College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tylogran, 1000 mg/g, granulate for use in drinking water/milk for cattle (calves), pigs, chickens and turkeys

August 2021

Tylogran 1000 mg/g, granulate for use in drinking water/milk for cattle, pigs, chickens and turkeys	NL/V/0189/001/MR
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0189/001/MR
Name, strength and pharmaceutical form	Tylogran, 1000 mg/g, granulate for use in drinking water/milk for cattle (calves), pigs, chickens and turkeys
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Tylosin tartrate
ATC Vetcode	QJ01FA90
Target species	Cattle (calf), pig, chicken and turkey
Indication for use	Calves: treatment and metaphylaxis of - pneumonia caused by *Mycoplasma* spp. Pigs: treatment and metaphylaxis of - enzootic pneumonia caused by *Mycoplasma hyopneumoniae* and *Mycoplasma hyorhinis*; - Porcine Intestinal Adenomatose (PIA or Ileitis) associated with *Lawsonia intracellularis*. Turkeys: treatment and metaphylaxis of - infectious sinusitis caused by *Mycoplasma gallisepticum*. Chickens: treatment and metaphylaxis of - chronic respiratory diseases (CRD) caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*; - necrotic enteritis caused by *Clostridium perfringens*. The presence of the disease in the group/flock must be established before the product is used.

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MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	22nd October 2014
Date product first authorised in the Reference Member State (MRP only)	4th January 2005
Concerned Member States for original procedure	AT, BE, DE, DK, EE, EL, FR, HR, HU, IT, LT, LV, PL, PT, RO

I. SCIENTIFIC OVERVIEW

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 1 g of tylosin (1000000 IU tylosin, corresponding to 1.1 g of tylosin tartrate) and no excipients.

The container/closure system consists of the following packages:

- a hardboard can provided with an inner lining of aluminium-paper (polyethylene terephthalate coated) and a seamed tin-plate bottom, closed with a low density polyethylene lid. The can contains 550 g of product.

- a white polypropylene square bucket provided with a polypropylene lid. The bucket contains 1 kg, 4 kg or 5 kg of product.

- a white polypropylene cylindrical securitainer provided with a low density polyethylene lid. The securitainer contains 100 g, 550g, 800 g or 1000 g of product.

The choice of the formulation and the absence of preservatives are justified.

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

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B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at 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 Tylosin tartrate, an established active substance. 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.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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 has 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.

The claim of a 24 hours stability after reconstitution is based on the demonstration of stability for a batch broached and stored 72 hours at +25°C and +40°C.

Shelf life of the veterinary medicinal product as packaged for sale:
- Composite can: 3 years.
- Bucket: 3 years.
- Securitainer: 2 years.

Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours.
Shelf life after reconstitution in milk replacer: 3 hours.

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G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

Warning statements and precautions as listed in the product literature are based on those of the reference product and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to the animals, users, consumers and the environment.

III.A Safety Testing

Environmental Risk Assessment

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

The outcome of the environmental risk assessment was a negligible risk for the terrestrial and surface water compartment and a predicted groundwater concentration <0.1 µg/L. Tylosin is not PBT, nor vPvB.

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (for all target species) is greater/equal to 100 µg/kg and no mitigations exist that alter the PECsoil.

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.

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Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	pH4.5 > 178g/L pH 6.3 109 g/L pH6.8 55.3 g/L pH 9.5 17.8 g/L	
Dissociation constants in water pKa	OECD 112	pKa =7.65 ± 0.03	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	pH 3.5 Log Pow= -1.08 pH 5.4 Log Pow = -0.33 pH 6.9 Log Pow= 0.50 pH 7.0 Log Pow = 0.43 pH 9.2 Log Pow = 0.97 pH 10.6 Log Pow = 0.94	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc= 233 L/kg Koc =146 L/kg Koc= 177 L/kg Koc= 4023 l/kg Koc= 1412 L/kg	Loamy Sand: Organic carbon: 0.8%, pH: 3.2 Silt Loam: Organic carbon: 3.3%, pH: 6.4 Silt Loam: Organic carbon: 5.5%, pH: 4.1 Heavy clay: Organic carbon: 7.2%, pH: 4.6 Clay Loam: Organic carbon: 3.0%, pH: 7.2
Soil Adsorption/Desorption	OECD 106	Koc= 5781 L/kg Koc =17166 L/kg Koc= 1581 L/kg Koc= 1981 l/kg Koc= 5043 L/kg	n.r.: Organic carbon: 2.2%, pH: 6.1 n.r. :Organic carbon: 2.2%, pH: 5.6 n.r. : Organic carbon: 3.2%, pH: 7.2 n.r.: carbon: 3.9%, pH: 7.4 n.r.: Organic carbon:

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Environmental fate			
		Koc= 1453 L/kg Koc= 15095 L/kg Koc= 303 L/kg	5.9%, pH: 7.4 n.r.: Organic carbon: 3.1%, pH: 6.3 n.r.: Organic carbon: 2.6%, pH: 7.4 n.r.: Organic carbon: 12.2%, pH: 4.9
Soil Adsorption/Desorption	OECD 106	Koc= 2742 L/kg Koc =309 L/kg	Sandy clay loam: Organic carbon: 3.1%, pH: 7.0 n.r. :Organic carbon: 2.2%, pH: 6.8
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} = 9, 10 and 50 d Transformation products > 10 %: D1, D2, D3, D4, D5 % Mineralisation: 0.02 - 0.77 % NER: 1.6 - 25	Loamy sand (pH 3.5, C_{org} 1.6%); silt loam (pH 4.5, C_{org} 3.6%); silty clay loam (pH 5.4, C_{org} 3.4%); heavy clay (pH 5.0, C_{org} 5.0%)

n.r.= soil type not reported.

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Cyanobacteria, growth inhibition test	OECD 201	EC50	>390	mg/l	*Anaebena flosaquae*
Cyanobacteria, growth inhibition test	OECD 201	NOEC	0.011	mg/l	*Tier B* *Anaebena flosaquae*
Daphnia sp. immobilisation	OECD 202	NOEC	102	mg/l	
Fish, acute toxicity *Brachydanio rerio*	OECD 203	LC50	>100	mg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25	%	After 28 days
Terrestrial Plants, growth test	OECD 208	EC50	130	mg/kg	*Raphanus sativus*
Terrestrial Plants, growth	OECD 208	NOEC	39.8	mg/kg	*Tier B*

test					*Raphanus sativus*
Earthworm subacute toxicity	OECD 220/222	NOEC	121	mg/kg	*Eisenia fetida*

*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	cyanobacteria: 3.9 µg/L crustaceans: 102 µg/L Fish: >100 µg/L	Calf: 1.6 µg/l Weaner pig: 0.89 µg/l Fatt. pig: 0.60 µg/l Sow +litter: 0.21 µg/l Broiler: 2.4 µg/l Laying hens: 0.72 µg/l Replacement layer: 0.54 µg/l Broiler breeder: 0.41 µg/l Turkey: 1.1 µg/l	**cyanobacteria:** Calf: 0.42 Weaner pig: 0.23 Fatt. pig: 0.16 Sow +litter: 0.055 Broiler: 0.62 Laying hens: 0.19 Replacement layer: 0.14 Broiler breeder: 0.10 Turkey: 0.29 **crustacea**: Calf: 0.016 Weaner pig: 0.00087 Fatt. pig:0.0059 Sow +litter: 0.0021 Broiler:0.024

			Laying hens: 0.0071 Replacement layer: 0.0053 Broiler breeder: 0.0040 Turkey: 0.011 **Fish**: Calf: 0.016 Weaner pig: 0.0089 Fatt. pig: 0.0060 Sow +litter: 0.00021 Broiler: 0.024 Laying hens: 0.0072 Replacement layer: 0.0054 Broiler breeder: 0.0041 Turkey: 0.011
groundwater		Calf: 4.9 µg/l Weaner pig: 2.7 µg/l Fatt. pig: 1.8 µg/l Sow +litter: 0.64 µg/l Broiler: 7.2 µg/l Laying hens: 2.2 µg/l Replacement layer: 1.6 µg/l Broiler breeder: 1.2 µg/l	

		Turkey: 3.4 µg/l	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	micro-organisms: n.c earthworms: 12100 µg/kg plants: 1300 mg/kg	Calf: 1511 µg/kg Weaner pig: 821.1 µg/kg Fatt. pig: 556.9 µg/kg Sow +litter:197.7 µg/kg Broiler: 2223 µg/kg Laying hens: 665.4 µg/kg Replacement layer: 499.1 µg/kg Broiler breeder: 374.3 µg/kg Turkey: 1058 µg/kg	**micro-organisms:** n.c **earthworms**: Calf: 0.12 Weaner pig: 0.068 Fatt. pig: 0.046 Sow +litter: 0.016 Broiler: 0.18 Laying hens: 0.055 Replacement layer: 0.041 Broiler breeder: 0.031 Turkey: 0.087 **Plants**: Calf: 1.2 Weaner pig: 0.63 Fatt. pig: 0.43 Sow +litter: 0.15 Broiler: 1.7 Laying hens: 0.51 Replacement layer: 0.38 Broiler breeder: 0.29 Turkey: 0.81

The risk characterisation resulted in risk quotients (RQs) below or close enough to 1 for the surface water, groundwater and soil> compartments indicating that the product will not pose a risk to those compartments when used as recommended.

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PBT assessment

PBT-assessment	
PBT-statement :	The compound is not considered as PBT nor vPvB

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this is an application in accordance with article 13(1) of directive 2001/82/EC, as amended by 2004/28/EC and has been demonstrated to be a generic of Tylan W.O., powder for oral use in chickens, turkeys, pigs and calves. Therefore, a routine analytical method for the detection of residues is not submitted.

MRLs

Tylosin tartrate is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All food producing species
Muscle	100 µg/kg
Liver	100 µg/kg
Kidney	100 µg/kg
Fat	100 µg/kg
Milk	50 µg/kg
Eggs	200 µg/kg

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:
Calves (meat and offal): 12 days.
Pigs (meat and offal): 1 day.
Turkeys (meat and offal): 2 days.
Turkeys (eggs): Zero days.
Chickens (meat and offal): 1 day.
Chickens (eggs): Zero days.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, according to exemption 7.1. c) of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2.).

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Therefore, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product."

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.

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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 Heads of Vetrinary Medicines 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.

Summary of change	**Section updated in Module 3**	**Approval date**
Replacement of a manufacturing site for part of the manufacturing process of the finished product, except batch-release, batch control, primary packaging and secondary packaging. (NL/V/0189/001/1B/001)	NA	3rd October 2015
Addition of the new containers: 1 , 4 and 5 kg buckets and 100, 800 and 1000 g securitainers Change in the fill weight/fill volume of the pack size of the finished product. (NL/V/0189/IB/002/G)	Module 3 II.A	24th May 2017
Update of European Pharmacopoeial Certificates of Suitability to the relevant Ph. Eur. Monograph. from already approved manufacturers for an active substance (NL/V/0189/IA/003/G)	N/A	10th April 2019
Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product (NL/V/0189/IB/004/G)	N/A	23th May 2019
Renewal (NL/V/0189/001/R/001)		18th December 2019
change in pack size of the finished product (addition of 550 g securitainer). Change in dimension of the container (securitainer). (NL/V/0189/IB/007/G)	Module 3 II.A	08th April 2021