



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CEFQUINOME (extension to pigs)

SUMMARY REPORT (1)

1. Cefquinome (CAS no.: 84957-30-2) is a third-generation cephalosporin which has been developed solely for veterinary use. It shows antimicrobial activity against a broad spectrum of Gram-positive and Gram-negative bacterial species, and is regarded as being highly stable to β -lactamases. An injectable product is available: a suspension of cefquinome sulphate (CAS no.: 123766-80-3) in ethyl oleate (2.5% w/v cefquinome). The product has been approved for treatment of respiratory tract diseases in cattle. Recommended treatment regimen: 1 mg cefquinome/kg bw, administered intramuscularly once daily for 3 to 5 days. Cefquinome is also used by the intramammary route in lactating cows with a treatment regimen of three infusions of 75 mg cefquinome per affected quarter immediately after each of three successive milkings.
2. Currently, cefquinome is included in Annex I of Council Regulation (EEC) 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Cefquinome	Cefquinome	Bovine	200 µg/kg 100 µg/kg 50 µg/kg 50 µg/kg 20 µg/kg	Kidney Liver Muscle Fat Milk	

3. Since cefquinome is of low toxicity the CVMP considered it reasonable to base an Acceptable Daily Intake (ADI) on the effect of cefquinome on the human intestinal flora. The microbiological ADI currently agreed by the CVMP is 3.8 µg/kg bw, i.e. 225 µg for a 60 kg person. No toxicologically based ADI has been established.
4. Cefquinome is proposed for the treatment of pigs against respiratory tract infections. The proposed treatment schedule is 2 mg cefquinome per kg bw administered intramuscularly once daily for 3 to 5 days.
5. When used according to recommendation cefquinome administered in the commercial formulation was well tolerated in the target species.
6. In a radiolabelled study two pigs were treated intramuscularly 5 times with 1 mg ^{14}C -cefquinome per kg bw at 24 hour intervals and sacrificed 24 and 48 hours after administration of the last dose. For the animal sacrificed at 24 hours, 89% of the total dose had been excreted at the time of sacrifice, 83% having been recovered from urine plus cage washings and an additional 7% from the faeces. The corresponding percentages for the animal sacrificed at 48 hours were 95, 86, and 9. Parent cefquinome was the only excretion product positively identified in urine, accounting for 33% and 49%, respectively, of the total radioactivity recovered from the urine of the two animals, when measured by HPLC. Because cefquinome is unstable at alkaline pH, the percentages must be regarded as minimum values for the actual percentages as they were not adjusted for recovery rate of the method for cefquinome.

Examination of urine excreted in the period of 2 to 8 hours after administration of the last dose yielded considerably higher percentages of parent substance when determined by TLC (77% and 75% of the last dose, respectively) than the percentages obtained by HPLC (42% and 41%). The proportions of total cefquinome contents identified as parent substance by TLC in urine collected from the two animals during the 0 to 2 hour period after the last dose, were 45% and 63% respectively, while the corresponding figures for urine collected during the 2 to 8 hour period were 84% and 80%. The remaining radioactivity was tied to 2 to 3 other substances, none of which were further identified.

The highest activity in the carcass was found at the injection site (7810 µg cefquinome-equivalents/kg tissue in the animal sacrificed 24 hours after the last administration; 7523 µg cefquinome-equivalents/kg in the animal sacrificed at 48 hours), in the kidney (1145 µg cefquinome-equivalents/kg at 24 hours; 2157 µg cefquinome-equivalents/kg at 48 hours), and in the liver (688 µg cefquinome-equivalents/kg at 24 hours; 570 µg cefquinome-equivalents/kg at 48 hours). Radioactivity in muscle and fat tissues was negligible at 24 hours.

7. Non-radiolabelled residue depletion studies were carried out in pigs using the recommended treatment regimen, i.e. 5 times 2 mg cefquinome/kg bw at 24 hour intervals. The first four injections were administered at the same site while the last injection was administered at a separate site. Groups of four animals were sacrificed 24, 48, 72, 96, 120 and 144 hours after the last dose. Tissue residues were determined by means of the HPLC method proposed as routine analytic method for pigs. Samples were stored at -70° C until examination. The storage period varied between 3 and 18 months. The stability of naturally incurred cefquinome at -70°C has been demonstrated in muscle tissue for 15 months and in kidney for 12 months. No stability studies have been carried out for other tissues.

At 24 hours all injection site samples contained measurable amounts of cefquinome. Minimum and maximum concentrations measured were 18 and 34 µg/kg in tissue from the site of the first to fourth injection, and 100 and 208 µg/kg in tissue from the site of the fifth injection, respectively. At later time points only samples from the site of the fifth injection were examined. At 48 hours all samples were above 13 µg/kg. At 72 and 96 hours cefquinome could be detected in two of four samples (16 and 19 µg/kg, and 14 and 20 µg/kg, respectively). At 120 hours only one injection site sample (14 µg/kg) was above the limit of quantification, and all samples were below the limit of quantification at 144 hours.

All samples from kidney were above the limit of quantification at 24 hours; minimum and maximum concentrations measured were 88 and 293 µg/kg. Kidney samples from 48, 72, and 120 hours contained no measurable residues, while one of four 96 hour-samples (40 µg/kg) was above the limit of quantification. Samples from liver, fat, skin and muscle tissue (non-injection site) were examined only up to 72 hours after last treatment. No unchanged cefquinome was detected in these samples except for one 72 hour-sample of fat tissue containing 27 µg/kg.

8. The proportion of cefquinome relative to total residues in porcine tissues has not been studied. Using the data from the radiolabelled study in which only half the recommended dose was employed, together with the results from the depletion studies, adjusted for recovery of cefquinome, a rough estimate of the content of parent cefquinome relative to total residues in kidney tissue are 22 to 73%.
9. An analytic method (Matrix Solid Phase Dispersion/HPLC-Diode Array Assay) for determination of extractable cefquinome-residues in kidney, muscle, fat and liver tissue is available. The respective limits of detection and quantification using fortified samples of porcine tissues are: muscle: 11 and 25 µg/kg, liver: 13 and 60 µg/kg, kidney: 35 and 80 µg/kg, and fat: 14 and 25 µg/kg. Recovery rates at the limit of quantification are: muscle: 50%, liver and kidney: 35%, and fat: 30%. The limit of quantification and the recovery for pig skin are not clear (the target tissue is skin + fat in natural proportions), and the routine analytical method for pigs was not described in an internationally recognised format (e.g. ISO 78/2).

Conclusions and recommendation

Having considered that:

- the ADI currently agreed by CVMP is 3.8 µg/kg bw, i.e. 225 µg for a 60 kg person,
- cefquinome is the marker residue,
- 24 hours after parenteral administration of cefquinome detectable residues are only found in injection site tissue, kidney and liver,
- an analytical method is available for monitoring residues in all edible porcine tissues, but it has not been described in an internationally recognised format (e.g. ISO 78/2) and limit of quantification and recovery for the porcine target tissue skin + fat are not clear;

the Committee recommends the inclusion of cefquinome in Annex III to 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
Cefquinome	Cefquinome	Porcine	50 µg/kg 50 µg/kg 100 µg/kg 200 µg/kg	Muscle Skin + fat Liver Kidney	Provisional MRLs expire 1.1.2000

Based on these MRL values, the daily intake will represent about 17% of the ADI.

LIST OF QUESTIONS

1. The applicant should re-present the routine analytical method for porcine tissues in an internationally recognised format (e.g. ISO 78/2), accompanied by validation data for the target tissue skin + fat.