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

EMEA/MRL/857/02-FINAL
November 2002

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BACITRACIN
(Extension to rabbits)

SUMMARY REPORT (3)

1. Bacitracin is an antibiotic from the group of peptide antibacterial compounds. In veterinary medicine, bacitracin is used in combination with tetracyclin, neomycin and prednisolone for intramammary treatment of mastitis in lactating cows. The recommended dosage is 2000 IU bacitracin (standard potency 74 IU/mg, i.e. 1 IU/13.5 µg) per infected quarter, to be repeated after 12 or 24 hours if necessary. In the past, bacitracin has been used as a feed additive for poultry, pigs, calves, lambs and kids, but in 1998 the authorisations for this use were withdrawn in accordance with Council Regulation (EC) No. 2821/98.

   In human medicine, (zinc) bacitracin is used in the topical treatment of local infections, often in conjunction with other antibiotics.

   Bacitracin was assessed by the CVMP in 1995, 1998 and 2000. Upon these evaluations, it was concluded that the microbiological endpoint was most relevant for the safety assessment of bacitracin. A microbiological ADI of 3.9 µg/kg bw (i.e. 234 µg/person) was established, based on *in vitro* susceptibility data with human enteric micro-organisms and using the recommended CVMP formula.

   Currently, bacitracin is included 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	MRLs	Target tissue	Other provisions
Bacitracin	Sum of bacitracin A, bacitracin B, and bacitracin C	Bovine	100 µg/kg	Milk	

   and for other tissues except milk, bacitracin is currently included in Annex II of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Animal species	Other provisions
Bacitracin	Bovine	For intramammary use in lactating cows only and for all tissues except milk

   Based on the MRL value for milk, the daily intake represents about 64% of the ADI.

   An application for the extension of the current MRLs to rabbits has now been submitted. In rabbits, bacitracin is indicated for the treatment of enzootic rabbit enterocolitis, and is given orally in drinking water or in feed at a dose of 420 IU/kg bw/day for 10 consecutive days, corresponding to approximately 5.7 mg/kg bw/day.

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. After oral application to rats, chickens and pigs, bacitracin is hardly absorbed from the gastro-intestinal tract, and the distribution to organs and tissues is negligible. In rats, chickens and pigs, approximately 95% of an oral dose is excreted via faeces, and only 3% or less via urine. Bacitracin is metabolised to amino acids and smaller peptides via the main metabolite desamidobacitracin, which is microbiologically inactive. Main metabolites in faeces are bacitracin A, B1, B2, F, desamidobacitracin and catabolic peptides. In urine and bile only hydrolytic cleavage products (di- and tripeptides) are present.

3. Residues of bacitracin were studied in rabbits following application of bacitracin zinc via the drinking water during 6 weeks in dosages of 0, 25, 50 and 100 µg/l (equivalent to a daily dose of 0, 5-11, 10-15 and 17-31 mg/kg bw). Samples of blood and faeces were taken during and after the treatment period and stored for a period of maximally 54 days (first at –20°C and later at –80°C). Tissue samples were taken after the treatment period. Bacitracin was analysed in blood samples taken on the last day of treatment and 3, 7 and 10 days after the treatment period using a microbiological method with an indicated limit of quantification of 200 µg/l. No bacitracin above 200 µg/l was found in any of these samples. However, the analytical method was not completely validated with respect to accuracy, precision, and storage stability, so based on the information available, no conclusion could be drawn.

4. Residues of bacitracin were studied in rabbits (8 males, 8 females) following application of bacitracin zinc via the drinking water at a clinical target dose of 420 IU/kg bw/day for 30 consecutive days. Groups of 2 males and 2 females were slaughtered at 24, 48, 72, and 96 hours after treatment. Just before the end of treatment, blood was taken from the jugular vein from eight randomly selected rabbits and the content of bacitracin analysed. At slaughter, the liver, the kidneys, and samples of muscle (approximately 50 g) and fat (approximately 20 g) were taken and the content of bacitracin analysed. The tissues taken at 72 and 96 hours were not analysed because plasma levels and tissue levels at earlier time points were all below the estimated limit of detection of 37.5 µg/kg for the marker residue, and there were no detectable amounts of bacitracin in plasma of animals sampled on the last day of the treatment period.

5. A validated LC-MS/MS method was proposed as routine analytical method for the determination of bacitracin A, B and C in rabbit tissues. The method is based on the method for bovine milk. The method was described in ISO 78/2 format; limits of quantification were 39.8 µg/l for bacitracin A and 26.3 µg/l for bacitracin B, at this level the concentration of bacitracin C could not be quantified.

Conclusions and recommendation

Having considered that:

- the microbiological ADI is 3.9 µg/kg bw (i.e. 234 µg/person);
- bacitracin was retained as the marker residue, and since bacitracin consists mainly of bacitracin A, B, and C, the marker residue is defined as the sum of bacitracin A, B, and C,
- residues were not detectable in tissues 24 hours after oral administration, MRLs were set approximately at twice the limit of quantification of the (combined) marker residue,
- A validated LC-MS/MS method for the routine determination of bacitracin A, B, and C in rabbit tissues is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of bacitracin for rabbits 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
Bacitracin	Sum of bacitracin A, bacitracin B, and bacitracin C	Rabbit	150 µg/kg 150 µg/kg 150 µg/kg 150 µg/kg	Muscle Fat Liver Kidney	

Based on the MRL values for rabbit tissues, and taking into account the intake calculated from the MRL for bovine milk, the maximum daily intake will represent about 95% of the ADI.