



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SODIUM SALICYLATE (Extension to oral use in bovine and porcine)

SUMMARY REPORT

1. Sodium salicylate belongs to the salicylic acid derivatives. Sodium salicylate is used topically in creams, ointments or solution for the cleaning of wounds of the skin and the teat, in cattle, horses, sheep, goats and poultry. The recommended dose is 2 to 400 µg/kg bw/day.

Salicylic acid, sodium salicylate, basic aluminium salicylate and methyl salicylate were previously evaluated by the Committee for Veterinary Medicinal Products (CVMP). No pharmacological or toxicological ADI was established for salicylic acid, or its salts.

Currently sodium salicylate is included in Annex II of Council Regulation (EEC) No 2377/90 for all producing animals except fish and topical use only in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Sodium salicylate	All food producing species except fish	For topical use only

An application has now been submitted for the extension of the current Annex II entry of sodium salicylate to include the oral use in calves and pigs. The proposed indication for calves and pigs is as antipyretic, antiphlogistic and analgesic. The proposed doses are 40 mg/kg bw/day for cattle during a maximum of 5 days, administered in the milk replacer and 35 mg/kg bw/day for pigs during a maximum of 5 days, administered in drinking water.

2. Although no ADI was established for salicylic acid or its salts, during the assessment of acetylsalicylic acid a pharmacological ADI of 0.0083 mg/kg bw (0.5 mg /person) was established, which is considered relevant to sodium salicylate as sodium salicylate as well as acetylsalicylic acid exert their pharmacological effects through salicylic acid.
3. A pharmacokinetic study was carried out in 8 calves of 11 weeks of age. After a single intravenous administration of 40 mg/kg of sodium salicylate, salicylic acid elimination was best described by a one-compartment elimination model. The decrease in plasma concentrations following treatment administration was characterized by a half-life ($T_{1/2}$) elimination of 1.23 ± 0.31 h. The volume of distribution (V_{dss}) of salicylic acid was 0.24 ± 0.04 l/kg. Salicylic acid clearance (Cl_{tot}) was 0.16 ± 0.04 l/h/kg. This value was associated to a mean residence time of 1.34 ± 0.24 h.

After oral administration of 40 mg/kg of sodium salicylate, plasma concentration times curves were fitted using a one-compartment elimination model, with first-order resorption. The decrease in plasma concentrations following treatment administration was characterized by a half-life elimination of 1.17 ± 0.26 h. $C_{\max}$ was 53.98 ± 11.11 mg/l and was attained quickly (1.97 ± 0.84 h after administration). The volume of distribution (Vd) of salicylic acid was 0.30 ± 0.06 l/kg. Salicylic acid clearance (Cl_{tot}) was 0.20 ± 0.04 l/h/kg. This value was associated to a mean residence time of 2.77 ± 0.42 h. Bioavailability was 77.8%.

4. A pharmacokinetic study was carried out in 12 pigs, 8 weeks of age. After a single intravenous administration of 35 mg/kg of sodium salicylate, salicylic acid elimination was best described by a one-compartment elimination model. The decrease in plasma concentrations following treatment administration was characterized by a half-life elimination of 1.15 ± 0.16 h. The volume of distribution (V_{dss}) of salicylic acid was 0.19 ± 0.03 l/kg. Salicylic acid clearance (Cl_{tot}) was 0.12 ± 0.03 l/h/kg. This value was associated to a mean residence time of 1.65 ± 0.23 h.

After oral administration of 35 mg/kg of sodium salicylate, plasma concentration times curves were poorly fitted using a one-compartment elimination model, with first-order resorption. They were therefore evaluated by means of non-compartmental analysis. The decrease in plasma concentrations following treatment administration was characterized by a half-life elimination of 1.23 ± 0.43 h. $C_{\max}$ was 92.10 ± 8.72 mg/l and was attained quickly (1.07 ± 0.46 h after administration). Salicylic acid clearance (Cl_{tot}) was 0.11 ± 0.01 l/h/kg. This value was associated to a mean residence time of 2.51 ± 0.52 h. Calculated bioavailability was 103 %, with a 90% confidence interval of 89.3 - 118.7%.

5. Sixteen male calves weighing 90 ± 5 kg were administered with sodium salicylate, at a dose of 40 mg/kg bw/day for 5 consecutive days, as once-daily treatment. The animals were sacrificed on day 1, 3, 5 and 8 after the end of treatment. The salicylic acid concentrations in tissues (muscle, liver, kidney and fat) were determined by HPLC/UV analytical method. The limit of quantification was 0.01 µg/g, 0.04 µg/g, 0.15 µg/g and 0.18 µg/g, respectively for muscle, liver, kidney and fat. Residues of salicylic acid in edible tissues of calves were most of the time points below the limit of quantification of the analytical method. Only occasionally concentrations of salicylic acid were measured in kidney (0.339 µg/g and 0.176 µg/g, respectively 1 and 5 days after the last administration) and fat (0.220 µg/g, 3 days after the last administration). The limit of quantification was further validated and could be established as less than 110 µg/kg for fat, liver, kidney and muscle.

From the data available, it was calculated that the intake of total residues of salicylic acid from edible tissues 24 hours after the end of treatment would be 0.027 mg/person. When values were below the limit of quantification, this limit was considered for calculations. The pharmacological ADI considered relevant for sodium salicylate being 0.0083 mg/kg bw (i.e. 0.5 mg/person), the residues would represent approximately 5% of the ADI at 24 hours.

No residue information was provided in relation to lactating cows.

6. Sixteen male pigs (8 males, 8 females) weighing 39.6 ± 3.4 kg were administered with sodium salicylate, at a dose of 35 mg/kg bw/day for 5 consecutive days, as once-daily treatments. The animals were sacrificed on day 12, 24, 48 and 72 after the end of treatment. The salicylic acid concentrations in tissues (muscle, liver, kidney and fat) were determined by liquid chromatography/mass spectrometry (LC/MS/MS) analytical method. The limit of quantification was less than 0.05 µg/g for all tissues.

No residues of salicylic acid above the limit of quantification of 0.05 µg/g were found in kidney, liver, muscle, skin and fat of pigs after cessation of the medication with sodium salicylate as prescribed.

From the data available, it was calculated that the intake of total residues of salicylic acid from edible tissues 24 hours after the end of treatment would be 0.026 mg/person. When values were below the limit of quantification, the limit of quantification of the analytical method was considered for calculations.. The pharmacological ADI relevant for sodium salicylate being 0.0083 mg/kg bw (i.e. 0.5 mg/person), it would represent approximately 5% of the ADI at 12 hours.

Conclusions and recommendation

Having considered that:

- after oral administration of sodium salicylate to young cattle and pigs, the depletion of salicylic acid from edible tissues is rapid,
- 24 and 12 hours post-treatment of calves and pigs respectively, the calculated consumer intake represents approximately 5% of the pharmacological ADI considered relevant for sodium salicylate of 0.0083 mg/kg bw (i.e. 0.5 mg/person),
- no information on residue depletion was available for bovine milk;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for sodium salicylate regarding the oral use in bovine and porcine species and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Sodium salicylate	Bovine, porcine	For oral use only. Not for use in animals from which milk is produced for human consumption.