EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2015
EMA/CVMP/131462/2014
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Tulathromycin (ovine and caprine species)

On 30 January 2015 the European Commission adopted a Regulation[1] establishing maximum residue limits for tulathromycin in ovine and caprine 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.

Tulathromycin is used for treatment of bacterial respiratory disease in (non-lactating) cattle and pigs by subcutaneous injection to cattle and by intramuscular injection to pigs. In ovine species tulathromycin is intended for treatment of foot rot associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum*.

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

Zoetis Belgium SA submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 26 April 2013.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 5 June 2014 the extension of maximum residue limits for tulathromycin to ovine and the extrapolation of these MRLs to caprine species.

Subsequently the Commission recommended on 15 October 2014 that maximum residue limits in ovine and caprine species are established. This recommendation was confirmed on 5 November 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 2015/152 , O.J. L 26, of 31.01.2015
[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:	Tulathromycin (CP-472,295(e))
Therapeutic class:	Anti-infectious agents / Antibiotics
Procedure number:	EMEA/V/MRL/003262/EXTN/0003
Applicant:	Zoetis Belgium SA
Target species:	Ovine
Intended therapeutic indication:	Treatment of naturally occurring foot rot associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum*
Route(s) of administration:	Intramuscular

1. Introduction

Tulathromycin is a semi-synthetic macrolide (CAS 217500-96-4) prepared by fermentation followed by organic synthesis. It is a member of the triamilide subclass of macrolide antibiotics. Tulathromycin is a mixture of two isomers: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]oxy-]2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one (15-membered macrocyclic ring) and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl[oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one (translactonized 13-membered macrocyclic ring). The 13 or 15 member macrocyclic rings are referred to either as the macrocyclic ring or as the aglycone. Two carbohydrate moieties are connected to the aglycone by an ether linkage, a desosamine carbohydrate moiety and a modified cladinose carbohydrate moiety. In solution, the two isomers form a stable equilibrated mixture which is considered as the active substance. Typical lots of tulathromycin consist of 90% (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-Cmethyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl)oxy-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one and 10% (2R,3R,6R,8R,9R,10S,11S,12R)-11-[(2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl)oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one.

Tulathromycin is used for treatment of bacterial respiratory disease in (non-lactating) cattle and pigs by subcutaneous injection to cattle and by intramuscular injection to pigs.

Tulathromycin was previously assessed by the CVMP and the toxicological ADI of 0.05 mg/kg bw (i.e. 3 mg/person) was retained as the overall ADI for the substance.

Currently, tulathromycin is included in 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
Tulathro-mycin	(2R,3S,4R,5R,8R,10R, 11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one expressed as tulathromycin equivalents	Bovine	100 µg/kg 3 000 µg/kg 3 000 µg/kg	Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/ Antibiotics
		Porcine	100 µg/kg 3 000 µg/kg 3 000 µg/kg	Skin and fat Liver Kidney		

On 10 October 2013 the CVMP recommended the modification of these MRLs in accordance with the table below (these MRLs have yet to be adopted by the European Commission):

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Tulathro-mycin	(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one expressed as tulathromycin equivalents	Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption Provisional MRLs expire on 1 January 2015	Anti-infectious agents/ Antibiotics
		Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney	Provisional MRLs expire on 1 January 2015	

On 26 April 2013 Zoetis Belgium SA submitted to the European Medicines Agency an application for the extension of maximum residue limits for tulathromycin to sheep.

In sheep tulathromycin is intended for the treatment of foot rot associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum*. The proposed dosing regimen is a single intramuscular injection of 1.25 or 2.5 mg tulathromycin/kg bodyweight.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of tulathromycin and established a toxicological ADI of 0.05 mg/kg bw/day (3 mg/person), based on the NOEL of 5 mg/kg bw from 3-month subchronic toxicity studies in dogs and rats and a uncertainty factor of 100, and a microbiological ADI of 0.055 mg/kg bw (i.e.3.29 mg/person) for colonisation barrier effects. The toxicological ADI, being lower than the microbiological ADI, represents the overall ADI. 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

Data on plasma concentration-time profiles and balance-excretion kinetics were derived from a total radioactive residues depletion study in sheep. Thirty animals were treated at the intended dose of 2.5 mg of [^{14}C]-tulathromycin/kg body weight. The total residues plasma concentration showed highest group means at 8 hours after administration. The concentration of radioactivity declined with time and was near to background by day 49 after administration. Excretion of total radioactive residues declined with each subsequent timepoint to 0.04% of the administered dose at day 36 both in urine and faeces. Mean total recovery of radioactivity (including cagewash) was 75.29% by day 36.

2.2.2. Residue depletion studies

Two residue depletion studies, one radiometric and one non-radiometric study, were conducted in sheep. The radiometric study was used to determine total residues concentrations and marker to total residue ratios. The non-radiometric study was conducted to measure the depletion of the marker residue.

In the radiometric residue depletion study, 30 sheep were given a single intramuscular dose of 2.5 mg ^{14}C-tulathromycin/kg bw. Three sheep were killed on days 2, 4, 7, 14, 21, 28, 35, 42 and 49 after treatment.

In tissue samples, the group mean total radioactive residue concentrations declined with time. The highest mean concentration of total radioactive residue was detected at the injection site (mean 11023 µg equivalents/kg at 2 days after administration). The injection sites contained the highest concentrations of radioactivity at early time points (up to 21 days). The lungs (4408 µg equivalents/kg) had the highest mean total radioactive residue concentration in the organs analysed followed by the kidneys (3738 µg equivalents/kg) and the liver (3349 µg equivalents/kg), which had similar mean total radioactive residue concentrations at day 2. The loin muscle (1686 µg equivalents/kg) and small intestine (1526 µg equivalents/kg) day 2 samples also had similar mean

total radioactive residue concentrations. The heart followed by the peri-renal fat had the lowest concentration of total radioactive residue concentrations at day 2 (805 µg equivalents/kg and 738 µg equivalents/kg, respectively).

Concentrations of the common fragment, i.e. the sum of residues which may be hydrolysed to (2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one, (reported as tulathromycin equivalents) were highest at the injection site. At two days after injection, mean residues were 7310 µg/kg and depleted to 417 µg/kg on day 49, which was the last time of tissue collection. Mean tulathromycin residues in injection site surround tissue were lower than those seen in the corresponding core injection site tissue at all time points throughout the study. Loin muscle residues were highest at slaughter day 2, declined continuously and all tulathromycin muscle residues were below the limit of quantification by day 35. Kidney and lung had similar tulathromycin residue depletion profiles. Tulathromycin residues in liver tissue were 2740 µg/kg on day 2. However, there was a slower depletion from liver than was seen for kidney and lung. Tulathromycin residue concentrations in fat averaged 706 µg/kg on day 2 and depleted to 512 µg/kg, 222 µg/kg, and 92.1 µg/kg on days 4, 14, and 28. Mean tulathromycin fat residues were below the limit of determination on days 42 and 49.

As the sum of residues which may be hydrolysed to (2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one was shown to account for between 78% to 95% of all residues in sheep tissues no further metabolic profiling in sheep is considered necessary.

In the non-radiometric residue depletion study, 42 sheep were given a single intramuscular dose of 2.5 mg tulathromycin/kg bw. Four sheep (2 animals per sex) were killed on days 2, 4, 7, 14, 21, 28, 35, 42 and 49 after treatment. Tissue samples were analysed for marker residue concentrations by ultraperformance liquid chromatography with tandem-linked mass spectrometry (HPLC/MS/MS) with limits of quantification of 300 µg/kg for liver, 200 µg/kg for kidney, and 50 µg/kg for muscle and fat.

Marker residues were highest at the injection site. At two days after injection, mean residues were 5890 µg/kg and depleted to 3350 µg/kg after four days. Residues continued to deplete to 1330 µg/kg, 826 µg/kg, 361 µg/kg, and 153 µg/kg after 7, 28, 35, and 42 days withdrawal. Residues remained approximately the same at 49 days withdrawal (170 µg/kg), which was the last time of tissue collection.

No surrounding injection site samples from the animals slaughtered at days 2 and 4 were available. Marker residues in surrounding injection tissue were lower than those seen in the corresponding core injection site tissue at all time points with the exception of three individual samples where concentrations were higher than found in the corresponding core injection site.

Hind quarter muscle residues for tulathromycin were highest after two days withdrawal (1070 µg/kg). Concentration levels depleted to 664 µg/kg, 248 µg/kg, and 57.7 µg/kg on days 4, 7, and 21 respectively. All individual tulathromycin muscle concentrations were below the limit of quantification (50 µg/kg) by day 28.

In liver the highest residues values were measured at slaughter day 4 (up to 3800 µg the 15-membered macrocyclic ring per kg) and declined to concentrations below the limit of quantification at day 42. In kidney the highest concentrations were measured at slaughter day 2 (up to 2950 µg/kg) and declined to values below the limit of quantification in all animals at slaughter day 28. In fat concentrations declined from 413 µg/kg at day 2 to concentrations below the limit of quantification in all animals at day 21.

Selection of marker residue and ratio of marker to total residues

The marker residue for tulathromycin established for bovine and porcine species is the sum of residues which may be hydrolysed to (2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa- 6-azacyclopentadecan-15-one, expressed as tulathromycin equivalents. This residue was shown to account for between 78 and 95% of all residues in sheep tissues and is therefore considered to be an appropriate marker residue for use in sheep.

Marker to total ratios remained relatively constant with time, which suggested that it is appropriate to use the overall mean marker to total ratio per tissue. Average ratios of marker to total residues across all time points were 0.81, 0.85, 0.78, 0.88 and 0.95 for liver, kidney, muscle, injection site and fat, respectively.

2.2.3. Monitoring or exposure data

No monitoring or exposure data relevant to the use of tulathromycin in sheep in veterinary medicinal products were available in addition to the data presented in the residue section.

2.2.4. Analytical method for monitoring of residues

The SPE-UPLC/MS/MS method for the determination of tulathromycin in ovine tissues is sufficiently described and validated. Data for accuracy and precision meet the acceptance criteria laid down in Volume 8 of The Rules Governing Medicinal Products in the European Union. The marker residue used to determine the concentrations of tulathromycin residues in edible tissues of sheep was the sum of unchanged drug, tulathromycin, and the common fragment, i.e. the sum of residues which may be hydrolysed to (2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one, expressed as tulathromycin equivalents. The limits of quantification of the method for sheep tissues were 50 µg/kg for muscle and fat, 200 µg/kg for kidney and 300 µg/kg for liver.

The relevant European Reference Laboratory reviewed the proposed analytical method and reported the validation to be satisfactory considering the criteria according to Volume 8 of The rules governing medicinal products in the European Union.

Although it was not specifically demonstrated, the analytical method for monitoring of residues in sheep tissues is expected to be basically applicable for monitoring of residues in goats tissues.

2.2.5. Findings of EU or international scientific bodies

Tulathromycin has not been evaluated by other EU or international scientific bodies.

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 sheep and therefore potential effects in dairy products were not investigated.

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

Residue depletion data demonstrate that tulathromycin levels in carcass tissues (i.e. fat and muscle) other than injection site muscle were low compared to levels in liver and kidney in sheep. However, in order to enable residues control of meat when only lean cuts of muscle are available a MRL for muscle is required. For this substance the approach described in the CVMP revised reflection paper on injection site residues: consideration for risk assessment and residue surveillance (EMA/CVMP/520190/2007-Rev.1) was considered appropriate for derivation of the muscle MRL.

3.3. Elaboration of MRLs

Based on the residue depletion data, distribution of marker residue between target tissues and ratios of marker to total residues, and taking into account the toxicological ADI of 3000 µg/person the following MRL values for muscle, liver, kidney and fat of sheep can be calculated.

Tissue	MRL
Muscle	450 µg/kg
Fat	250 µg/kg
Liver	5400 µg/kg
Kidney	1800 µg/kg

In line with the approach described in the CVMP revised reflection paper on injection site residues, and in light of the slow depletion of residues from the injection site, an "Injection Site Residue Reference Value" (ISRRV), which specifies the level of residues at the injection site that can be considered as safe, of 6300 µg/kg is established. This value in not intended for use in routine residue surveillance but provides a value to be used by competent authorities when setting withdrawal periods for tulathromycin containing products.

Withdrawal periods for injectable tulathromycin products should ensure that residue levels present in non-injection tissues do not exceed the MRLs for muscle, liver, kidney and fat, respectively, and that residue levels present in injection site muscle do not exceed the ISRRV of 6300 µg/kg.

Calculation of residues intake

Table 1: Theoretical daily intake calculation based on the proposed MRLs in pigs using a revised ADI of 3000 µg/person/day

Tissue	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio marker/ total residue*	Amount total residues (µg)
Muscle	0.30	450	0.78	173.1

Fat	0.05	250	0.95	13.1
Liver	0.10	5400	0.81	666.7
Kidney	0.05	1800	0.85	105.9
			Estimated total daily intake (µg/person)	**958.8**
			Total % ADI	**32%****

* *Overall ratios per tissue*
** *Calculation based on an Injection Site Residue Reference Value (ISRRV) of 6300 µg/kg accounting for muscle tissue and a ratio of marker to total residue of 0.88, would result in consumer intake of residues of 2147.7 µg. When added to the intake of residues from fat, liver and kidney this would represent a total intake of approximately 97.8% of the ADI.*

Based on the recommended MRLs, the theoretical maximum daily intake from tissues calculated using the recommended maximum residue limits, represents 32% of the ADI for sheep. However, when the calculation is performed taking also into account the ISRRV of 6300 µg/kg, the consumer intake represents approximately 98% of the ADI.

Tulathromycin is not intended for use in dairy animals producing milk for human consumption, poultry (including those producing eggs for human consumption), or honey bees and therefore it is not considered necessary to reserve part of the ADI for other food commodities.

In the absence of MRLs for milk the use of tulathromycin is restricted to non-lactating ovine and caprine species.

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 tulathromycin 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
Goats	Yes	Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle, pigs and sheep is similar. Publicly available information indicates that the marker residue established for sheep is also present in goat tissues. Although it was not specifically demonstrated, the analytical method for monitoring of residues in sheep tissues is expected to be basically applicable for monitoring of residues in goat tissues.
Milk	No	No data are available that would allow conclusions to be drawn on the appropriate marker residue or marker to total residues ratio to use in milk. 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. The applicant has investigated use in dairy cows and

		tulathromycin was shown to partition extensively into milk. As such, the applicant concluded that, based on the required 1.5l consumption factor, the use of the substance in dairy animals would not be practicable. No analytical method for monitoring of residues in milk was available for evaluation.
Poultry (including eggs)	No	Metabolism can be significantly different in poultry compared to sheep. Consequently species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in poultry-derived food commodities. No analytical method for monitoring of residues in poultry tissues (or eggs) was available for evaluation.
Horses	No	Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle, pigs and sheep is similar. Based on this existing inter-species metabolism data, the assumption could be made that the same marker residue would be appropriate in horses. However, no specific pharmacokinetic or residue data were available for horses and therefore the assumption related to the marker residue could not be confirmed. No data are available to demonstrate that the analytical method used for monitoring of residues is applicable for monitoring of residues in horse tissues.
Rabbits	No	Existing data indicate that the pattern of metabolites seen in rats, dogs, cattle, pigs and sheep is similar. Based on this existing inter-species metabolism data, the assumption could be made that the same marker residue would be appropriate in rabbits. However, no specific pharmacokinetic or residue data were available for rabbits and therefore the assumption related to the marker residue could not be confirmed. No data are available to demonstrate that the analytical method used for monitoring of residues is applicable for monitoring of residues in rabbit tissues.
Fin fish	No	Metabolism is generally less complicated in fish than in mammals. As the marker residue in sheep 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 products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate

		evaluation of the risk to consumer safety posed by residues in honey. No data are available to demonstrate that the analytical method used for monitoring of residues is applicable for monitoring of residues in honey.

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

Having considered that:

- the toxicological ADI of 0.05 mg/kg bw (i.e. 3 mg/person) was established as the overall ADI for tulathromycin,
- liver, kidney and injection site muscle were the main target tissues for tulathromycin derived residues in sheep; residue concentrations were always low in fat and non-injection site muscle,
- the acid digest common fragment of the sum of residues which may be hydrolysed to (2R,3S,4R,5R,8R,10R,11R, 12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one (hydrolysis product of tulathromycin and selected metabolites) was identified as the marker residue in cattle and pigs and is also considered to be the appropriate marker residue in sheep,
- due to limited metabolism of tulathromycin ratios of marker to total residues were relatively constant during residue depletion; overall ratios from combined results for sheep were estimated to be 0.78 in muscle, 0.95 in fat, 0.81 in liver, 0.85 in kidney and 0.88 in injection site muscle,
- an Injection Site Residue Reference Values (ISRRVs) of 6300 µg/kg was established for sheep – this value should be taken into account when deriving withdrawal periods,
- the available data supports the view that the pharmacokinetic profile for tulathromycin in sheep will be similar in goats,
- a validated analytical method for the monitoring of residues of tulathromycin in edible ovine tissues (liver, kidney, muscle and fat) is available,
- although it was not specifically demonstrated, the analytical method for monitoring of residues in sheep tissues is expected to be basically applicable for monitoring of residues in goats tissues,
- for the purpose of monitoring of residues of tulathromycin it is recommended that, where the entire carcass is available, liver or kidney should be sampled in preference to muscle or fat as residues in liver and kidney deplete more slowly than residues in muscle and fat and so will provide a better basis for verifying compliance with the withdrawal period,

the CVMP recommends the establishment of maximum residue limits for tulathromycin in ovine species. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the Committee agreed to extrapolate the conclusion to goats, and therefore recommends by consensus to extend the entry for tulathromycin in table 1 of the Annex to Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Tulathro-mycin	(2R,3S,4R,5R,8R,10R, 11R,12S,13S,14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one expressed as tulathromycin equivalents	Ovine, caprine	450 µg/kg 250 µg/kg 5400 µg/kg 1800 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/ Antibiotics

Based on these MRLs, the total theoretical maximum daily intake (TMDI) from tissues is 958.8 µg/person which corresponds to 32% of the overall ADI. Taking into account the Injection Site Residue Reference Value (ISRRV) of 6300 µg/kg the TMDI from a food basket containing 300 g of injection site muscle represents approximately 98 % of the ADI for edible tissues.

4. Background information on the procedure

Submission of the dossier	26 April 2013
Steps taken for assessment of the substance	
Application validated:	15 May 2013
Clock started:	16 May 2013
List of questions adopted:	12 September 2013
Consolidated response to list of questions submitted:	6 December 2013
Clock re-started:	12 January 2014
List of outstanding issues	13 March 2014
Responses to list of outstanding issues submitted:	7 May 2014
Clock re-started:	13 January 2014
Opinion adopted	5 June 2014