College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pharmasin, 20 000 IU/g Oral Granules for pigs

Created: July 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0129/001/DC
Name, strength and pharmaceutical form	PHARMASIN 20 000 IU/g Oral Granules for pigs
Applicant	Huvepharma NV Uitbreidingsstraat 80 2600, Antwerpen Belgium
Active substance(s)	Tylosin phosphate (as tylosin phosphate) : 20 000 IU per g.
ATC Vetcode	QJ01FA90
Target species	Pigs
Indication for use	Treatment and prevention of clinical signs of porcine proliferative enteritis (porcine intestinal adenomatosis, proliferative hemorrhagic enteropathy, ileitis) associated with *Lawsonia intracellularis* when the disease has been diagnosed at the group level.

Pharmasin, 20 000 IU/g Orale Granules for pigs	NL/V/0129/001/DC
Huvepharma NV	Application for Decentralised Procedure
	Publicly available assessment report

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	Decentralised procedure application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	29th October 2008
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, 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 tylosin (as tylosin phosphate): 20 000 IU per g (quantitative) and the excipients (qualitative) wheat meal , dipotassium phosphate and pregelatinised starch (potato).

The container/closure system consists of LDPE/paper-paper-paper bag of 1 and 5 kg with sutured crimp.

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.

C. Control of Starting Materials

The active substance is tylosin (as 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

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.

G. Other Information

Shelf life of the veterinary product as packaged for sale: 24 months.
Shelf life of the veterinary after first opening the immediate package: 3 months

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

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

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

Pharmacological Studies

The applicant has conducted studies which show that tylosin phosphate acts by European Pharmacopoeia volume 1, section 2.9.3.

A mass of 725 mg of each premix was dissolved in 900 ml of test medium, over 20 minutes, under conditions described in the study report, at pH 1.2, 4.6 and 7.5 and at 37°C ± 0.5°C. SIX replicates were performed for each premix, at each pH. Samples were taken for analysis at 2, 5, 10, 15 and 20 minutes. Tylosin content in each premix was determined by a validated spectrophotometric method. The means and relative standard deviations (RSDs), of the percent tylosin phosphate (TP) dissolved from each premix at each pH, were calculated.

Results: mean (± RSD) of TP from each premix dissolved by 2, 5, 10, 15 and 20 minutes. Dissolution media at pH 1.2, 4.6 and 7.5

For both products, more than 85% of the tylosin phosphate (TP) was dissolved in less than 5 minutes and 100% in 15 minutes.

Toxicological Studies

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

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 = 912 µg/kg) is greater/equal to 100 µg/kg and no mitigations exist that alter the PECsoil.

Treatment group	PEC soil (□g kg)

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	5 g/L	25°C
Dissociation constants in water pKa	OECD 112	pKa = 7.73	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	logK_{ow} at pH … =1.63 logD 1.15	

Environmental fate			
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50, $_{\text{study temp., kinetics applied}}$ =8.3 $DT_{50,\ 12°C.\ \text{geo. mean of 4x soils or worst case if < 4 soils}}$ = Transformation products >10%: *<give name and structural formula>*	For each of the 4 soils. Information on soils used Sandy loam

Environmental fate			
		% non-extractable residues (NER):	
		DT50: 97	Sandy loam
		DT50:95	Clay loam
		DT50: 4.4	Sandy loam
Transformation in Manure (species)		$DT_{50,\ study\ temp.}$ [=] Transformation products >10% *<give name and structural formula>* % Transformation products $_{day\ ½\ default\ storage\ time}$ % parent $_{day\ ½\ default\ storage\ time}$ % non-extractable residues (NER):	Temperature (at which study was conducted):

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	0.42	µg/l	*Anabaena flosaquae*
			1.38		*Selenastrum capricornutum*
			16.3		*Green algae*
Daphnia sp. immobilisation	OECD 202	EC50	>700	µg/l	24 h survival
			680		48 h survival
			67		48 h survival
Daphnia magna, reproduction	OECD 211	EC10 or NOEC		µg/l	*Tier B*
Fish, acute toxicity/*species*	OECD 203	LC50	>100	µg/l	96 h survival *Oncorhynchys mykiss*
			152		96 h survival

Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect		µg/kg	Trigger value: 25% deviation from the control
Soil micro-organisms: nitrogen transformation test (100 days)	OECD 216	% effect	7264	µg/kg	*Only if effect is shown after 28 days*
Fish, early-life stage/s*pecies*	OECD 210	EC10 or NOEC	100	µg/l	*Tier BOncorhynchys* *mykiss*
Terrestrial Plants, growth test	OECD 208	EC50		µg/kg	6 species: (list names)
Terrestrial Plants, growth test	OECD 208	EC10 or NOEC		µg/kg	*Tier B* 6 species: (list names)
Earthworm/*Enchytraeidae* reproduction	OECD 220/222	EC10 or NOEC	3000	mgµg/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	µg/l Invertebrates: 680 Fish: >100 Algea: 4.2	µg/l Pigs (pharmasin 2% oral): 1.12	Invertebrates: 680 Pigs (pharmasin 2% oral): 0.0016 Fish Pigs (pharmasin 2% oral):

			0.011 Algea: Pigs (pharmasin 2% oral): 0.27
groundwater		Pigs (pharmasin 2% oral): 3.37	
soil	µg/kg Micro-organisms: 20000 Plants: 4540	µg/kg Pigs (pharmasin 2% oral): 912	Micro-organisms: Pigs (pharmasin 2% oral): 0.046 Plants: Pigs (pharmasin 2% oral): 0.20

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

III.B Residues documentation

Residue Studies

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.

Withdrawal Periods

Based on the above, the following withdrawal period is justified:

Pigs (meat) :zero days

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.

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 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**	**Approval date**
Extension of the shelf life of the finished product as packaged for sale (NL/V/0129/001/IB/001)	Module 3 II.G	28th April 2011
New DDPS and new QPPV (NL/V/xxxx/WS/001)	NA	23rd November 2012
Renewal- NL as RMS (NL/V/0129/001/R/001)	NA	5th December 2013
Change in the test procedure of 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