

8 September 2015
EMA/CVMP/380628/2014
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Tylvalosin (eggs)

On 3 September 2015 the European Commission adopted a Regulation¹ establishing maximum residue limits for tylvalosin in eggs, 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.

Tylvalosin is intended for use in laying hens for the treatment of mycoplasmosis.

Tylvalosin had maximum residue limits already established² for porcine and poultry species. Eco Animal Health Ltd submitted to the European Medicines Agency an application for the extension of maximum residue limits for tylvalosin to eggs, on 30 October 2013.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 6 November 2014 the extension of maximum residue limits for tylvalosin to eggs.

Subsequently the Commission recommended on 16 July 2015 that maximum residue limits in eggs are established. This recommendation was confirmed on 6 August 2015 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 3 September 2015.

¹ Commission Implementing Regulation (EU) No 2015/1492, O.J. L 231, of 03 September 2015

² Commission Regulation (EC) No 1286/2000, O.J. L 145, of 19 June 2000

Commission Regulation (EC) No 77/2002, O.J. L 16, of 17 January 2002

Commission Regulation (EC) No 75/2005, O.J. L 15, of 18 January 2005

Commission Regulation (EC) No 1518/2005, O.J. L 244, of 19 September 2005

Commission Regulation (EC) No 1353/2007, O.J. L 303, of 20 November 2007



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Tylvalosin
Therapeutic class:	Anti-infectious agents / Antibiotics
Procedure number:	EMEA/V/MRL/003044/EXTN/0005
Applicant:	Eco Animal Health Ltd
Target species:	Poultry (eggs)
Intended therapeutic indication:	Treatment of mycoplasmosis
Route(s) of administration:	Oral

1. Introduction

Tylvalosin (INN), formerly known as acetylisovaleryltylosin, used as the tartrate salt, is a macrolide antibiotic which is active against Gram-positive bacteria. Tylvalosin has a similar chemical structure to tylosin. The substance is manufactured from tylosin by a bioconversion process. The drug substance contains at least 80% tylvalosin and also contains some impurities derived from substances present in the starting material.

Tylvalosin is used orally in pigs in the prevention and treatment of swine enzootic pneumonia, treatment of porcine proliferative enteropathy (ileitis) and swine dysentery. Tylvalosin is also used in chickens for the treatment of mycoplasmosis and in turkeys for the treatment of disease due to *Ornithobacterium rhinotracheale*.

Tylvalosin was previously assessed by the CVMP and an ADI of 2.07 µg/kg bw (124.2 µg/person) established.

Currently, tylvalosin 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
Tylvalosin	Sum of tylvalosin and 3-O-acetyltylosin	Porcine	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Skin and fat Liver Kidney	NO ENTRY	Anti-infectious agents/ Antibiotics
		Poultry	50 µg/kg 50 µg/kg	Skin and fat Liver	Not for use in animals from which eggs are produced for human consumption.	

Eco Animal Health Ltd submitted an application for the extension of maximum residue limits to chicken eggs to the European Medicines Agency on 30 October 2013.

In laying hens, tylvalosin is intended for use in the treatment of mycoplasmosis, administered orally at the dose of 30 mg/kg bw for 7 days. Daily dosing should be split in two equal doses administered six hours apart.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP previously assessed the consumer safety of tylvalosin and established a microbiological ADI of 2.07 µg/kg bw, i.e. 124.2 µg/person, as the overall ADI based on potential effects on the gastrointestinal colonisation barrier.

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

2.2. Residues assessment

Pharmacokinetic and residue depletion data for tylvalosin in chickens and turkeys were previously submitted and reviewed by the CVMP as part of the Committee's evaluation for the establishment of MRLs for edible meat products from poultry (EMEA/CVMP/77339/2005-FINAL).

2.2.1. Pharmacokinetics in target species

A metabolite analysis in chicken eggs was performed as part of the residues depletion study described below (section 2.2.2). In the study, hens were dosed by oral gavage with two doses of 15 mg/kg bw (30 mg/kg bw daily) of radiolabeled tylvalosin for 7 days. Total radioactivity in whole egg increased throughout the dosing period starting at a mean concentration of 26 µg equivalents/kg on Day 1 and reaching a maximum mean concentration of 402 µg equivalents/kg on Day 7. However, as soon as treatment ceased, residues began to deplete rapidly. As well as the parent compound the following three major metabolites were identified: 3-O-acetyltylosin (M2) (7%), the cysteine conjugate of 3-O-acetyltylosin (M1) (14%) and the cysteine conjugate of tylvalosin (M4) (31%).

2.2.2. Residue depletion studies

A GLP compliant residues depletion study in eggs of chickens treated with the recommended daily dose of 30 mg radiolabeled tylvalosin/kg bw for 7 consecutive days was conducted. Fifteen eggs were collected daily for the seven days of treatment, and for several days after treatment was withdrawn. The total radioactivity found in egg homogenate samples was shown to rise for the first seven days (during treatment), reaching a peak value of 400 µg equivalents/kg after 7 days (last day of treatment) and then declining at a uniform rate over the subsequent 9 days following withdrawal of treatment. The mean total residue values were 34, 119, 176, 247, 303, 347 and 402 µg equivalent/kg after 1, 2, 3, 4, 5, 6 and 7 days respectively. The mean total residue levels following termination of treatment were 363, 279, 197, 136, 80, 35 µg equivalent/kg and below the limit of detection at 8, 9, 10, 11, 12, 13 and 14 days, respectively.

No data on residues depletion of tylvalosin in eggs from other poultry species than chicken were provided.

Selection of marker residue and ratio of marker to total residues

The major residues found in eggs on day seven of treatment were the parent molecule, tylvalosin, along with three other major metabolites. The proportion of tylvalosin residues in eggs at day 7 was 33%. The parent compound is considered to be an appropriate marker residue for residues monitoring. Based on data at day 7 the marker to total residues ratio is set at 0.33.

2.2.3. Monitoring or exposure data

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

2.2.4. Analytical method for monitoring of residues

A LC-MS/MS analytical method for the detection and quantification of tylvalosin residues in eggs was provided. The eggs to be analysed are individually homogenised and then subjected to liquid extraction and liquid-liquid partitioning, before the final extract is analysed using LC-MS/MS.

Validation data have been presented covering the concentration range 100 µg/kg to 400 µg/kg. The range validated represented 0.5 to 2 x the proposed MRL.

The validation studies were GLP compliant and designed to fulfil the requirements in Notice to Applicants and Guideline (Volume 8): Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin. The method has been presented in an internationally recognised standard layout.

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

2.2.5. Findings of EU or international scientific bodies

No relevant reports relating to residues of tylvalosin in eggs were identified.

3. Risk management considerations

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

The substance is not intended for use in dairy cattle and therefore potential effects in dairy products were not investigated.

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

Availability of veterinary medicines for laying hens is very limited. The lack of veterinary medicines for this category of animals was taken into account by the CVMP when considering the recommendation for the establishment of a MRL for tylvalosin in eggs. In total, there are 11 antimicrobial substances with MRLs established for eggs in the EU. Of these, tiamulin, tylosin, erythromycin and oxytetracycline are currently authorised for the treatment of mycoplasmosis in laying hens. Tetracyclines can affect egg shell quality and this limits their usefulness for this production class.

The currently limited availability of antimicrobials to treat laying hens may lead to over-reliance on those substances and potentially accelerate development of antimicrobial resistance in target pathogens.

Mycoplasmosis is an important chronic disease of poultry which predisposes to secondary infections and, if inadequately controlled, impacts seriously on animal health and welfare; therefore it is important to encourage availability and maintain effectiveness of treatments.

There is currently no MRL for tylvalosin in milk. However, there are 41 other antimicrobial substances covering a wide spectrum of activities with milk MRLs, and therefore the availability of antimicrobials with potential to treat lactating cows is far greater than that for laying hens. There are four alternative macrolide antibiotics with established MRLs in milk (tilmicosin, erythromycin, spiramycin and tylosin) which would have a similar spectrum of activity to tylvalosin and are used to treat a variety of diseases including respiratory disease (including mycoplasmas), foot rot, metritis and mastitis.

It is acknowledged that there are no antimicrobial substances with MRLs in honey. The most significant bacterial diseases of honey bees are American Foulbrood (AFB) and European Foulbrood (EFB). Where antimicrobial treatments are used for EFB, oxytetracycline is generally recommended. There are reports from outside the EU of another macrolide, tylosin, being used for treatment of AFB where there is resistance to the more commonly used oxytetracycline; however, antibiotics do not eradicate the disease and in the EU the primary method of control is to destroy affected colonies.

It should be recognised that prediction of future use of tylvalosin in lactating cattle and bees is speculative and there are alternative veterinary antimicrobials with a similar spectrum of activity, some of which already have milk MRLs.

The proposed treatment duration of tylvalosin for mycoplasmosis is 7 days and owing to the epidemiology of the disease and husbandry practices, the entire flock must be treated. As a result, a zero day withdrawal period for eggs is preferred as otherwise it will be necessary to dispose of the egg production from the whole flock for at least 8 days. This would have a substantial impact on the viability of treatment and would impact on animal health and welfare if treatment is therefore withheld.

Whilst CVMP considers that, for control purposes, it would be ideal to allow MRLs to be developed in all food commodities, this is not always practicable (case by case considerations are required, see 3.3, below).

There are no indications from the data available that there is any abuse potential with this substance.

Tylvalosin has no known use as a biocide or plant protection product.

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

3.3. *Elaboration of MRLs*

Based on the MRLs established for porcine and poultry tissues alone the theoretical maximum daily intake (TMDI) for a consumer is approximately 61 µg per day which equates to approximately 49% of the ADI. This leaves 51% of the ADI unused.

Considering the available 51% of the ADI, a MRL of 200 µg/kg can be proposed for eggs. It is likely that this would allow a zero-day withdrawal period to be achieved for eggs, taking into consideration the data from the radiolabelled residue depletion study and the ratio of tylvalosin (the marker residue) to total residues measured.

Although data on distribution of tylvalosin to milk are currently not available, macrolides generally distribute well into milk due to their high lipid solubility. Based on previous MRL applications for macrolides, a mean of 20% of the ADI is allocated to MRLs for milk. Therefore it is possible that a substantial portion of the ADI would otherwise need to be set aside for a practical MRL for this commodity. Whilst maintaining a free portion of the ADI would theoretically allow for future use of tylvalosin in lactating cattle and bees, at the same time this would have a negative impact on the availability of a potentially useful substance in egg laying hens.

It is recognised that the proposed MRL for eggs will prevent any further extension of the MRLs to other food commodities such as milk and honey. If, in the future, an application is received for the establishment of MRLs for tylvalosin in milk or honey the CVMP will need to consider amending established MRLs in order to accommodate this need.

There is no need to apply any additional restrictions on use for this substance.

Calculation of theoretical daily intake of residues

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product
Muscle				
Porcine	0.30	50	1	15.0
Poultry	-	-	-	-
Fat and skin #				
Porcine	0.05	50	1	2.5
Poultry	0.09	50	0.2	22.5
Liver				
Porcine	0.10	50	0.15	33.33
Poultry	0.10	50	0.15	33.33
Kidney				
Porcine	0.05	50	0.25	10.0
Poultry	0.01	-	-	-
Eggs	0.10	200	0.33	60.61

Fat and skin in natural proportions

Considering an MRL of 200 µg/kg in eggs as well as the existing established tissue MRLs, the theoretical maximum daily intake (calculated using porcine edible tissues) would be 121.6 µg/person, equivalent to 98% of the ADI (2.07 µg/kg bw, i.e. 124.2 µg/60 kg person).

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 tylvalosin in porcine tissues, poultry tissues and chicken eggs to other food producing species and commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as described below.

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
Eggs from poultry species other than chickens	Yes	As the marker residue is the parent molecule, it is probable that it would also be present in eggs from other poultry species. The analytical method can also be assumed to be basically applicable to eggs of other poultry species.
Ruminants	No	Cattle and sheep meat is consumed on a regular basis and in large quantities. Species specific data are therefore considered necessary to allow adequate evaluation of the risk

		<p>to consumer safety posed by residues in the tissues of ruminants.</p> <p>No analytical method for monitoring of residues in cattle or sheep tissues was available for this evaluation.</p>
Milk	No	<p>Milk is consumed on a regular basis and in large quantities and consequently data on residues in this commodity are considered necessary in order to allow adequate evaluation of the risk to consumer safety posed by residues in milk.</p> <p>No analytical method for monitoring of residues in milk was available for evaluation.</p>
Horses	No	<p>Metabolism can be significantly different in horses compared to poultry species. Consequently species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in horse-derived food commodities. Moreover, no data are available to demonstrate that the analytical method used for monitoring of residues in chicken eggs is applicable for monitoring of residues in horse tissues.</p>
Rabbits	No	<p>Metabolism can be significantly different in rabbits compared to poultry species. Consequently species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in rabbit-derived food commodities. Moreover, no data are available to demonstrate that the analytical method used for monitoring of residues in chicken eggs is applicable for monitoring of residues in rabbit tissues.</p>
Fin fish	No	<p>Metabolism can be significantly different in fish compared to poultry species. As the marker residue in tissues of mammalian and poultry species does not consist of the parent compound alone, residue data in fish would be required.</p> <p>No analytical method for monitoring of residues in fish meat was available for evaluation.</p>
Honey	No	<p>Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in chicken eggs is applicable for monitoring of residues in honey.</p>

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

Having considered that:

- the microbiological ADI of 2.07 µg/kg bw (124.2 µg/person) was established as the overall ADI for tylvalosin,
- tylvalosin is retained as the marker residue,
- the ratio of marker to total residues calculated at 7 days (final day of treatment) was 0.33 in chicken eggs,
- a validated analytical method for the monitoring of residues of tylvalosin in chicken eggs is available and can be assumed to be applicable also to eggs of other poultry species,
- extrapolation of the maximum residue limit recommended for chicken eggs to eggs of other poultry species is considered appropriate;

the CVMP recommends the establishment of a maximum residue limit for tylvalosin in eggs and the amendment of the entry in table 1 of the Annex to 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
Tylvalosin	Sum of tylvalosin and 3-O-acetyltylosin	Poultry	50 µg/kg 50 µg/kg	Skin and fat Liver	NO ENTRY	Anti-infectious agents / Antibiotics
	Tylvalosin	Poultry	200 µg/kg	Eggs		

Based on the MRLs for edible porcine tissues and poultry eggs (the worst case scenario), the theoretical maximum daily intake (TMDI) is 121.6 µg/person, which equates to 98% of the ADI.

4. Background information on the procedure

Submission of the dossier 30 October 2013

Steps taken for assessment of the substance

Application validated: 13 November 2013

Clock started: 14 November 2013

List of questions adopted: 13 March 2014

Submission of response to the list of questions: 9 May 2014

Adoption of the opinion: 10 July 2014

Commission request for review of opinion: 1 October 2014

Revised CVMP opinion adopted: 6 November 2014