DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

TILMICOSIN CALIER 250 mg/ml
Solution for use in drinking water/milk

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0338/001/DC
Name, strength and pharmaceutical form	TILMICOSIN CALIER 250 mg/ml Solution for use in drinking water/milk (DE, EL, ES, HU, PT) TILMICOSINA CALIER 250 mg/ml Solution for use in drinking water/milk (IT)
Applicant	Laboratorios Calier, S.A. C/Barcelonès, 26 08520 Les Franqueses del Vallès (Barcelona) Spain
Active substance(s)	Tilmicosin (as phosphate)
ATC vet code	QJ01FA91
Target species	Chickens (except hens producing eggs for human consumption), Turkeys Pigs Calves (non-ruminant)
Indication for use	Pigs: For the treatment and metaphylaxis of respiratory disease in pig herds, associated with *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to tilmicosin. The presence of the disease in the group/flock must be established before the product is used. Chickens (except hens producing eggs for human consumption): For the treatment and metaphylaxis of respiratory disease in chicken flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin. The presence of the disease in the group/flock must be established before the product is used. Turkeys: For the treatment and metaphylaxis of respiratory disease in turkey flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin. The presence of the disease in the group/flock must be established before the product is used. Calves: For the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica, Mycoplasma bovis, M. dispar* and *Pasteurella multocida* susceptible to tilmicosin. The presence of the disease in the group/flock must be established before the product is used.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13(1) Generic application of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 16/12/2020
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	DE, EL, HU, IT, PT.

I. SCIENTIFIC OVERVIEW

This was a generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended. TILMICOSIN CALIER 250 mg/ml is the generic veterinary medicinal product and contains tilmicosin (as phosphate) as active substance for use in drinking water. The product is indicated for the treatment and metaphylaxis of respiratory diseases. The reference product is Pulmotil AC authorised in Spain since 2000.

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains tilmicosin phosphate and propyl gallate, disodium edetate, phosphoric acid concentrate and purified water as excipients.

The container/closure system is white opaque high-density polyethylene bottles closed with white high density polyethylene screw cap with strapping and removable polyethylene sealing disk.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is tilmicosin phosphate, an established active substance described in the USP. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

Appropriate data have been provided to support the in-use shelf-life of the product.

G. Other Information

Appropriate data have been provided to support the stability of the product in drinking water and milk replacer.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of safety tests are not required.

The safety and residues aspects of this product are identical to the reference product.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that risk is envisaged for the user after ingestion and dermal contact with the VMP.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil,initial= 868.89 µg/kg, "weaner pig", worst case) is greater than 100 µg/kg and no mitigations exist that alter the PECsoil less than the cut off value. The PECsoil, initial is lower than 100 µg/kg (33.51 µg/kg) for broiler breeders.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	700 g/l at 20ºC	(flask method)
Dissociation constants in water pKa	OECD 112	pKa = 8.191 at 20°C	(titration method)
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	- 2.19 (pH 5); - 0.39 (pH 7); 2.25 (pH 9)	(shake flask method)

Environmental fate			
Soil Adsorption/Desorption	OECD 106	<table><tr><td></td><td>Kf</td><td>Kfoc</td><td>1/n</td><td>r2</td></tr><tr><td>A</td><td>4.45</td><td>626.70</td><td>0.80</td><td>0.9992</td></tr><tr><td>B</td><td>47.17</td><td>2370.55</td><td>0.91</td><td>0.9721</td></tr><tr><td>C</td><td>205.31</td><td>11534.31</td><td>0.65</td><td>0.9640</td></tr><tr><td>D</td><td>10.5</td><td>136.20</td><td>0.88</td><td>0.9918</td></tr><tr><td>E</td><td>540.43</td><td>28147.35</td><td>0.42</td><td>0.9493</td></tr><tr><td>a.m.</td><td>161.48</td><td>8563.02</td><td>0.73</td><td></td></tr><tr><td>g.m.</td><td>47.19</td><td>2309.42</td><td>0.71</td><td></td></tr></table> a.m.=arithmetic mean g.m.=geometric mean **mean Kfoc** = 2309.42 µg(1-1/n)(cm3)(1/ng)g-1 (range 136.20-28147.35, n=5) **Mean 1/n**=0.7 (n=5, range 0.42-0.91)	List all values with pH, Corg, soil textureinclud ing clay content

<table>
<tr><td colspan="4">Environmental fate</td></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Soil</th><th>Texture class[1]</th><th>pH</th><th>Clay content[1]</th><th>C_{org}</th></tr>
<tr><td>A:</td><td>Lufa 2.1</td><td>Loamy sand</td><td>4.9</td><td>3.0</td><td>0.71</td></tr>
<tr><td>B:</td><td>LUFA 2.4</td><td>Loam</td><td>7.4</td><td>25.8</td><td>1.99</td></tr>
<tr><td>C:</td><td>LUFA 6S</td><td>Clay</td><td>7.2</td><td>40.5</td><td>1.78</td></tr>
<tr><td>D</td><td>Labsoil-F</td><td>Silt loam</td><td>3.4</td><td>19.6</td><td>7.38</td></tr>
<tr><td>E</td><td>RefeSol 05-G</td><td>Loam</td><td>5.4</td><td>20.3</td><td>1.92</td></tr>
</table>
1: according to USDA
</td><td></td></tr>
<tr><td>Aerobic and Anaerobic Transformation in Soil</td><td>OECD 307</td><td>
Test condition: 20 °C ± 2 °C in the dark
DT50 for Persistence extrapolated at 12ºC: 30.4 (Lufa 2.2, DFOP) to 234 d (Lufa 6S, DFOP)

DT50 for Modelling (SFO)
Modelling geomean :

DT50=114.7d (n=4, range 77.13-296)
DT90=347.63 d

<table>
<tr><th></th><th>(max)Deg (%)</th><th>day</th><th>NER(%) (max)</th><th>day</th></tr>
<tr><td>LUFA 2.1</td><td>70</td><td>120</td><td>18.2</td><td>120</td></tr>
<tr><td>LUFA 2.2</td><td>76.3</td><td>120</td><td>14.8</td><td>120</td></tr>
<tr><td>LUFA 2.3</td><td>68.9</td><td>120</td><td>21.1</td><td>90</td></tr>
<tr><td>LUFA 6</td><td>83.1</td><td>120</td><td>10</td><td>56</td></tr>
</table>
Max volatiles : Lufa 2.1 : 2.3% (day 120), Lufa 2.2 : 2 % (day 120), Lufa 2.3 : 6.2% (day 120) and Lufa 6S : 3.3% (day 120)

19 total unknown signals. 4 unknown signal detected >10% AR
• Maximum amount Unknown #6: 24.0% AR in LUFA 2.1 (day 29), 25.6% AR in LUFA 2.2 (day 14), 23.0% AR in LUFA 2.3 (day 14) and 18.2% AR in LUFA 6S.

• Maximum amount Unknown #7 : 11.3% AR in LUFA 2.1 (day 29), 12.4% AR in LUFA 2.2 (day 14), 11.1% AR in LUFA 2.3 (day 14) and 9.3% AR in LUFA 6S.

• Maximum amount Unknown #13: 7.2% AR (LUFA 2.1, day 90), 5.0% AR (LUFA 2.2, day 120) and 11.7% AR (LUFA 2.3, day 56).
</td><td>For each of the 4 soils.

Information on soils used</td></tr>
</table>

Environmental fate			
		• Maximum amount Unknown #15: 13.0% AR in LUFA 2.1 (day 120), 3.7% AR in LUFA 2.2 (day 120) and 19.9% AR in LUFA 2.3 (day 90).	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Cyanobacteria, growth inhibition test/ *Synechococcus leopoliensis*	OECD 201	EC50	EC50 (growth) >5.29 µg/l (72h) ErC10 =3.50 µg/L (72h) NOECr=1.57 µg/L (72h)	µg/l	(Measured)
Daphnia magna immobilisation	OECD 202	EC50	24 and 48-hour EC50 > 100 mg/l	µg/l	nominal
Fish, acute toxicity/ *Oncorynchus mykiss*	OECD 203	LC50	LC50 > 100 mg/l NOEC>100 mg/L	µg/l	nominal
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	≤ 25% of control	µg/kg	No risk
Terrestrial Plants, growth test	OECD 208	EC50	*C. sativus* EC50 (fresh weight)= 222 mg/kg NOEC (fresh weight) = 111 mg/kg EC10 (fresh weight)= 54.8 mg/kg	µg/kg	Dicot: *Brassica napus, Glycine max, Cucumis sativus, Solanum lycopersicum,* Monocot: *Lollium perenne, Allium cepa*
Earthworm/	OECD	EC10 or	Tier A endpoint	µg/kg	

Eisenia andrei reproduction	222	NOEC	NOEC (mortality), (weight) (reproduction) >500 mg/kg		

*add information on analytical verification of test substance (nominal (n) or measured (m)), on exposure (e. g. semi-static, flow-through, sediment spiked, etc.), on test substance (salt, base), and on test medium (e. g. Corg content)

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	0.35 µg/L	1.14 µg/L (Thiva, D6 ditch, FOCUS SWASH)	**3.25**
groundwater		0.000000 ug/L (FOCUS PEARL, Okehampton)	No risk
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	No risk
soil	2220 µg/kg	869 µg/kg	0.39

The risk characterisation resulted in risk quotients (RQ) below 1 for the groundwater and for the soil compartment indicating that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the surface water compartment points that a risk for the environment is indicated. Benefit/Risk assessment was included in the evaluation resulting in a positive balance.

The following information on environmental properties needs to be included in the product literature: warning for toxicity to aquatic organisms -cyanobacteria, warning for persistence and advising for a safe disposal of the unused medicine or waste materials.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	log Know < 4	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	306.6 d (geomean)	**vP**
Toxicity	NOEC or CMR	1.47 µg/L (NOECr)	**T**
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this application is for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, and bioequivalence with the reference product has been demonstrated.

MRLs

The active substance Tilmicosin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010. The marker substance is Tilmicosin.

MRLs are listed below:

Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Poultry	75 µg/kg 75 µg/kg 1000 µg/kg 250 µg/kg	Muscle Skin and fat Liver Kidney	For fin fish the muscle MRL relates to a 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which eggs are produced for human consumption.
All other food producing species	50 µg/kg 50 µg/kg 1000 µg/kg 1000 µg/kg 50 µg/kg	Muscle Fat Liver Kidney Milk	

Withdrawal Periods

The same withdrawal periods than the reference products are proposed:

Pigs: 14 days

Chickens: 12 days

Turkeys: 19 days

Calves: 42 days

Not authorised for use in laying birds producing eggs for human consumption.

Do not use within 14 days of onset of the laying.

Not authorised for use in animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC. As bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

As this was a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC, and Bioequivalence with a reference product was demonstrated, pre-clinical studies are not required.

IV.B Clinical Studies

As this was a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC, and Bioequivalence with a reference product was demonstrated, clinical studies are not required.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None