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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CEFAZOLIN (extension to sheep and goats)

SUMMARY REPORT

1. Cefazolin (CAS 25953-19-9) is a first-generation cephalosporin showing antimicrobial activity mainly against Gram-positive bacteria including the common mastitis pathogens in cattle. The substance is current licenced for treatment of mastitis in lactating cows; recommended treatment regimen: Intramammary administration of 300 mg cefazolin per affected quarter immediately after each of two successive milkings. The substance has also been approved for treatment at drying off by intramammary administration of one dose of 250 mg cefazolin per quarter.

2. Cefazolin has been entered into Annex I of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRL	Target tissue	Other Provisions
Cefazolin	Cefazolin	Bovine	50 µg/kg	Milk	

For tissues other than milk, cefazolin has been entered into Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Cefazolin	Bovine	For intramammary use only (except if the udder may be used as food for human consumption)

3. A toxicologically based ADI of 100 µg/kg bw (6000 µg for a 60 kg person) was calculated by applying a safety factor of 100 to the NOEL for maternal toxicity of 10 mg/kg bw in an oral rat teratogenicity study. Since cefazolin is of low toxicity the Committee considered it reasonable to base an ADI on the effect of the compound on the human intestinal flora. The microbiological ADI established by the Committee is 10 µg/kg bw, i.e. 600 µg for a 60 kg person.

4. Cefazolin is proposed for prevention and treatment of udder infections during the dry period. The recommended treatment schedule in ewes and nanny-goats is 250 mg cefazolin (one dose syringe) administered intramammarily into each udder half at drying off.

5. Data were provided documenting acceptable in vitro activity of cefazolin against *Staphylococcus* spp. commonly occurring in the milk of ewes and nanny-goats at the time of drying off.

6. When used according to recommendations (i.e. intramammary administration of one dose of 250 mg cefazolin per quarter using the commercial formulation) cefazolin was well tolerated, both locally and systemically, in animals of both target species.

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7. In ewes treated at drying-off according to recommendations (i.e. intramammary administration of one dose of 250 mg cefazolin per quarter using the commercial formulation), peak concentrations in plasma (0.040-0.103 µg per ml) were observed 4-7 days after treatment. Concentrations were below the limit of quantification (LOQ) of the analytic method (0.020-0.025 µg/ml) from day 14 and onwards after treatment. The concentration in urine also peaked during days 4-7 (range 113-218 µg/ml). At day 21 cefazolin was still detectable in small concentrations in the urine from two of five ewes, indicating that absorption was still taking place from the udder at a low rate. During the 21 day follow-up period estimated urinary recovery rates varied from 74% to 138% of the administered dose. Concentrations of cefazolin in the same order of magnitude were obtained by an HPLC method and by microbiological assay.

   In nanny-goats treated at drying-off according to recommendations (i.e. intramammary administration of one dose of 250 mg cefazolin per quarter using the commercial formulation), peak concentrations in plasma (0.047-0.102 µg/ml) were observed at 4-24 hours. Cefazolin was still measurable in one day-7 sample, but no substance was detectable from day 14 and onwards. The concentration in urine peaked on day 1 (38-131 µg/ml). At day 14 the concentration was below the limit of quantification (0.0250 µg/ml) in all samples. During the 21-days follow-up period estimated urinary recovery rates varied from 21% to 54% of the administered dose. Concentrations of cefazolin in the same order of magnitude were obtained by an HPLC method and by microbiological assay.

8. No radiolabelled residue studies have been carried out in sheep and goats. Consequently, the proportion of cefazolin relative to total tissue residues is not known for either species. However, since cefazolin is metabolized only to a very limited extent in all species in which this aspect has been examined, any residues that may be present in tissues of treated animals can be assumed to consist of parent substance.

9. Concentrations of cefazolin in all edible tissues from ewes and nanny-goats were below the limit of quantification (50 µg/kg) of the analytic method (HPLC) at day 21 following recommended treatment. Tissue residues of cefazolin were not studied during the intervening 3-week period.

10. When ewes and nanny-goats were treated according to recommendations (i.e. intramammary administration of one dose of 250 mg cefazolin per quarter using the commercial formulation) the contents of cefazolin were below the limit of quantification in all milk samples from ewes and nanny-goats, collected at the three first milkings following parturition. For the ewes included in the study the length of the dry period averaged 137 days (range 70-173 days), while the corresponding figures for nanny-goats were 76 days (69-95 days). Contents of cefazolin residues in udder secrete was not studied during the intervening period.

11. An analytical method, presented in ISO 78/2 format, is available for monitoring of residues of cefazolin in milk of ewes and nanny-goats. Cefazolin is determined by HPLC. The method has a limit of quantification of 25 µg cefazolin/l and has been appropriately validated for milk. Its specificity with respect to other cephalosporins/ß-lactam antibiotics is acceptable. The method has been adequately described.

12. According to the CVMP policy on minor species, sheep are defined as a major species as regards edible tissues and as a minor species as regards milk. Goats are defined as a minor species for both edible tissues and milk. Furthermore its also considered that the existing MRL entry for a substance in Annex II for a major species should normally also apply to a corresponding minor species with the same restrictions, where applicable.

13. In accordance with the CVMP policy on minor species the MRL value established for milk of cows (50 µg/kg) is acceptable for milk from the two target species sheep and goats.

Proof has been provided that no hazardous amounts of cefazolin residues will be present in parts of the carcass of sheep officially designated as edible, at 21 days after recommended treatment. Evidence is available that also during the intervening period residues in edible tissue of the target species will be insignificant as regards consumer safety: the volume of distribution for cefazolin is in the order of 0.2 l/kg bw in most species examined, and virtually all of an intramuscular or subcutaneous dose of cefazolin has been excreted via the kidneys within 24 hours after administration. Consequently, it is unlikely that any cefazolin, that may temporarily reside in edible tissues, will be present in concentrations resulting in cefazolin contents in the standard food package coming even close to the 525 µg left over within the ADI after allowance has been made for the 75 µg contained in 1.5 litre of milk. Thus it is reasonable also to enter cefazolin into Annex II as far as edible tissues of sheep are concerned.

In addition, cefazolin can be entered into Annex II as far as edible tissues of goats are concerned.

Conclusions and recommendation

Having considered:

- the kinetics of cefazolin in sheep and goats after intramammary administration as well as the kinetic data for cefazolin available for other mammalian species, it is unlikely that hazardous residues of cefazolin will be present in edible tissues of ewes and nanny-goats at any point in time following intramammary administration of the substance at drying off, and
- the availability of a validated analytical method for monitoring of cefazolin residues in milk from ewes and nanny-goats

the Committee rec commends the inclusion of cefazolin in Annex I of Council Regulation (EEC) No. 2377/90 for milk in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRL	Target tissues	Other provisions
Cefazolin	Cefazolin	Ovine, caprine	50 µg/kg	Milk	

and for all other tissues the inclusion of cefazolin in Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Cefazolin	Ovine, caprine	For intramammary use only and for all tissues except milk