16 September 2015
EMA/CVMP/587362/2014
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Aluminium salicylate, basic (bovine, caprine, *Equidae* and rabbit)

On 29 July 2015 the European Commission adopted a Regulation[1] establishing provisional maximum residue limits for aluminium salicylate, basic in milk of bovine, caprine and equine species, valid throughout the European Union. The same Regulation amends the maximum residue limits already established (no MRL required classification) for tissues in bovine, caprine, equine and rabbit species. The maximum residue limits established were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Aluminium salicylate, basic is intended for the treatment of diarrhoea when administered orally and for the cleaning of wounds of the skin and the teat when administered topically.

Aluminium salicylate had maximum residue limits previously established (no MRL required classification) in all food producing species except fin fish following topical use[2] and in bovine species, except animals producing milk for human consumption, following oral use[3].

COOPHAVET submitted to the European Medicines Agency an application for the modification of maximum residue limits for aluminium salicylate in bovine species in order to include animals producing milk for human consumption, on 30 January 2013.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 9 October 2014, the modification of the maximum residue limits previously established for aluminium salicylate (no MRL required classification) in bovine species and the establishment of provisional MRLs.

Subsequently the Commission recommended on 10 June 2015, the modification of the existing maximum residues limits and the establishment of provisional maximum residue limits in bovine, caprine, *Equidae* and rabbit. This recommendation was confirmed on 1 July 2015 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 29 July 2015.

[1] Commission Implementing Regulation (EU) No 2015/1308, O.J. L200, of 29 July 2015
[2] Commission Regulation (EC) No 1286/2000, O.J. L 145, of 19 June 2000
[3] Commission Regulation (EC) No 1937/2002, O.J. L 297, of 30 October 2002

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Aluminium salicylate, basic
Therapeutic class:	Antidiarrhoeal and intestinal anti-inflammatory agents
Procedure number:	EMEA/V/MRL/003298/MODF/0004
Applicant:	COOPHAVET
Target species:	Bovine
Intended therapeutic indication:	Symptomatic treatment of diarrhoea
Route(s) of administration:	Oral

1. Introduction

Aluminium salicylate, basic belongs to the salicylic acid group of substances. The substance is administered orally in the treatment of diarrhoea in neo-natal calves in combination with other active ingredients at doses of up to 10 g of basic aluminium salicylate per 50 kg of bodyweight twice daily for 3 to 5 consecutive days.

Basic aluminium salicylate was previously evaluated by the Committee for Medicinal Products for Veterinary Use (CVMP) (see EMEA/MRL/696/99-FINAL and EMA/MRL/796/01-FINAL). The CVMP's original evaluation led to the establishment of maximum residue limits for topical use only and did not establish an ADI for the substance. In a subsequent evaluation, focused on extending the use of the substance to include oral use in bovine species, the CVMP considered that, as only salicylic acid is absorbed, the ADI of 0.0083 mg/kg bw (0.5 mg/person) established for acetylsalicylic acid could be used as a starting point from which to calculate an ADI for basic aluminium salicylate.

Currently, aluminium salicylate, basic is included in 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
Aluminium salicylate, basic	NOT APPLICABLE	Bovine	No MRL required	NOT APPLICABLE	For oral use only. 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.	

COOPHAVET submitted an application for the modification of maximum residue limits for aluminium salicylate, basic in bovine species, to the European Medicines Agency, on 30 January 2013 in order to modify the existing classification to allow oral use of the substance in cows producing milk for human consumption.

The intended use in adult cattle including dairy cows is the symptomatic treatment of diarrhoea at doses of 9 g per animal two or three times per day for 3 consecutive days.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP previously assessed the consumer safety of aluminium salicylate, basic and considered that the pharmacological ADI of 0.0083 mg/kg bw established for acetylsalicylic acid could be used as a starting point from which to calculate an ADI for basic aluminium salicylate, since for both substances only salicylic acid is absorbed. The pharmacological ADI for acetylsalicylic acid was established based on the LOEL of 0.167 mg/kg bw day for bleeding time and thromboxane B-2 production observed in humans using a safety factor of 20 to take into account the fact that a LOEL instead of a NOEL was used to derive the ADI[4].

In order to apply this ADI to basic aluminum salicylate, a conversion on the basis of salicylate equivalents has been made according to the difference in molecular weights as the residues are measured as salicylic acid (the molecular weights are 198.11 for aluminum salicylate, basic, 180.2 for acetylsalicylic acid and 138.1 for salicylic acid). As a result the ADI for basic aluminium salicylate is calculated to be 0.55 mg/person (0.0091 mg/kg bw), which corresponds to 0.38 mg/person of salicylic acid (0.0063 mg/kg bw).

No further assessment regarding the consumer safety of the substance is required for the purpose of this modification application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

The following study in calves was reviewed as part of the evaluation of the application to extend the maximum residue limit status for aluminium salicylate to include oral use. After oral administration of 139 mg salicylic acid in calves as aluminium salicylate, basic, the half-life of salicylic acid was estimated to be at least 4.6 hours. Absorption rate during one treatment interval (12 hours) was variable, with bioavailability of 4.2 to 34.9%. However, as 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 bioavailability could be reached. After 12 hours, i.e. the last sampling point, blood concentrations reached a maximum of 13.7 to 85.3 µg/ml.

[4] Summary Report for acetylsalicylic acid, sodium acetylsalicylate, acetylsalicylic acid DL-lysine and carbasalate calcium (EMEA/MRL/695/99-FINAL)

2.2.2. Residue depletion studies

The following study in calves was reviewed as part of the evaluation of the application to extend the maximum residue limit status for aluminium salicylate to include oral use. Eight calves (4 males, 4 females), weighing a mean of 53 kg, were administered aluminium salicylate, basic according to the recommended therapeutic regimen for calves, i.e. 400 mg aluminium salicylate, basic per kg bw/day for 5 consecutive days, as twice-daily treatments. The animals were sacrificed 24 hours or 3 days after the end of treatment. Salicylic acid concentrations in tissues were determined by HPLC with spectrofluorimetric detection and limits of quantification of 100 µg/kg in muscle and 50 µg/kg in liver, kidney and fat. Mean salicylic acid concentrations 24 hours after administration were 871 µg/kg in muscle, 1886 µg/kg in liver, 6702 µg/kg in kidney and 1289 µg/kg in fat. Concentrations three days after dosing 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 slower elimination from liver than from other tissues.

A new depletion study using adult dairy cows to collect data in milk was provided. In this GLP study, the highest recommended therapeutic dose in adult cattle, corresponding to 9 g aluminium salicylate, basic per animal was administered three times daily, for 3 consecutive days by the oral route to 10 Holstein Frisian cows. This dose corresponds to approximately 43.5 mg salicylic acid equivalent/kg bw/day. Salicylic acid residues in milk were determined by HPLC MS/MS from before the last administration (i.e. during the treatment period) up to 48 hours after the last administration (including 12 hours, 24 hours, 36 hours and 48 hours after the last treatment). The study included 5 low yield milk cows (less than 10.5 kg milk per day) and 5 high yield cows (more than 10.5 kg milk per day). All salicylic acid concentrations except one (178 µg/kg, during treatment) were below 110 µg/kg. Mean concentrations were 89 µg/kg one hour before the last administration, and then depleted to 34, 14, 5 and 5 µg/kg at 12, 24, 36 and 48 hours after last administration respectively.

Selection of marker residue and ratio of marker to total residues

No radiolabelled studies in bovine milk or bovine tissues were available. However salicylic acid has been identified in bovine milk and bovine tissues and is considered suitable for use as the marker residue.

For the purpose of calculating consumer intake of residues the ratio of marker residue to total residues can be considered to be 1 as long as the estimated intake is compared with the ADI for salicylic acid. This is appropriate as only salicylic acid is absorbed following oral administration of aluminium salicylate, basic.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described in other sections of this report were available.

2.2.4. Analytical method for monitoring of residues

An analytical method for the determination of salicylic acid residues in bovine tissues was provided as part of the application to extend the maximum residue limit status for aluminium salicylate to include oral use in bovine species. An HPLC method with spectrofluorimetric detection was described in the ISO 78/2 format. The limit of quantification was 50 µg/kg for fat, liver and kidney, and 100 µg/kg for muscle. However, no further validation of this method was provided.

A new LC/MS/MS method has now been provided for monitoring of residues in bovine tissues. The method has been validated in accordance with the requirements of Volume 8 of The rules governing medicinal

products in the European Union over a range of 50 to 500 µg/kg for all tissues. This range does not include the required upper limit of twice the maximum residue limit.

An LC/MS/MS method for monitoring of residues of salicylic acid in milk has been provided. The method is well described but is not fully validated according to the requirements of Volume 8 of the Rules Governing Veterinary Medicinal Products in the European Union. Deficiencies have been identified with regard to specificity and claimed limit of quantification of 4 µg/kg.

The relevant European Reference Laboratory has reviewed the proposed analytical methods and is in agreement with the evaluation summarised above.

2.2.5. Findings of EU or other international scientific bodies

No relevant report relating to residue of aluminium salicylate, basic in bovine species were identified.

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

Aluminium salicylate, basic has been used orally as an antidiarrhoeal agent and topically as an antiseptic/anti-inflammatory agent.

Aluminium salicylate, basic in bovine species is currently included in Regulation (EU) No 37/2010 with a "No MRL required" classification with regard to oral use in bovine species. During its previous assessment of the substance and in particular in relation to the intended use in calves, the CVMP took the following points into consideration:

- aluminium salicylate, basic is used mainly in neonatal calves for infrequent or non-regular treatments
- the animals are unlikely to be sent for slaughter immediately after treatment.

As the substance is now proposed for use in adult animals the points above are no longer valid and further consideration on the need for limits in bovine tissues and milk is required. From data in calves the intake of salicylic acid residues in edible tissues 24 hours after the end of treatment would be 850 µg (223% of the ADI for salicylic acid). If the highest mean salicylic acid residue values determined in milk (89 µg/kg) are also considered, total intake of salicylic acid would be 983 µg, representing 258% of the ADI for salicylic acid. The intake from tissues three days after treatment (180 µg) combined with intake from milk produced during treatment would account for 82% (313 µg) of the ADI for salicylic acid.

As the theoretical maximum daily intake (TMDI) from tissues and milk would considerably exceed the ADI at 24 hours after treatment, maintaining the classification of "No MRL required" for the oral use of the substance in bovine species (tissues and milk) is not appropriate and consequently numerical MRLs are recommended.

If numerical MRLs are to be established in relation to oral use in bovine species, a “No MRL required” status cannot be maintained in relation to topical administration in this species as this could lead to confusion at a residue monitoring level (residue monitoring authorities would not be able to distinguish between residues arising from oral use and residues arising from topical use). The MRL category for bovine species must therefore be independent of the route of administration, which means that the proposed numerical MRLs for oral use must also apply to topical use. It follows that, in principle, withdrawal periods could be needed for existing topically applied products. However, in its original MRL evaluation for aluminium salicylate the Committee considered that withdrawal periods were not required for topical products (as a “No MRL required” classification was recommended). This remains the position of the Committee – while numerical MRLs are recommended for both oral and topical use, it is considered that for topically applied products a withdrawal period will not be necessary in order to ensure consumer safety.

When reflecting on possible numerical maximum residue limits, consideration should be given to the fact that numerical MRLs have been established for sodium salicylate in turkeys and that, consequently, consumers may be exposed to salicylic acid as a result of ingestion of turkey meat. Exposure to total salicylic acid residues from meat (whether bovine or poultry) and milk must not exceed the ADI.

Finally, and of relevance for residue control, compliance with the proposed MRLs for aluminium salicylate, basic would ensure the safety of the consumer, since the measured salicylic acid would be the total amount of the substance derived from all potential sources of exposure of the animal. However, it is noted that a range of salicylic acid yielding active substances are approved for use in bovine species and that these currently have a “No MRL required” status. Detection of salicylic acid residues will provide no information on whether residues are the result of use of a veterinary medicinal product containing aluminium salicylate, basic or a veterinary medicinal product containing an alternative salicylate for which a “No MRL required” status applies.

No additional relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

The following maximum residue limits in bovine tissues are recommended based on the depletion profile seen in calves administered basic aluminium salicylate at the maximum recommended dose:

Muscle: 200 µg/kg
Fat: 500 µg/kg
Liver: 1500 µg/kg
Kidney: 1500 µg/kg

For milk, based on the depletion profile of salicylic acid in milk and on the limit of quantification of 4 µg/kg, an MRL can be set at 9 µg/kg.

Detailed calculation of theoretical daily intake of residues

Intake of residues (salicylic acid) from consumption of tissues and milk from bovine animals treated with aluminium salicylate:

Edible tissue or products *(bovine)*	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product (µg)**
Muscle	0.30	200	1	60

Edible tissue or products *(bovine)*	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product (µg)**
Fat	0.05	500	1	25
Liver	0.10	1500	1	150
Kidney	0.05	1500	1	75
Milk	1.50	9	1	13.5
Total				323.5

Based on the above figures the maximum theoretical intake of residues from bovine tissues and milk would represent 85% of the ADI for salicylic acid.

Intake of residues (salicylic acid) from consumption of turkey tissues from animals treated with sodium salicylate and bovine milk from animals treated with aluminium salicylate:

Edible tissue or products *(turkey meat and bovine milk)*	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product (µg)**
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
Milk	1.50	9	1	13.5
Total				380

Based on the above figures the maximum theoretical intake of residues from turkey tissues and bovine milk would represent 100% of the ADI for salicylic acid. The CVMP considered whether the MRL for milk should be reduced to a lower level in order to accommodate possible future uses of the substance, for example in egg producing animals. However, while residue depletion data in milk beyond 48 hours after the last dose were not available, it was considered that the discarding of milk beyond this timepoint could not be justified on the basis of a hypothetical application for oral use of the substance in egg producing or honey producing animals. In addition, there is not considered to be a particular need for orally administered aluminium salicylate in egg laying poultry or in honey bees and consequently there is not a need to maintain an unused portion of the ADI to allow development of aluminium salicylate containing products for treatment of these groups of animals. Reducing the tissue MRLs for sodium salicylate is not possible as part of the current procedure.

It was also noted that as the regulatory analytical method must be validated at levels down to half the MRL, the establishment of a maximum residue limit for milk at a level below 8 µg/kg would require further analytical method validation.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009 the CVMP considered the possibility of extrapolating its recommendation on maximum residue limits for aluminium salicylate basic on the basis of residue data in cattle to other food producing species and commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	**Extrapolation possible (Yes/No)**	**Justification**
Sheep (including milk)	No	While no specific pharmacokinetic or residue data were available for sheep, based on experience with other salicylates in other species it could be assumed that salicylic acid would be a suitable marker residue in sheep tissues and milk. However since sheep meat is consumed on a regular basis and in large quantities species specific data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in sheep tissues. No data are available to demonstrate that the analytical methods for monitoring of residues are applicable for monitoring of residues in sheep tissues or milk but there is no reason for believing that they would not be.
Goats (including milk)	Yes	While no specific pharmacokinetic or residue data were available for goats, based on experience with other salicylates in other species it could be assumed that salicylic acid would be a suitable marker residue in goat tissues and milk. No data are available to demonstrate that the analytical methods for monitoring of residues are applicable for monitoring of residues in goats tissues or milk but there is no reason for believing that they would not be.
Poultry (including eggs)	No	While no specific pharmacokinetic or residue data were available for poultry tissues, based on experience with other salicylates in other species including chickens and turkeys it could be assumed that salicylic acid would be a suitable marker residue in poultry. However since poultry is consumed on a regular basis and in large quantities, species specific data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in poultry commodities. No analytical method for monitoring of residues in poultry tissues or eggs was available for evaluation.

Horses (including milk)	Yes	While no specific pharmacokinetic or residue data were available for horses, based on experience with other salicylates in other species it could be assumed that salicylic acid would be a suitable marker residue in horse tissues and milk. No data are available to demonstrate that the analytical methods used for monitoring of residues in cattle are applicable for monitoring of residues in horse tissues or milk but there is no reason for believing that they would not be.
Rabbits	Yes	While no specific pharmacokinetic or residue data were available for rabbits, based on experience with other salicylates in other species it could be assumed that salicylic acid would be a suitable marker residue in rabbit tissues. No data are available to demonstrate that the analytical method used for monitoring of residues in cattle tissues is applicable for monitoring of residues in rabbit tissues but there is no reason for believing that it would not be.
Fin fish	No	Metabolism can be significantly different in fish compared to cattle. As the marker residue in bovine tissues is not the parent compound, residue data in fish would be required. No analytical method for monitoring of residues in fish meat was available for evaluation.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food commodities cannot be extrapolated to honey. Moreover the parent compound is not the marker residue. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey. No analytical method for monitoring of residues in honey was available for evaluation.

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

Whereas:

- the pharmacological ADI for aluminium salicylate, basic of 0.55 mg/person (0.0091 mg/kg bw) was established as the overall ADI, and corresponds to 0.38 mg/person of salicylic acid (0.0063 mg/kg bw),
- the ADI would be exceeded at 24 hours when considering the total intake of residues from milk and tissue and consequently a “No MRL required” classification is no longer considered appropriate,
- salicylic acid was retained as the marker residue in bovine tissues and milk,

- the ratio of marker to total residues in tissues and milk was considered to be 1 as only salicylic acid is absorbed following oral administration of basic aluminium salicylate and as the intake of residues was compared to the ADI for salicylic acid,
- for the establishment of MRLs in milk, consumer exposure to salicylic acid resulting from ingestion of turkey tissues from animals treated with sodium salicylate should be considered,
- extrapolation of the provisional maximum residue limits recommended for bovine species to goats, horses and rabbits is considered appropriate,

and having considered that:

- an analytical method for monitoring of residues of salicylic acid in bovine tissues is available but has not been validated over the full range of concentrations required by Volume 8 of The rules governing medicinal products in the European Union,
- an analytical method for monitoring of residues of salicylic acid in bovine milk is available but some further data are required before it can be considered to fully comply with the requirements of Volume 8 of The rules governing medicinal products in the European union,

the CVMP recommends the modification of the maximum residue limit classification for aluminium salicylate, basic with the establishment of provisional maximum residue limits in bovine species, caprine species, *Equidae* and rabbits, in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Aluminium salicylate, basic	Salicylic acid	Bovine, caprine, *Equidae*, rabbit	200 µg/kg 500 µg/kg 1500 µg/kg 1500 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 31 December 2016.	Antidiarrhoeal and intestinal anti-inflammatory agents
		Bovine, caprine, *Equidae*	9 µg/kg	Milk		
	NOT APPLICABLE	All food producing species except bovine, caprine, *Equidae*, rabbit and fin fish	No MRL required	NOT APPLICABLE	For topical use only.	

Based on these recommended MRLs, the total theoretical maximum daily intake (TMDI) of residues from bovine tissues and milk from bovine animals treated with aluminium salicylate would be 323.5 µg salicylic acid which accounts for 85% of the ADI of 380 µg for salicylic acid.

Taking into account the MRLs established for sodium salicylate in turkeys, the theoretical maximum daily intake of residues from turkey tissues and bovine milk would account for 100% of the ADI of 380 µg for salicylic acid.

4. List of questions

1. A fully validated analytical method for monitoring of residues in bovine tissues should be provided. For the LC-MS/MS method this means that data should be provided to demonstrate the validity of the method at half the MRL value, the MRL and twice the MRL.
2. In relation to the analytical method proposed for monitoring of residues in milk, in relation to susceptibility to interference, it is unclear whether NSAIDs were injected simultaneously with salicylic acid or separately. If the results have been presented separately, then an interference of salicylic acid with commonly used NSAIDs cannot be excluded because salicylic acid and the NSAID mix were analysed separately from each other. Co-eluting NSAIDs could suppress the signal intensity of salicylic acid leading to an underestimation. Evidence is required to demonstrate that there is no interference between salicylic acid and NSAIDs.
3. Also in relation to the analytical method proposed for monitoring of residues in milk, the limit of quantification determined is questionable; the area for blank milk samples was 8,000 to 14,000 (units not specified) at the retention time for salicylic acid while the area for 5 µg/kg salicylic acid in milk is 19,000 to 21,000. Data should be provided to demonstrate that the claimed limit of quantification of 4 µg/kg can be quantified reliably.

5. Background information on the procedure

Submission of the dossier:	30 January 2013
Steps taken for assessment of the substance	
Application validated:	13 February 2013
Clock started:	14 February 2013
List of questions adopted:	13 June 2013
Consolidated response to list of questions submitted:	10 July 2014
Clock re-started:	14 July 2014
CVMP opinion adopted:	9 October 2014