EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 January 2013
EMA/CVMP/71291/2012
Committee for Medicinal Products for Veterinary Use (CVMP)

European public MRL assessment report (EPMAR)

Sodium salicylate (turkeys)

On 12 December 2012 the European Commission adopted a Regulation[1] establishing maximum residue limits for sodium salicylate in turkeys, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Maximum residue limits had previously been established for sodium salicylate in cattle and pigs for oral use only and for all food producing species except fin fish for topical use only. For turkeys provisional maximum residue limits had been established[2] with an expiry date of 1 January 2015.

On 4 January 2007 Chevita Tierarzneimittel GmbH submitted the application to the European Medicines Agency for the extension of maximum residue limits to turkeys. Further to the establishment of provisional MRLs in October 2010, additional data on the validation of the analytical method proposed for the monitoring of residues in turkey was submitted on 11 November 2011, in order to allow the establishment of final maximum residue limits.

Sodium salicylate is intended for use in turkeys for antipyretic treatment of acute respiratory diseases in combination with an appropriate anti-infective treatment at a proposed dose regimen of 100 mg/kg bw/day over 3 days divided into 2 daily doses of 50 mg/kg. In other food producing species sodium salicylate is used topically for cleaning of wounds of the skin. Orally it is used as an antipyretic, antiphlogistic and analgetic agent.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 9 February 2012 the establishment of maximum residue limits for sodium salicylate in turkeys.

Subsequently the Commission recommended on 25 October 2012 that maximum residue limits in turkeys are established. This recommendation was confirmed on 15 November 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 12 December 2012.

[1] Commission Implementing Regulation (EU) No 1191/2012, O.J. L 340/35, of 13.12.2012

[2] Commission Regulation (EU) No 914/2010, O.J. L 269/5, of 13.10.2010

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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 teats, 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. In turkey the indication is antipyretic treatment of acute respiratory diseases in combination with an appropriate anti-infective treatment at a proposed dose regimen of 100 mg/kg bw/day over 3 days divided into 2 daily doses of 50 mg/kg.

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.

Sodium salicylate is included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 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	
	Salicylic acid	Turkey	400 µg/kg 2500 µg/kg 200 µg/kg 150 µg/kg	Muscle Skin and fat Liver Kidney	Not for use in animals producing eggs for human consumption Provisional maximum residue limits shall expire on 1 January 2015	Anti-inflammatory agents/Non-steroidal anti-inflammatory agents

Further to the establishment of provisional MRLs in October 2010, the applicant submitted on 11 November 2011 additional data on the validation of the analytical method proposed for the monitoring of residues in turkey, in order to allow the establishment of final maximum residue limits.

2. Scientific risk assessment

2.1. Safety assessment

Sodium salicylate was 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 sodium salicylate, a conversion on the basis of salicylate equivalents was made. This conversion of the ADI for acetyl salicylate was made 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, skin and fat) were determined by an HPLC analytical method. Skin and 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 and fat. Residue values dropped dramatically from 12 hours to 24 hours by factors of 6, 19, 72 and 4 in muscle, liver, kidney and skin and fat, respectively. 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 and 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 and 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 maker residue for sodium salicylate in turkeys. The ratio of maker 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 with fluorescence detection after liquid-liquid extraction for the determination of residues of salicylic acid in tissues of turkey is available. The limits of quantification are 100 µg/kg for muscle, 50 µg/kg for liver, 37.5 µg/kg for kidney and 625 µg/kg for skin and fat. The method is validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union and the Guideline on safety and residues data requirements for veterinary medicinal products intended for Minor Uses or Minor Species (EMEA/CVMP/SWP/66781/2005).

The analytical method has been reviewed by the relevant European Reference Laboratory, which confirmed the suitability of the method for monitoring of residues and its validation according to Volume 8 of the Rules Governing Medicinal Products in the European Union and the Guideline on safety and residues data requirements for veterinary medicinal products intended for Minor Uses or Minor Species.

2.2.5. Findings of EU or international scientific bodies

No evaluations by Codex Alimentarius or other international committees were available.

3. Risk management considerations

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

Microbiological effects are not expected for this type of substance and therefore no data were required.

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

None.

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 and 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.

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
Skin and Fat*	0.09	2500	1	225
Liver	0.10	200	1	20
Kidney	0.01	150	1	1.5
Estimated daily intake (µg/person)				366.5
Proposed ADI (µg/person)				380 96% of ADI

* Refers to skin and fat in natural proportions

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits established for sodium salicylate based on data in turkeys to

other food producing species and food commodities. A “no MRL required” status has been established for topical use of sodium salicylates in all food producing species. In addition a “no MRL required” status has been established for oral use in bovine and porcine species.

No residue data other than those provided in support of the the application to establish the MRLs described above and those related to turkey tissues have been provided. In the absence of these data a marker residue could not be identified in additional species’ tissues or commodities and no marker to total ratio could be determined. In addition no validated analytical methods for monitoring of residues in additional species’ tissues or commodities were available for evaluation. Consequently, a recommendation to extrapolate the recommended MRLs for turkey to other animal species could not 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 is considered relevant for sodium salicylate. However, in order to take account of the difference in molecular weights and taking account of the fact 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;
- a validated analytical method for monitoring of residues is available for monitoring salicylic acid in turkey tissues;
- no residue information was provided in relation to eggs;

The Committee for Medicinal Products for Veterinary Use recommends the establishment of maximum residue limits for sodium salicylate in turkeys and the amendment of table 1 of the Annex to Commission Regulation (EU) No 37/2010, as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Sodium salicylate	Salicylic acid	Turkeys	400 µg/kg 2500 µg/kg 200 µg/kg 150 µg/kg	Muscle Skin and fat* Liver Kidney	Not for use in animals producing eggs for human consumption	Anti-inflammatory agents/Non steroidal anti-inflammatory agents

* Refers to skin and fat in natural proportions

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

4. 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
Revised CVMP opinion on provisional MRLs adopted:	13 January 2010
Submission of responses to the list of questions:	11 November 2011
CVMP opinion after provisional MRLs adopted:	9 February 2012