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EMA/CVMP/562066/2007
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Sodium salicylate (turkeys)

On 12 October 2010 the European Commission adopted a Regulation¹ establishing provisional maximum residue limits for sodium salicylate in turkeys, valid throughout the European Union. These provisional maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

In turkeys, sodium salicylate is intended for use orally as an antipyretic in the treatment of acute respiratory diseases.

Sodium salicylate was previously assessed for the purpose of establishing maximum residue limits and was entered in Annex II of Regulation (EEC) No 2377/90² (no MRL required) for topical use in all food producing species except fish and for oral use in bovine and porcine species.

Chevita Tierarzneimittel GmbH submitted to the European Medicines Agency on 4 January 2007 an application for the extension of existing entry in Annex II of Regulation (EEC) No 2377/90 for sodium salicylates to turkeys.

On 12 December 2007 the Committee for Medicinal Products for Veterinary Use adopted an opinion recommending the amendment of the entry in Annex II of Regulation (EEC) No 2377/90 to include sodium salicylate for oral use in turkeys. The European Commission subsequently returned the opinion to the Committee to consider whether its opinion should be reviewed to take into account issues raised during the Commission's inter service consultation and in particular to consider whether establishment of maximum residue limits for sodium salicylate in turkeys should be established.

Based on the original and complementary data in the dossier and taking into account the requests from the European Commission, the Committee for Medicinal Products for Veterinary Use recommended the establishment of provisional maximum residue limits for sodium salicylate in turkeys. Subsequently the Commission recommended on 29 July 2010 that provisional maximum residue limits in turkeys be established. This recommendation was confirmed on 19 August 2010 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 12 October 2010.

¹ Commission Regulation (EU) No 914/2010, O.J. L269, of 13.10.2010

² Annexes to Regulation (EEC) No 2377/90 were repealed by Regulation (EC) No 37/2010, OJ L15, of 21.01.2010



Summary of the scientific discussion for the establishment of MRLs

Substance name: Sodium salicylate
Procedure number: EU/07/159/CHV
Applicant: Chevita Tierarzneimittel GmbH
Target species: Turkeys
Intended therapeutic indication: Antipyretic treatment of acute respiratory diseases
Route (s) of administration: Oral use

1. Introduction

Sodium salicylate (CAS 54-21-7) is a salicylic acid derivative. Sodium salicylate is used topically in creams, ointments and solutions for the cleaning of wounds of the skin and the teat, in cattle, horses, sheep, goats and poultry. Sodium salicylate is also used orally. The indication for calves and pigs is as an antipyretic, antiphlogistic and analgesic agent.

Salicylic acid is a common compound in plants. Methyl salicylate (an ester of the pharmacologically active salicylic acid) is widely used as a flavouring agent in numerous foods and beverages.

Prior to the current MRL application sodium salicylate was included in Annex II of Regulation (EEC) No 2377/90. With the repeal of the annexes of Regulation (EEC) No 2377/90 sodium salicylate was included in Table 1 of allowed substances of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco- logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Sodium salicylate	NOT APPLICABLE	Bovine, porcine	No MRL required	NOT APPLICABLE	For oral use. Not for use in animals from which milk is produced for human consumption	NO ENTRY
		All food producing species except fin fish	No MRL required	NOT APPLICABLE	For topical use only	

An application has subsequently been submitted for the extension of sodium salicylate for oral use to turkeys. The proposed indication is as antipyretic treatment of acute respiratory diseases in combination with an appropriate anti-infective treatment at a proposed dose regimen of 100 mg/kg w/day during 3 days divided into 2 daily doses of 50 mg/kg.

2. Scientific risk assessment

2.1. Safety assessment

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

Although no ADI was established for salicylic acid or its salts, during the assessment of acetylsalicylic acid a pharmacological ADI of 0.0083 mg acetyl salicylate/kg bw (0.5 mg acetyl salicylate/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. In order to apply this ADI to the substance under examination, i.e. sodium salicylate, a conversion on the basis of salicylate equivalents had to be made. The CVMP considered that the ADI for acetyl salicylate had to be converted to salicylic acid according to the difference in molecular weights as the residues are measured as salicylic acid. As a result the relevant ADI for sodium salicylate was recalculated to be 0.44 mg/person, which corresponds to 0.38 mg/person of salicylic acid (0.0063 mg/kg bw).

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

A pharmacokinetic study was carried out in 48 female turkeys of 6 weeks of age administered 0, 25, 50 and 100 mg/kg of sodium salicylate in drinking water by gavage. T_{max} is reported to be 2 to 4 hours indicating rapid absorption. The AUC showed a dose dependent linearity. After oral administration of the recommended dose of 50 mg/kg of sodium salicylate, C_{max} (median) was 42 µg/ml. The plasma elimination half-life was 2.3 hours and the volume of distribution was 0.6 l/kg. Salicylic acid clearance was 3.1 ml/min/kg and the mean residence time was 5 hours. Bioavailability has not been determined.

2.2.2. Residue depletion studies

Twenty-four male turkeys of 6 weeks of age were administered sodium salicylate in water by gavage, at a dose of 50 mg/kg bw twice daily for 3 consecutive days. The animals were sacrificed 12 hours, 24 hours and 96 hours after the end of treatment. One of the animals slaughtered at 12 hours was considered as an outlier. The salicylic acid concentrations in tissues (muscle, liver, kidney, fat and skin) were determined by an HPLC analytical method. Skin+fat was the target tissue. At 12 hours, the mean values were high in all edible tissues: 2420 ± 1550 µg/kg in muscle, 3230 ± 2430 µg/kg in liver, 9230 ± 8770 µg/kg in kidney and 9010 ± 7000 µg/kg in skin+fat. Residue values dropped dramatically from 12 hours to 24 hours by factors of 6, 19, 72 and 4 respectively in muscle, liver, kidney and skin+fat. The mean values were 390 ± 160 µg/kg in muscle, 170 ± 30 µg/kg in liver, 130 ± 40 µg/kg in kidney and 2310 ± 890 µg/kg in skin+fat. At 96 hours, the mean values were 470 ± 170 µg/kg in muscle, 200 ± 80 µg/kg in liver, 300 ± 50 µg/kg in kidney and 1320 ± 710 µg/kg in skin+fat.

No residue data were provided in relation to eggs.

Selection of marker residue and target tissues

No radiolabelled studies are available, the pharmacokinetic data available for turkeys demonstrate that no metabolites other than salicylic acid were detected in plasma. Similarly, information available for chickens demonstrates that salicylic acid is the main metabolite in plasma and excreta. Consequently, salicylic acid could be accepted as marker residue for sodium salicylate in turkeys. The ratio of marker to

total residues would be assumed to be 1 when comparing residue levels to the ADI recalculated for salicylic acid.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report are available.

2.2.4. Analytical method for monitoring of residues

An HPLC analytical method for the determination of residues of salicylic acid in tissues of turkey is available with limits of quantification of 50 µg/kg for fat, 100 µg/kg for muscle, liver and kidney and 150 µg/kg for skin. However, the method is not validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union taking also into account the Guideline on safety and residues data requirements for veterinary medicinal products intended for Minor Uses or Minor Species (EMA/CVMP/SWP/66781/2005) with regard to accuracy (for muscle, liver and kidney, the accuracy results are below the lower limit at 500 µg/kg fortification), susceptibility to interference and stability (regarding liver and kidney).

2.2.5. Findings of EU or international scientific bodies

No MRLs for sodium salicylate have been established by the Codex Alimentarius.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

No data were provided but as microbiological effects are not expected for this type of substance this was considered acceptable.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No data were provided but none were expected from this type of substance.

3.3. Elaboration of MRLs

Based on residue data at 24 hours, MRL values of 400 µg/kg for muscle, 2500 µg/kg for skin+fat, 200 µg/kg for liver and 150 µg/kg for kidney can be recommended.

Calculation of theoretical daily intake of residues

From the data available, it was calculated that the intake of total residues of salicylic acid from edible tissues at 12, 24 and 96 hours after the end of treatment would be 2.32, 0.34 and 0.27 mg/person, respectively. The pharmacological ADI considered relevant for sodium salicylate being 0.0063 mg/kg bw (0.38 mg/person) expressed as salicylic acid, the residues would represent approximately 513%, 90% and 69% of the ADI at 12 hours, 24 hours and 96 hours, respectively.

Edible tissue or products (poultry)	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product
Muscle	0.30	400	1	120
Fat	0.09 [#]	2500	1	225
Liver	0.10	200	1	20
Kidney	0.01	150	1	1.5

fat and skin in natural proportion

Based on the recommended MRLs, the theoretical maximum daily intake of residues of turkeys represents 96% of the ADI (380 µg/person).

3.4. Considerations on possible extrapolation of MRLs

No residue data has been provided for the major species chicken. For this reason, a recommendation to extend the entry to poultry cannot be made.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- a pharmacological ADI of 0.0083 mg/kg bw, i.e. 0.5 mg/person established for acetylsalicylic acid was previously considered relevant for sodium salicylate. However, in order to take into account the difference in molecular weights considering that residues are measured as salicylic acid the ADI was recalculated to be equivalent to 0.38 mg/person of salicylic acid,
- salicylic acid was retained as the marker residue,
- the marker to total residues ratio was assumed to be 1,
- an analytical method for monitoring of residues is available for monitoring salicylic acid in turkey tissues, but has not been validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union,
- no residue information was provided in relation to eggs;

the Committee for Medicinal Products for Veterinary Use recommends the establishment of provisional maximum residue limits for sodium salicylate, in accordance with the following table:

Pharmaco- logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Sodium salicylate	Salicylic acid	Turkey	400 µg/kg 2500 µg/kg 200 µg/kg 150 µg/kg	Muscle Skin+fat Liver Kidney	Not for use in animals producing eggs for human consumption Provisional maximum residue limits expire on 1 January 2015	Anti- inflammatory agents/Non- steroidal anti- inflammatory agents

4. List of questions

1. The applicant should provide the analytical method validated according to Volume 8 and the Guideline on safety and residues data requirements for veterinary medicinal products intended for minor uses or minor species (EMA/CVMP/SWP/66781/2005) particularly in relation to:
 - accuracy (for muscle, liver and kidney, at a level appropriate for the MRL)
 - susceptibility to interference
 - stability regarding liver and kidney

5. Background information on the procedure

Submission of the dossier

Steps taken for assessment of the substance

Application validated:	18 January 2007
Clock started:	19 January 2007
List of questions adopted:	18 April 2007
Consolidated response to list of questions submitted:	13 November 2007
Clock re-started:	14 November 2007
CVMP opinion adopted:	12 December 2007
Request from Commission for reconsideration	31 March 2008
CVMP revised opinion adopted	13 May 2008
Further request from Commission for reconsideration	3 November 2009
CVMP opinion adopted:	13 January 2010