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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BRONOPOL

SUMMARY REPORT (2)

1. Bronopol (2-bromo-2-nitropropane-1,3-diol) is an antimicrobial preservative which is used in shampoos, cosmetics, in food-contact materials and in topical pharmaceutical preparations intended for human use. It is being developed for use as a bath treatment for control of fungal infections in farmed salmonid eggs, at a dose rate of 50 mg bronopol per litre of water for 30 minutes. There may be up to 8 treatments each of 30 minutes during a typical incubation.

   A toxicological ADI of 20 µg/kg bw (i.e. 1200 µg/person) was previously established for bronopol by the Committee for Veterinary Medicinal Products (CVMP). This was calculated by applying a safety factor of 200 to the NOEL of 4 mg/kg bw per day, which was established in the 13-week repeated-dose toxicity study in dogs. A safety factor of 200 was choosen to compensate for the limited range of clinical chemistry investigations carried out in this study and the lack of analysis of the dosing solutions.

   Currently, bronopol is included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance	Animal species	Other provisions
Bronopol	Salmonidae	For use only on farmed fertilised eggs

   An application for the extension of the MRLs to all stages of life for Salmonidae has now been submitted. Bronopol is intended to be used to treat fish at a dose rate of 20 mg bronopol/l of water. The intended treatment period is 30 minutes, and repeated treatments could be made for up to 14 consecutive days.

2. Atlantic salmon (mean bw 32.4 g) were exposed by immersion in a tank containing a solution of (^{14}C)-bronopol (21.91 mg/l water) at 14º C, for a period of 30 minutes. At the end of treatment, the fish were transferred to a clean water tank. Groups of 10 fish were collected at the end of the exposure period (0 hours) and at 6, 12, 24, 72 and 168 hours after treatment. Concentrations of radioactivity in samples of muscle with skin were determined by combustion followed by liquid scintillation counting. The mean total residues depleated from 259 µg equivalents/kg at 0 hours, to 266 µg equivalents/kg at 6 hours, to 255 µg equivalents/kg at 12 hours, to 194 µg equivalents/kg at 24 hours, to 102 µg equivalents/kg at 3 days and to 39 µg equivalents/kg at 7 days.

3. Attempts were made to identify the components of the residues in pooled tissue samples, by comparison with authentic samples of known mammalian metabolites and degradation products of bronopol. Radioactivity was extracted from the samples with extraction efficiencies of 79 to 93%. HPLC analysis indicated one major metabolite, which could not be identified. LC-MS indicated 2 possible structures for the unknown metabolite.

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.eudra.org http://www.eudra.org/emea.html

4. Based on the results of the study in which salmon were given a single treatment of (^{14}C)-bronopol, the estimated mean consumer intakes of total residues were 80 µg, 77 µg and 58 µg at 6 hours, 12 hours and 24 hours respectively, after the end of the exposure period. These values represented approximately 7%, 6% and 5% of the ADI for bronopol. Because up to 14 consecutive daily treatments were possible, a risk assessment of the likely consumer intake of total residues in muscle plus skin from fish treated with bronopol for 14 days was conducted. A worst case estimate of consumer intake of total residues was determinated assuming that residues are depleted only on the day of dose administration and that fish are eaten 6 hours after the 14th and final treatment. This scenario would result in the accumulation of 13 times 200 µg/kg (the average residue concentration a day after a single treatment) plus 300 µg/kg (the average intake of total residues after 6 hours) equalling a cumulative concentration of 2900 µg/kg resulting in a consumer intake of 870 µg, representing around 73% of the ADI.

Conclusions and recommendation

Having considered that:

- an ADI of 20 µg/kg bw (i.e. 1200 µg/person) was established for bronopol,
- the worst case estimation for the daily consumer intake of total residues, resulting from the treatment of salmon with bronopol, was calculated to be no more than 870 µg, representing around 73% of the ADI,
- taking into account the approach outlined in the CVMPs Notes for guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97-FINAL) and on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL), the assessment should be extrapolated to fin fish,

the Committee for Veterinary Medicinal Products recommends to amend the existing entry for bronopol in Annex II of Council Regulation (EEC) No 2377/90 to cover all life stages in fin fish in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Bronopol	Fin fish	