College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pharmasin 250 000 IU/g Premix for medicated feeding stuff for pigs, broilers and pullets

Created: July 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0130/003/DC
Name, strength and pharmaceutical form	Pharmasin 250 000 IU/g Premix for medicated feeding stuff for pigs, broilers and pullets
Applicant	Huvepharma NV Uitbreidingstraat 80, 2600 Antwerp Belgium
Active substance(s)	Tylosine (as tylosin phosphate)
ATC Vetcode	QJ01FA90
Target species	Pigs, broilers and pullets
Indication for use	Pigs - Treatment and prevention of Porcine Intestinal Adenomatosis (Ileitis)associated with *Lawsonia intracellularis* when the disease has been diagnosed at the group or herd level, Broilers and pullets: - Treatment and prevention of respiratory infections caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae,* when the disease has been diagnosed in the flock. - Treatment and prevention of necrotic enteritis caused by *Clostridium perfringens*, when the disease has been diagnosed in the flock.

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).

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 decentralised procedure	27 January 2009
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Greece, Spain, Hungary, Ireland, Italy, Poland, Portugal, Romania, United Kingdom

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 250 000 IU/g tylosin (as tylosine phosphate) and the excipients wheat meal, dipotassium phosphate en pregelatinised starch (potato).

The container/closure system consists of a LDPE/paper-paper-paper bag of 1 and 5 kg with sutured crimp and a 1 kg PE/Alu/PET sachet.

The choice of the formulation is justified.

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 at a licensed manufacturing site.

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

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C. Control of Starting Materials

The active substance is tylosine (as tylosin phosphate), an established substance described in the European/ Veterinary Pharmacopoeia. 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.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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

The analytical methods are identical to those of the finished products.

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.

G. Other Information

Shelf life of the finished product as packaged for sale: 2 years.

Shelf life after first opening of the immediate package: 3 months in a premixture or feed.

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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 and toxicological tests are not required.

The pharmacological and toxicological aspects of this product are identical to the reference product.

III.A Safety Testing

User Safety

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.

Environmental Risk Assessment

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

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = pigs 6447µg/kg and broilers 11264 µg/kg) is greater 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 <not> considered to be complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	5000 mg/L	
		5000 mg/L	25°C

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Dissociation constants in water pKa	OECD 112	pKa = 7.73	Triplicate determination 25°C
		pKa = 7.1	
		pKa = 7.7	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	logK_{ow} pH …5.0 =0.36	
		logK_{ow} pH 7.0 = 1.18	
		logK_{ow} pH 9.0 =1.36	

Environmental fate			
Soil Adsorption/Desorption	OECD 106 or …	Koc = K_d =	List all values with pH, Corg, soil texture including clay content
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50, study temp., kinetics applied = $DT_{50,\ 12°C.\ geo.\ mean\ of\ 4x\ soils\ or\ worst\ case\ if < 4\ soils}$ = Transformation products >10%: *<give name and structural formula>* % non-extractable residues (NER): 8.3	Sandy loam
		97	Sandy loam
		95	clay loam
		4.4	Sandy loam

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***

Algae and, growth inhibition test/*species*	OECD 201	EC50	0.42 1.38	mg/l	blue-green algal species *Anabaena flos-aquae* *Green algae* *Selenastrum capricornutum*
Daphnia sp. immobilisation	OECD 202	EC50	>700 680	µg/l	*24 h survivalDaphnia magna* 48 h survival
Earthworm/*Enchytraeidae* reproduction	OECD 220/222	NOEC	3000 3000 3000	Mg/kg	Folsomia fimetaria NO Enchytreaus crypticus Apperectodea caliginosa

*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	µg.L invertebrate Pigs: 680 Broilers: 680 Fish Pigs: >100 Broilers: >100 Algea	µg.L invertebrate Pigs: 7.97 Broilers: 13.9 Fish Pigs: 7.97 Broilers: 13.9	 Invertebrate Pigs: 0.012 Broilers: 0.020 Fish Pigs: 0.080 Broilers: 0.14

	Pigs: 4.2 Broilers: 4.2	Algea Pigs: 7.97 Broilers: 13.9	Algea Pigs: 1.90 Broilers: 3.31
groundwater	µg.L	µg.L Pigs: 23.9 Broilers: 41.7	
soil microorganisms: Nitrogen transformation test	<>25% difference in N transformation	NA	NA
soil	µg.kg invertebrate Pigs: 20.000 Broilers: 20.000 Plant Pigs: 11930 Broilers: 11930	µg.kg invertebrate Pigs: 6.447 Broilers:111.264 Plant Pigs: 6447 Broilers: 11.264	invertebrate Pigs: 0.32 Broilers: 0.56 Plant Pigs: 0.54 Broilers: 0.54

n.d.= not determined.
RQ values in bold exceed one and indicate that an unacceptable risk is possible
The risk characterisation resulted in risk quotients (RQs) below 1 for the <surface water, soil compartments indicating that the product will not pose a risk to those compartments when used as recommended.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

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

MRLs

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

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

* For fin fish this MRL relates to 'muscle and skin in natural proportions'
** For porcine and poultry species this MRL relates to 'skin and fat in natural proportions'

Withdrawal Periods

Based on the above, the following withdrawal periods are justified:

Pigs (meat) :zero days

Broilers and pullets (meat): 1 day

Do not use in laying hens producing eggs for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and 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.

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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 Heads of Veterinary 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**	**Approval date**
Change to the withdrawal period for Pigs for meat and offal from 1 day to 0 days. (NL/V/0130/003/II/001)	Module 3 III.B	20th January 2012
Introduction of a new DDPS and a new QPPV. (NL/V/xxxx/WS/001)	NA	23rd November 2012
Renewal – NL as RMS. (NL/V/0130/003/R/001)	NA	5th December 2013
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure. (NL/V/0130/003/IA/004)	NA	20th November 2014
Change(s) to a test procedure for the finished product. (NL/V/xxxx/WS/012)	NA	25th May 2018
Change(s) to a test procedure for the active substance. (NL/V/XXXX/WS/019)	NA	3rd August 2019
C.I.3. a) Implementation of wording agreed by the competent authority (NL/V/xxxx/WS/029)	Module 1 & 2	25th April 2020
Change in test procedure of active substance (NL/V/XXXX/WS/031)	NA	20th august 2020
Update of product information to version 9.0 of the QRD templates (NL/V/0130/003/A/010)	NA	22nd October 2023