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

EMEA/MRL/160/96-FINAL
January 1997

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SARAFLOXACIN (salmonidae)

SUMMARY REPORT (1)

1. Sarafloxacin is a fluoroquinolone antibiotic which works by inhibition of bacterial DNA-gyrase. It has been proposed for use in the drinking water of poultry to treat bacterial disease, and in fish feed to treat diseases such as furunculosis, vibriosis and enteric redmouth. The recommended dose rate is 10 mg/kg bw fish, administered in the feed as the hydrochloride for 5 consecutive days.

2. Sarafloxacin was entered into Annex I of Regulation 2377/90 with MRLs for chicken of 100 µg/kg for liver and 10 µg/kg for skin+fat. The marker residue is parent sarafloxacin. Additional data have been provided to support extension of the entry to Salmonidae.

3. Feeding studies in Atlantic salmon using radiolabelled sarafloxacin hydrochloride at 0.7 and at 9.5 mg/kg bw indicate that excretion of the drug is rapid and is mainly via the urine. The time to maximum plasma concentration after treatment with sarafloxacin was affected by vehicle and temperature and ranged from 6-24 h for single oral doses to 103.5 h for repeated oral doses. The oral bioavailability ranged from 4-24% of the dose.

4. Following a single oral treatment with ^{14}C sarafloxacin hydrochloride at 9.5 mg/kg bw, whole body autoradiography indicated the highest amounts of radioactivity were present in the intestines of salmon maintained at 11-13°C. Liquid scintillation counting indicated total residues in the liver, kidney, skin and muscle depleted from 304, 222, 158 and 124 µg sarafloxacin equivalents/kg at 12 h to 25, 82, 57 and 22 µg sarafloxacin equivalents/kg at 7 days respectively. Residues in the intestines were not quantified. In a similar study in salmon maintained at 6 - 8 °C and receiving a single oral dose of ^{14}C sarafloxacin hydrochloride at 9.7 mg/kg bw, whole body autoradiography confirmed the highest amounts of radioactivity were present in the intestines. Liquid scintillation counting indicated total residues in the liver, kidney, skin and muscle depleted from 679, 192, 166 and 239 µg sarafloxacin equivalents/kg at 12 hours to 94, 80, 18 and 12 at 7 days respectively.

5. Studies in skin and muscle from salmon and trout maintained at 14-16 °C and treated with 10 mg/kg bw of radiolabelled ^{14}C-sarafloxacin HCl and on muscle from channel catfish treated with ^{14}C-sarafloxacin lactobionate indicated that parent sarafloxacin was the only detectable residue in the extractable fraction when analysed by HPLC. In the salmon and trout studies, the total residues present in muscle plus skin 18 hours after dosing were equivalent to 200-1330 µg sarafloxacin HCl/kg tissue. Approximately 25% of labelled residues in skin and muscle of salmon and trout were not readily extractable. The nature of this bound residue was not determined. Based on these studies, sarafloxacin is proposed as the marker residue and the calculations of the MRL should allow for the fact that the marker residue measures only 75% of the total residue.

6. The residue depletion data indicated that the sarafloxacin residues in skin and muscle of Atlantic salmon maintained at 15 or 5 °C fell below the limit of determination of the method used (50 µg/kg) at 75 degree days after treatment with 10 mg/kg bw sarafloxacin hydrochloride daily for 5 days. At 83 degree days (5.5 days) after withdrawal, residues in muscle of fish maintained at the higher temperature were below the limit of determination whereas residues up to 166 µg/kg were found in the muscle of fish maintained at 5 °C. At the same withdrawal time, residues in skin were in the range of less than 50-54 µg/kg in fish maintained at 15 °C and less than 50 µg/kg in fish maintained at 5 °C. Residue depletion data in trout were carried out using sarafloxacin lactobionate rather than sarafloxacin hydrochloride. The lactobionate is stated to be of higher bioavailability than the

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hydrochloride and residues would therefore be predicted to be higher than those deriving from sarafloxacin hydrochloride treatment. Residues in muscle and skin were below the limit of detection (6.7 µg/kg in this study) at 60 degree days.

7. An analytical method based on HPLC with fluorimetric detection, suitable for measuring the marker residue in skin and muscle of salmon and trout has been presented. The limit of quantitation for sarafloxacin in skin + muscle of both trout and salmon is 10 µg/kg tissue. Lack of interference from enrofloxacin, flumequine and oxolinic acid has been demonstrated. The limit of detection in the validation study was stated to be 6.5 µg/kg tissue for trout and 4 µg/kg tissue for salmon tissue but the limit of detection was not determined by the procedure recommended in Volume VI of the Rules Governing Veterinary Medical Products in the European Union and full details have not been provided.

Conclusions and recommendation

Having considered that :

- a microbiological ADI has been previously set at 0.4 µg/kg (24 µg/person) for sarafloxacin,
- sarafloxacin is the marker residue and measures 75% of total residues,
- the physico-chemical analytical method available to detect residues of sarafloxacin in skin and muscle of salmonidae is not fully validated;

The Committee recommends the inclusion of sarafloxacin in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table :

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Sarafloxacin	Sarafloxacin	Salmonidae	30 µg/kg	Muscle and skin in natural proportions	Provisional MRL expire on 01.07.1998

Based on these MRLs values, the daily intake will represent about 50 % of the microbiological ADI which allows for a margin of error in estimating the ratio between the marker residue and the total residues.

LIST OF QUESTIONS

1. The applicant should provide the following information on the analytical method :

   - complete details of the limit of quantification, validated and documented in accordance with Volume VI of Rules Governing Veterinary Medicinal Products in the European Union. In particular, it should be clearly indicated that individual samples were analysed, rather than repeated analysis of a single sample and the relevant individual chromatograms supplied.

   - information on the limit of detection, validated and documented in accordance with Volume VI.

   the complete method should be presented in an internationally recognised format (e.g. ISO 78/2).