EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/347870/2014
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Doxycycline (all food producing species)

On 30 January 2015 the European Commission adopted a Regulation[1] establishing maximum residue limits for doxycycline in all food producing species, 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.

Doxycycline is used in cattle, pigs, poultry, turkeys, dogs and cats for the treatment of infections due to bacteria susceptible to doxycycline. In rabbits doxycycline is intended for treatment of infections of the digestive tract susceptible to doxycycline.

Doxycycline had maximum residue limits already established[2] for bovine and porcine species and for poultry.

Industria Italiana Integratori TREI spA submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 4 September 2013.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 10 July 2014 the extension of maximum residue limits for doxycycline to rabbits and the extrapolation of the MRLs to all food producing species.

Subsequently the Commission recommended on 15 November 2014 that maximum residue limits for all food producing species are established. This recommendation was confirmed on 6 December 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 30 January 2015.

[1] Commission Implementing Regulation (EU) No 2015/151, O.J. L26, of 31.1.2015
[2] Commission Regulation (EU) No 37/2010, of 22.12.2009

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Doxycycline
Therapeutic class:	Antibacterials
Procedure number:	EMEA/V/MRL/003660/EXTN/0003
Applicant:	Industria Italiana Integratori TREI spA
Target species:	All food producing species
Intended therapeutic indication:	Treatment of infections of the digestive tract susceptible to doxycycline
Route(s) of administration:	Oral

1. Introduction

Doxycycline is a semisynthetic tetracycline derivative. As the hyclate salt, doxycycline is presented as an injectable solution (intramuscular, intravenous), water soluble or lactodispersable powders, and (for dogs and cats) tablets and capsules. Doxycycline hyclate is indicated in cattle, pigs, poultry, turkeys, dogs and cats for the treatment of infections due to bacteria susceptible to doxycycline at dose of 10-20 mg/kg bw/day, for 3-5 days. Doxycycline is not for use in lactating cattle and layers.

Doxycycline has a long history of use in human medicine.

Doxycycline was previously assessed by the CVMP and an ADI of 3 µg/kg bw, i.e. 180 µg/person, established.

Currently, doxycycline 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
Doxycycline	Doxycycline	Bovine	100 µg/kg 300 µg/kg 600 µg/kg	Muscle Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Anti-infectious agents/ Antibiotics
		Porcine, poultry	100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg	Muscle Skin and fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption.	

Industria Italiana Integratori TREI spA submitted the application for the establishment of maximum residue limits in rabbits to the European Medicines Agency, on 4 September 2013.

In rabbits doxycycline is intended to treat infections of the digestive tract susceptible to doxycycline with a recommended dose of 6 mg/kg bw/day for 15 consecutive days.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP previously assessed the consumer safety of doxycycline and established a microbiological ADI as the overall ADI. The microbiological activity of doxycycline was demonstrated to be similar to that of oxytetracycline in *in vitro* MIC studies with human enteric isolates and, on this basis, the microbiological ADI of 3 µg/kg bw (i.e. 180 µg/person) established for oxytetracycline was also adopted for doxycycline.

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

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

Pharmacokinetic studies examining doxycycline in plasma and caecal contents in rabbits were provided. From the pharmacokinetic study in plasma no quantifiable levels of doxycycline were measured during and at the end of treatment when doxycycline was administered at a dose of 6 mg/kg bw/day for 15 consecutive days. Significant levels of doxycycline were measured in the caecal content, which is consistent with the product being used for the treatment of enteric infections in rabbits. The recovery of doxycycline from faeces in total intestine (when compared to the doses administered) however was not determined, with the result that it is not possible to conclude from this study on the proportion of the drug that remains in the intestine.

2.2.2. Residue data

A residue depletion study in rabbits was submitted. This study was performed in 20 animals (New Zealand White; bodyweight of 1.16 to 1.99 kg at start of administration; n=4/group). The dose regime was 6 mg of doxycycline/kg bw and 120,000 IU of colistin sulfate/kg bw/day by the oral route for 15 consecutive days. An additional group of animals received the same daily dose for 21 consecutive days.

In the groups dosed for 15 consecutive days residue levels declined rapidly and were below the limit of quantification of the analytical method (muscle: 50 µg/kg, fat and liver: 150 µg/kg and kidney: 300 µg/kg) and below the MRL values established in other animal species at 4, 9, 12 and 15 days after treatment.

In the group treated for 21 consecutive days doxycycline residue levels in muscle, liver and kidney at the last day of administration were at levels close to half of the MRL values established in other animal species.

The results observed in the residue study were not expected based on the pharmacokinetic study in plasma, where concentrations of doxycycline could not be measured during and after treatment when dosed at
6 mg/kg bw/day for 15 consecutive days.

It can be concluded that doxycycline (marker residue) is absorbed resulting in significant residue levels in tissues. Most residues can be found in kidney, followed by liver and subsequently muscle. This reflects the tissue distribution seen in the other species for which MRLs are currently established.

Selection of marker residue and ratio of marker to total residues

Residue data available demonstrate that the marker residue doxycycline, retained for other animal species for which MRLs have been established, also exists in rabbits. Considering that rabbit is a minor species and in line with the note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL), doxycycline is also considered the suitable marker residue in rabbits.

The ratio of marker to total residues of 1 established for bovine, porcine and poultry species is retained for rabbit as well.

2.2.3. Monitoring or exposure data

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

2.2.4. Analytical method for monitoring of residues

The CVMP Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-Final) indicates that, for minor species, it is sufficient to demonstrate that the method developed for the major species is basically applicable in the minor species, for instance by using the method in a confirmatory depletion experiment. However, in this case the analytical method proposed is not the same as that developed for the major species. The validation of the analytical method for monitoring residues of doxycycline in rabbit tissues has therefore been performed taking account the requirements laid down in Volume 8 of the Rules of Governing Medicinal Products in the European Community and the requirements for validation as described in the CVMP Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005).

The validation was performed for the following parameters: specificity, limit of detection, limit of quantification, accuracy, precision, stability of solutions, practicability and susceptibility to interference. In addition the linearity of the method for the different tissues was successfully proven.

The relevant European reference laboratory has reviewed the proposed analytical method. The reference laboratory concluded that the overall results of validation of the method with regard to rabbits as a minor species are satisfactory considering the performance parameters checked against validation criteria according to the Volume 8 criteria of performance.

2.2.5. Findings of EU or international scientific bodies

No information on evaluations by other international scientific bodies was available.

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

Rabbits are considered a minor species and therefore the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) and the note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL) were taken into account for the evaluation of the reduced data package which complied with the requirements of the guidelines mentioned above.

3.3. Elaboration of MRLs

Identical MRLs have been established in cattle, pigs and poultry. The marker residue, doxycycline, established for the major species has now been demonstrated to be present in rabbit tissue. From the residue depletion study in rabbits it also appears that most residues can be found in kidney, followed by liver and subsequently muscle. This reflects the tissue distribution seen in the other (major) species. In addition, a sufficiently validated analytical method is available for the monitoring of residues in rabbit tissues. It is therefore concluded that the MRLs as established for porcine and poultry (which include MRLs for all edible tissues) can be extended to rabbits.

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 (µg)
Muscle	0.30	100	1	30
Fat	0.05	300	1	15
Liver	0.10	300	1	30
Kidney	0.05	600	1	30
Milk*	1.50	-	-	-
Eggs*	0.10	-	-	-
Honey*	0.02	-	-	-
			Total (µg) % ADI	105 58%

*Not for use in animals from which milk or eggs are produced for human consumption. No MRLs for honey are in place.

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 doxycycline in bovine, porcine, poultry and rabbit to other food producing species and commodities.

Identical MRLs have been established in bovine species, porcine species, poultry, and are now recommended in rabbits. In line with the CVMP guideline on safety and residue data requirements for VMPs intended for minor uses or minor species, it would be possible to extrapolate these MRLs to all food producing species, as long as there is confidence that available analytical methods for monitoring of residues would be applicable. HPLC methods were submitted with the applications for the establishment of maximum residue limits for cattle, pigs and poultry. In 2002 the CVMP reviewed these methods and concluded, at that time that, due to concerns over the methods, extrapolation would not be appropriate. However, doxycycline, as a second generation tetracycline, has now been used in a range of minor species for decades, and many analytical methods are available for monitoring residues of doxycycline in food commodities. Therefore extrapolation of the MRLs for doxycycline to all food producing species is supported.

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

Having considered that:

- the microbiological ADI of 3 µg/kg bw (i.e. 180 µg/person) was established as the overall ADI for doxycycline,
- rabbit is considered a minor species and therefore data requirements as defined in the Note for guidance on the risk assessment analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL) apply,
- the marker residue, doxycycline, established for cattle, pigs and poultry also exists in the rabbit and can be retained as marker residue in rabbits as well,
- a validated analytical method for the monitoring of residues of doxycycline in edible rabbit tissues (liver, kidney, muscle and fat) is available,
- extrapolation of the maximum residue limits recommended for rabbit tissues and previously established for tissues of bovine, porcine and poultry species is considered appropriate;

the CVMP recommends the establishment of maximum residue limits for doxycycline in rabbits and the extrapolation of these MRLs, which are already established for bovine, porcine and poultry species, to all food producing species as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Doxycycline	Doxycycline	All food producing species	100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg	Muscle Fat Liver Kidney	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which milk or eggs are produced for human consumption.	Anti-infectious agents / Antibiotics

Based on these MRLs the theoretical maximum daily residue intake (TMDI) from tissues is 105 µg/kg which represents 58% of the ADI.

4. Background information on the procedure

Submission of the dossier	4 September 2013
Steps taken for assessment of the substance	
Application validated:	18 September 2013
Clock started:	19 September 2013
List of questions adopted:	15 January 2014
Submission of response to the list of questions	4 April 2014
Adoption of the opinion	10 July 2014