloxacin plus ciprofloxacin (the marker residue) accounted for around 65% of the residues in liver, 80% of the residues in kidney, 88% of the residues in muscle and 50% of the residues in fat, within a few hours of dosing,
- the sum of enrofloxacin plus ciprofloxacin was also a suitable marker residue for tissues of sheep; in sheep, residues were most persistent in liver and the distribution of residues resembled that in the bovine,
- a validated routine analytical method is available;

the Committee recommends the inclusion of enrofloxacin for sheep 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
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Ovine	100 µg/kg 100 µg/kg 300 µg/kg 200 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption

Based on these MRLs, the daily intake of total residues from the consumption of ovine meat and cows' milk will represent about 74% of the ADI.

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