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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ALUMINIUM SALICYLATE, BASIC
(Extension to oral use in cattle)

SUMMARY REPORT (2)

1. Basic aluminium salicylate belongs to the salicylic acid group of substances. Basic aluminium 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 could be established for salicylic acid, or most of its salts or esters. However a pharmacological ADI of 0.0083 mg/kg bw (0.5 mg/person) was established for acetylsalicylic acid.

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

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

   An application for the extension of the entry for basic aluminium salicylate to oral use in cattle has now been submitted. Basic aluminium salicylate is intended for use as an antidiarrhoeal in the treatment of diarrhoea in neonatal calves, in combination with other active ingredients such as neomycin, sulfaguanidine or kaolin.

   The highest recommended therapeutic dose is 10 g basic aluminium salicylate per 50 kg body weight in calves, twice daily, for 3 to 5 consecutive days by the oral route. This dose corresponds to a daily dose equivalent to 275 mg/kg bw of salicylic acid. Basic aluminium salicylate is unlikely to be used in ruminant cattle because the dilution in the rumen would require large quantities of the substance to be effective.

   Basic aluminium salicylate corresponds to a pro-drug of aluminium hydroxide ($Al(OH)_3$) which is released in the intestinal lumen to cover and protect the intestinal mucosa by creating an astringent coating. In addition to aluminium hydroxide, sodium salicylate is also released in the gut. Sodium salicylate exerts its anti-inflammatory activity through the inhibition of prostaglandin synthesis.

   Since only salicylic acid is absorbed, the application referred to the pharmacological ADI established for acetylsalicylic acid and related salts (0.5 mg per person) of which the pharmacological activity is due to the salicylic acid.

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2. A pharmacokinetic study was carried out in 6 calves, 5 weeks of age. After a single intravenous administration of 139 mg of salicylic acid (as sodium salicylate)/kg bw, salicylic acid elimination from plasma was best described by a one-exponential model. The decrease in plasma concentrations between 0 and 12 hours following administration was characterised by an elimination half-life ($t_{½}$) of 3.68 hours. After 12 hours, the plasma concentration was 60.7 µg/ml. The volume of distribution of salicylic acid was 0.39 l/kg. Salicylic acid clearance was 1.18 ml/min/kg. This value was associated with a mean residence time of 5.48 hours.

   After oral administration of 139 mg of salicylic acid as basic aluminium salicylate, an absorption half-life ($t_{½}$) of at least 4.6 hours was estimated. Absorption rate during one treatment interval (12 hours) was variable with a bioavailability factor of 4.2 to 34.9%. However, as the blood samples had been collected only over a limited period of 12 hours, and in the absence of data during the elimination phase, no firm conclusion on the bioavailability could be reached. At 12 hours, i.e. the latest point studied, the concentrations reached a maximum, and were in the range of 13.7 to 85.3 µg/ml.

3. Eight calves (4 males, 4 females) weighing 53 kg, were administered basic aluminium salicylate according to the recommended therapeutic regimen for calves, i.e 400 mg basic aluminium salicylate/kg bw/day for 5 consecutive days, as twice-daily treatments. The animals were sacrificed 24 hours and 3 days after the end of treatment. The salicylic acid concentrations in tissues were determined by HPLC with spectrofluorimetric detection with limits of quantification of 100 µg/kg in muscle and 50 µg/kg in liver, kidney and fat. Twenty-four hours after treatment, mean salicylic acid concentrations were 871 µg/kg in muscle, 1886 µg/kg in liver, 6702 µg/kg in kidney and 1289 µg/kg in fat. Three days after treatment, mean salicylic acid concentrations were below the limit of quantification in muscle, 1203 µg/kg in liver, 646 µg/kg in kidney and 236 µg/kg in fat. The depletion of salicylic acid was therefore rapid, with a slower elimination rate in liver, compared with the other tissues. No increase in bovine plasma aluminium concentrations was recorded, indicating that aluminium was not systemically absorbed.

   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 the treatment would be 850 µg. Three days after the end of treatment in calves the intake would be 180 µg. This salicylic acid residue depletion is comparable to the one observed after the administration of acetylsalicylic acid derivates. For acetylsalicylic acid, which is hydrolysed into salicylic acid, it was considered that the residues following oral and parenteral administration do not represent a risk for the consumer (EMEA/CVMP/695/99-FINAL).

4. No residue information was provided in relation to lactating cows.

5. An HPLC analytical method with spectrofluorimetric detection was described in the ISO 78/2 format and was proposed for the determination of salicylic acid residues in cattle tissues. The limit of quantification was 50 µg/kg for fat, liver, and kidney, and 100 µg/kg for muscle. No method for the determination of residues in milk was provided.

Conclusions and recommendations

Having considered that

- basic aluminium salicylate is used orally mainly in neonatal calves for infrequent or non-regular treatments,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- after oral administration of basic aluminium salicylate to cattle, the depletion of salicylic acid from edible tissues is rapid,
- the residue intake of salicylic acid after oral administration does not represent a risk for the consumer,
- no residue information was available for bovine milk;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for basic aluminium salicylate 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
Aluminium salicylate, basic	Bovine	For oral use only. Not for use in animals from which milk is produced for human consumption.