European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/80785/2006-FINAL
March 2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

CEFTIOFUR
(Extension to ovine and extrapolation to all mammalian species)

SUMMARY REPORT (4)

1. Ceftiofur (CAS Number 80370-57-6) is a third generation cephalosporin antibiotic. Ceftiofur has a wide spectrum of activity against both Gram-positive and Gram-negative bacteria. It exerts its antibacterial action by inhibition of bacterial cell wall synthesis. Ceftiofur is administered to cattle and pigs for control of bacterial infections of the respiratory tract. It is used in veterinary medicine as the sodium salt (CAS Number 104010-37-9), and the hydrochloride (CAS Number 103980-44-5) intramuscularly in cattle, including lactating cows, at doses of up to 2 mg/kg bw/day for up to 5 days and in pigs at doses of up to 5 mg/kg bw/day for up to 3 days. It is also used as crystalline free acid for intramuscular and subcutaneous administration in cattle and pigs.

   A microbiological ADI of 20 µg/kg bw/day (i.e. 1200 µg/person) for ceftiofur was previously established by the Committee for Veterinary Medicinal Products (CVMP) based on the MIC_{50} of 2.0 µg/ml for the most sensitive strains of human gut flora (*Escherichia coli, Lactobacillus* spp and *Clostridium* spp).

   Currently, ceftiofur is included in Annex I of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ceftiofur	Sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur	Bovine, porcine	1000 µg/kg 2000 µg/kg 2000 µg/kg 6000 µg/kg	Muscle Fat Liver Kidney	
		Bovine	100 µg/kg	Milk	

   An application has now been submitted for the extension of the MRLs for ceftiofur to sheep. The proposed indication for sheep is the treatment of ovine respiratory disease (pneumonia) associated with *Pasteurella trehalosi* (former *P. haemolytica* serovar T), *Mannheimia haemolytica* (former *P. haemolytica* biogrup I) and *Pasteurella multocida*. The recommended doses for sheep are 1 to 2 mg ceftiofur/kg bw intramuscularly, to be repeated every 24 hours for a total of 3 treatments. Animals which have not recovered after the initial 3 treatments may be given 2 more injections on days 4 and 5.

2. Ceftiofur was rapidly absorbed after intramuscular administration. Peak plasma concentrations of over 7 µg equivalents/ml were attained within 120 minutes after intramuscular administration of 2.2 mg/kg bw/day to sheep. In *in vivo* studies in rats and cattle and in *in vitro* studies with liver extracts from rats, pigs, cattle and chickens ceftiofur was rapidly metabolised to (initially) desfuroylceftiofur and furoic acid. Maximum blood concentrations of ceftiofur and its metabolites were achieved within 0.5 and 2 hours after dosing. No unmetabolised ceftiofur was detected in blood from 2 to 4 hours after dosing. Blood concentrations declined biphasically.

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3. When sheep were administered 2.25 mg ^{14}C-ceftiofur/kg bw/day intramuscularly for 5 days at 24-hour intervals, more than 98% of the intramuscularly administered dose was excreted within 108 hours of administration; about 92% of this was in the urine and the remainder in the faeces. Desfuroylceftiofur-dimer was the most abundant ceftiofur related residue (up to 68%) with desfuroylceftiofur cysteine accounting for just over 13%.

4. Three male and three female sheep were administered 2.25 mg ^{14}C-ceftiofur/kg bw/day intramuscularly for 5 days at 24-hour intervals. The sheep were then slaughtered 10 to 12 hours following the last dose and muscle (non-injection site and injection site), kidneys, liver, fat, heart, lungs and other minor tissues were removed and analysed for total residues. The mean total residue levels found were 9016, 619, 128, 123 and 1069 µg/kg in kidney, liver, muscle (non injection site), fat and injection site respectively.

5. Nine lactating sheep were treated with 2 mg free acid equivalents of ceftiofur sodium/kg bw/day intramuscularly for 5 days at 24 hour intervals and both the HPLC and an microbial inhibition assay for the screening of antibacterial substances (Delvotest) methods did not measure residues in milk above the limit of quantification (50 mg/kg) from the first time point, which was 12 hours after the last administration.

6. Twelve male and twelve female sheep were randomly divided into 4 treatment groups (3 of each sex) and dosed with ceftiofur sodium at 1.1 (groups 1 and 3) or 2.2 (groups 2 and 4) mg ceftiofur free acid equivalents/kg. Groups 1 and 2 received the intravenous dose first followed by the intramuscular dose 2 weeks later and groups 2 and 4 received the reverse. Sheep from each of the treatment groups were then selected, and 2 weeks after the last injection in the crossover study, were dosed with ceftiofur sodium intramuscularly for 5 consecutive days at either 1.1 or 2.2 mg ceftiofur free acid equivalents/kg. After all injections, tissue samples were obtained for determination of residue levels of ceftiofur and metabolites (measured as the derivative desfuroylceftiofur acetamide). Residue levels were the highest at the injection site followed by the kidneys. In the group that received 1.1 mg/kg bw dose, mean residue levels were 2700, 200, 170, 170 and 270 µg/kg in kidney, liver, muscle, fat and injection site muscle respectively 12 hours after the last administration. Residue levels in the group that received 2.2 mg/kg were 4170, 230, 130, 200 and 1000 µg/kg in kidney, liver, muscle, fat and injection site muscle respectively after the same length of time.

   It was concluded that the metabolic profile and distribution of residues to ovine tissues was very similar to that in cattle and pigs.

7. A validated routine analytical method, which is based on HPLC with UV detection, was presented in ISO format, this method is the same as the one available for bovine tissues and milk. Free and bound metabolites of ceftiofur, retaining a β-lactam ring, are derivatised to a common desfuroylceftiofur acetamide derivative and measured as desfuroylceftiofur equivalents. The limits of quantification of the method were less than or equal to 100 µg/kg for all ovine tissues and 50 µg/kg for ovine milk. There was no evidence of interference in this assay from residues of other β-lactam ring containing compounds. This method should also be applicable to other ruminants other than cattle and sheep.

8. MRLs recommended for ovine tissues are the same as those for bovine and porcine species. Therefore, in accordance with the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) it was possible to extrapolate the MRLs to all mammalian tissues.

9. Following parenteral administration of ceftiofur to milking sheep, residues in milk remained low from the first time point. An MRL had been established for bovine milk (allowing for intramammary use). Therefore, in accordance with the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) it was possible to extrapolate this MRL to milk for all mammalian species.

Conclusions and recommendation

Having considered that:

- a microbiological ADI of 20 µg/kg bw/day, i.e. 1200 µg/person, was previously established for ceftiofur,
- the sum of the metabolites retaining a ß-lactam ring that may be expressed as desfuroylceftiofur equivalents had been identified as the marker residue in bovine species and can be recommended as the marker residue for all other mammals,
- the ratio of marker to total residue in the relevant tissues of the target species was not determined, however, this information was considered unnecessary due to the marker residue accounting for all residues with anti-microbiological activity,
- following parenteral administration of ceftiofur to milking sheep, residues in milk remained low from the first time point,
- MRLs had previously been established in bovine and porcine species; these MRLs are identical to those recommended for all food producing mammals,
- the metabolic profile and residues distribution is similar in ovine, bovine and porcine species,
- an analytical method for the monitoring of residues in tissues and milk of all mammalian food producing species was available;

the Committee recommends the modification of the current entry for ceftiofur for bovine and porcine species in Annex I entry in Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Ceftiofur	Sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur	All mammalian food producing species	1000 µg/kg 2000 µg/kg 2000 µg/kg 6000 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	

Based on these MRLs, it was calculated that consumer intake of total residues will represent 87.5% of the ADI.