



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SARAFLOXACIN (Salmonidae)

SUMMARY REPORT (2)

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. A microbiological ADI of 0.4 µg/kg bw per day (24 µg/person/day) was calculated for sarafloxacin. The antimicrobial activity of 4 potential metabolites was shown to be less than that of the parent sarafloxacin. The microbiological ADI is well below the toxicological ADI of 100 µg/kg bw/day, based on the overall NOEL of 10 mg/kg bw/day obtained in the 13-week study in immature dogs, and applying a safety factor of 100. 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. Sarafloxacin is currently entered into Annex III of Council Regulation (EEC) 2377/90 for Salmonidae as follows:

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 expires on 01.07.1998

Additional information concerning the validation of the analytical method had been provided in support of the inclusion of sarafloxacin in Annex I.

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 kidneys. The time to maximum plasma concentration after treatment with sarafloxacin was affected by vehicle and temperature and ranged from 6 to 24 hours for single oral doses to 103.5 hours for repeated oral doses. The oral bioavailability ranged from 4 to 24% of the dose.
4. Following a single oral treatment with ¹⁴C-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 to 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 hours 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 to 8 °C and receiving a single oral dose of ¹⁴C-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 µg sarafloxacin equivalents/kg at 7 days respectively.

5. Studies in skin and muscle from salmon and trout maintained at 14 to 16°C and treated with 10 mg/kg bw of radiolabelled ¹⁴C-sarafloxacin hydrochloride and on muscle from channel catfish treated with ¹⁴C -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 + skin 18 hours after dosing were equivalent to 200 to 1330 µg sarafloxacin hydrochloride/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 accounts for around 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°C or 5°C fell below the limit of quantification 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 detection 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 to 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 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. A validated analytical method based on HPLC with fluorimetric detection, suitable for determining residues of sarafloxacin marker residue in skin and muscle of salmon and trout, has been presented in the ISO 78/2 format. The limit of quantitation for sarafloxacin in muscle + skin of both trout and salmon is 10 µg/kg tissue. Enrofloxacin was used as an internal standard. Lack of interference from flumequine and oxolinic acid has been demonstrated.

Conclusions and recommendation

Having considered that :

- a microbiological ADI has been previously set at 0.4 µg/kg bw (24 µg/person) for sarafloxacin,
- sarafloxacin is the marker residue and accounts for 75% of total residues,
- a validated analytical method described in the ISO 78/2 format is available for the determination of residues of sarafloxacin in skin and muscle of salmonidae;

the Committee recommends the inclusion of sarafloxacin 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 tissues	Other provisions
Sarafloxacin	Sarafloxacin	Salmonidae	30 µg/kg	Muscle and skin in natural proportions	

Based on these MRL values, the daily consumer intake will represent about 50% of the microbiological ADI.