The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/MRL/883/03-FINAL
July 2003

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CEFQUINOME
(Extension to horses)

SUMMARY REPORT (3)

1. Cefquinome (CAS no.: 84957-30-2) is a fourth-generation cephalosporin with antimicrobial activity against a broad spectrum of Gram-positive and Gram-negative bacterial species, and is regarded as being highly stable to ß-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, acute mastitis and foot rot in cattle, calf septicemia, respiratory diseases in pigs and Metritis-Mastitis-Agalactia (MMA) syndrome in sows. The recommended treatment regimen for cows is 1 mg cefquinome/kg bw, administered intramuscularly once daily for 2 days (acute mastitis) or 3 to 5 days (respiratory tract diseases and foot rot), for calves 2 mg/kg cefquinome/kg bw addministered intramuscularly once daily for 3 to 5 days (septicemia) and for pigs 2 mg/kg bw administered intramuscularly once daily for 2 days (MMA syndrome) or 3 to 5 days (respiratory tract diseases). Cefquinome is also used by the intramammary route in lactating cows for the treatment of clinical mastitis caused by cefquinome sensitive organisms (*Streptococcus uberis, Streptococus dysgalactiae, Staphylococcus aureus and Escherichia coli*) with a treatment regimen of three infusions of 75 mg cefquinome per affected quarter immediately after each of three successive milkings.

   Cefquinome was previously assessed by the CVMP and a microbiological acceptable daily intake (ADI) of 3.8 µg/kg bw, i.e. 225 µg for a 60 kg person was established based on the NOEL of 1.5 µg/g for effect on the human intestinal flora.

   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	50 µg/kg 50 µg/kg 100 µg/kg 200 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	
		Porcine	50 µg/kg 50 µg/kg 100 µg/kg 200 µg/kg	Muscle Skin + fat Liver Kidney	

   An application has now been submitted for the extrapolation of the current MRLs for cefquinome to horses. The proposed indications are the treatment of respiratory diseases in horses with a recommended dose regimen of 1 mg/kg bw administered intramuscularly once daily and of foal septicaemia with the recommended dose regimen of 1 mg/kg administered intramuscularly twice daily.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eu.int http://www.emea.eu.int

2. A GLP compliant pharmacokinetic study was performed in horses after a single intramuscular administration of 1.0 mg cefquinome/kg bw and a single intravenous administration of 0.5, 1.0 and 2.0 mg/kg bw, respectively. After intravenous administration of 1 mg/kg bw the maximal plasma concentration was 11.07 mg/l, plasma clearance was estimated to be 1.73 ml/min/kg and the elimination half life was 2.17 hours. A linear dose-response relationship was seen within the dose range of 0.5 to 2.0 mg/kg bw administered intravenously. Cefquinome concentrations in plasma were under the limit of quantification (30 ng/ml) 24 hours after administration for all dose regimes. After intramuscular administration of 1 mg/kg bw the maximal plasma concentration was 2.47 mg/l, plasma clearance was estimated to be 1.79 ml/min/kg and the elimination half life was 1.98 hours. Bioavailability was 98% and AUC was 9.33 mg·h/l, which was comparable to values obtained from cattle. Urinary cefquinome concentrations and metabolism in horses was not investigated.

3. A GLP compliant non-radiolabelled residue depletion study was performed on two horses treated with 1 mg cefquinome/kg bw administered intramuscularly, once daily for 5 days. Injections were given in 5 different application sites and the horses were slaughtered 24 hours after last application. Concentrations of cefquinome in muscle and kidney were assayed by an HPLC-MS/MS method. The mean concentration at the injection site was 90.35 µg/kg 24 hours after last administration. At 48 hours all concentrations were under the limit of quantification (25 µg/kg). Mean concentration in kidney was 105.55 µg/kg, 24 hours after last application.

   The non-labelled residue depletion study shows that cefquinome is present in the edible tissues of the horse and can therefore be retained as the marker residue according to the *Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species* (EMEA/CVMP/153a/97-FINAL) and the *Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin* (EMEA/CVMP/187/00-FINAL).

4. A routine analytical method based on HPLC-MS/MS was developed for the determination of extractable cefquinome residues in muscle, liver, kidney and fat. The method was fully validated and sufficiently described in an international recognised format (e.g. ISO 78/2) according to the requirements of Volume 8 of the Rules Governing Veterinary Medicinal Products in the European Union. The limits of quantification values for cefquinome in tissue samples are 25 µg/kg for muscle, 50 µg/kg for liver, 100 µg/kg for kidney and 25 µg/kg for fat. The limits of detection for cefquinome in tissue samples are 0.7 µg/kg in muscle, 0.8 µg/kg in liver, 7 µg/kg in kidney, and 0.3 µg/kg in fat.

Conclusions and recommendation

Having considered that:

- an ADI of 3.8 µg/kg bw (225µg for a 60 kg person) was previously established by the CVMP for cefquinome,
- MRLs have been established for the major species bovine and porcine and horse is a minor species,
- cefquinome was confirmed as the marker residue in horses,
- a validated analytical method is available for monitoring residues in the muscle, fat, liver and kidney in horses;

The Committee for Veterinary Medicinal Products recommends the inclusion of cefquinome 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 tissue	Other provisions
Cefquinome	Cefquinome	*Equidae*	50 µg/kg 50 µg/kg 100 µg/kg 200 µg/kg	Muscle Fat Liver Kidney	

Based on these MRL values and the established MRLs for milk, the daily intake will represent about 30 % of the ADI.