The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/005/95

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CEFQUINOME

SUMMARY REPORT

1. Cefquinome is a new third-generation cephalosporin intended for treatment of cattle against bacterial infections of the respiratory tract and the udder. Cefquinome shows antimicrobial activity against a broad spectrum of gram-positives as well as gram-negatives, and appears to be highly stable to β−lactamases.

2. Pharmacokinetics: absorption of orally administered cefquinome is poor, i.e. a few percentages in both laboratory species and cattle. Absorption following intramuscular or subcutaneous administration proceeds relatively quickly with C_{max} within ½ -2 hrs. Only a small fraction of intramammarily administered cefquinome is absorbed systemically.

3. Distribution of cefquinome is not extensive as cefquinome is an organic acid with pK_a values of 2.51 & 2.91 and low fat solubility. In dogs the apparent volume of distribution at steady-state approx. 0.2 litre per kg bw. Binding to plasma proteins is in the order of 5-15%. Following parenteral administration of radio-labelled cefquinome highest activities are found in injection-site tissue, kidney, and liver.

4. Excretion: plasma elimination half-lives for cefquinome are 1-2 hrs in dogs, and 1½-3 hrs in cattle - with no dose dependency. Excretion of parenterally administered cefquinome is predominantly renal. In calves 50-80% of the dose was recovered in the urine within four hours, and 90% within 24 hrs, while about 5% of the dose was recoverable from faeces. Intramammarily administered cefquinome is excreted mainly with the milk.

5. Metabolism: cefquinome is metabolized only to a small extent. Using radiolabelled cefquinome the only compound positively identified in cefquinome -treated animals was unchanged cefquinome, which in calves accounted for 90% of the urinary activity excreted during the first 8 hrs after administration. The parent compound cefquinome should be the “Marker Residue”.

6. Toxicology: the acute toxicity of cefquinome is low.

7. Repeated dose toxicity: no signs of toxicity were observed in an oral 90-day dog study employing doses of 0, 3.2, 32, and 320 mg cefquinome/kg bw. The main toxic manifestations observed in rats during a 90-day study employing oral doses of 0, 25, 250, and 2500 mg cefquinome/kg bw were dose-dependent hemolytic anemia, clinically observable only in the high-dose group (pale eyes), but indicated by changes in haematological and urinary parameters also at 250 mg, and dose-dependent renal impairment, indicated by a slight rise in BUN (250 and 2500 mg groups only).

8. Reproductive toxicity: a two-generation reproductive study carried out in rats employing oral doses of 0, 25, 250, and 2500 mg cefquinome/kg bw provided no evidence of specific reproductive effects.

9. Teratogenicity : a study carried out in rats employing oral doses of 0, 25, 250 & 2500 mg cefquinome per kg bw/day, and a rabbit study which employed daily oral doses of 0, 0.10, 0.32 & 1.0 mg cefquinome/kg bw, revealed no teratogenic potential.

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10. Mutagenicity : Cefquinome has been evaluated for gene mutation in Chinese hamster cells ("HGPRT-test"), for clastogenic effect in mammalian cells *in vivo* (micronucleus test in mice), and by *in vitro* unscheduled DNA synthesis. All test were negative.

11. Carcinogenicity : no carcinogenicity studies have been carried out, which is acceptable, as the chemical structure of cefquinome offers no grounds to suspect carcinogenic properties, and the genotoxicity assays were negative.

12. Immunotoxicity : Cefquinome showed no evidence of sensitizing potential when examined by the "Guinea Pig Maximization Test".

13. No observations in humans are available.

14. Antimicrobial effect on the human gut flora: Data on sensitivity to cefquinome (agar dilution test) have been submitted for 68 bacterial strains, representing *E.coli, Proteus spp, Bacteroides spp., Bifidobacterium spp., Clostridium spp., Peptostreptococcus spp, Peptococcus spp.*, and *Eubacterium*. The geometric mean MIC for an initial bacterial density of 1.5×10^9 cfu/ml - which corresponds to the bacterial density in the human colon - was calculated to be 1.5 µg/ml based on the MICs for *Bacteroides spp., Bifidobacterium spp., Peptococcus spp., Clostridium spp.,* and *Eubacterium*. Consequently, a NOEL of 1.5 µg/ml [or gram] can be set for the antimicrobial effect of cefquinome on the human gut flora.

15. Effect of cefquinome on microorganisms used in the dairy industry: the NOEL (a change in pH of ≤ 0.1 unit) of cefquinome for five different species of bacteria commonly used in the dairy industry (*Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus acidophilus, Lactobacillus casei, & Bifidobacterium bifidum)* was measured. *Streptococcus thermophilus* was found to be the most cefquinome-sensitive species with a NOEL of 20 ng/ml.

16. Residue depletion studies carried out in cattle show that intramuscular administration of 5x1 mg radiolabelled cefquinome /kg bw at 24 hour intervals results in highest activity at the injection site (approx. 40 µg cefquinome -eqv/g tissue 12 hours after the last administration), in the kidney (3-5 µg/g), and the liver (1-1½ µg/g), within the following 8-9 days declining according to first-order kinetics to 2-5, 1½, and ½ µg per g, respectively. In all samples extractable residues (= antimicrobially active residues) at 12 hours account for less than one third of total cefquinome-eqv. As regards injection-site tissue only a small proportion (3-4%) could be accounted for by antimicrobial activity following "digestion", i.e. treatment with hydrochloric acid and/or digestive-tract enzymes, while higher proportions of antimicrobial activity remained after digestion in samples from kidney (approx. 10%) and liver (virtually 100% of total cefquinome-eqv.). However, in all tissues examined at timepoints later than 12 hrs extractable residues as well as antimicrobial activity after digestion were at levels below the detection limits.

17. Residue depletion studies have been performed after intramammary administration of cefquinome to lactating cows. Residues in edible tissues could be detected only in kidney tissue and only at 24 hours post-treatment and at concentrations below 200 µg/kg. High concentrations of cefquinome were found in milk at the first milking after the last administration. At the 10th milking the residue concentrations in all bucket samples were below 20 µg/l.

18. An analytic method for determination of "extractable" cefquinome-residues in kidney, muscle, and liver tissue is available. The method (MSPD[1]/LC-Diode Array Assay) has been fully validated. The limits of detection and quantitation using fortified tissue samples are 0.01-0.02 and 0.05 µg/g tissue, respectively. The method appears suitable for confirmatory as well as a screening purposes.

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[1] "Matrix Solid Phase Dispersion"

19. An analytic method for cefquinome-residues in milk has been developed. The method - Reversed-Phase HPLC - has been validated and has a Limit of Detection of 10 µg/l and a Limit of Quantification of 15 µg/l.

20. Since cefquinome is of low inherent toxicity it is reasonable to base an Acceptable Daily Intake (ADI) on the effect of cefquinome on the human intestinal flora. Using a NOEL of 1.5 µg/g as regards effect on the gut flora, a daily faecal bolus of 150 g, a 10 pct availability of cefquinome-residues to intestinal bacteria, and a safety factor of 10, ADI for a 60-kilo person amounts to 225 µg ≈ 3.8 µg per kg bw.

21. The following MRLs for cefquinome in bovine tissue have previously been included in Annex I of Regulation 2377/90/EEC:

Kidney	200 µg/kg
Liver	100 µg/kg
Muscle	50 µg/kg
Fat	50 µg/kg

22. It is recommended that an MRL for cefquinome in milk of 20 µg/kg be included in Annex I of Regulation No 2377/90/EEC.