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agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PIRESOL 300 mg/ml oral solution for pigs

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0303/001/DC
Name, strength and pharmaceutical form	PIRESOL 300 mg/ml oral solution for pigs
Applicant	S.P. Veterinaria S.A
Active substance(s)	Paracetamol
ATC Vet code	QN02BE01
Target species	Pigs
Indication for use	Symptomatic treatment of fever in the context of respiratory diseases in combination with an appropriate anti infective therapy, if necessary.

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MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Art 13.3 of Directive 2001/82/EC (Hybrid Application), as amended
Date of completion of the original decentralised procedure	5 th June 2019
	-
Concerned Member States for original procedure	BE; BG, DE, DK, EL, FR, HU, IE, IT, LU, NL, PL, PT, RO, UK

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 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.

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II. QUALITY ASPECTS

A. *Qualitative and quantitative particulars*

The product contains paracetamol (300 mg/ml) and excipients benzyl alcohol (E1519), azorubine (E122), macrogol 300, dimethylacetamide, saccharin sodium and purified water.

The container/closure system is an opaque and white high density polyethylene 1 litre bottle and a 5 litres barrel with a high density polyethylene screw-on cap containing a polyethylene induction seal.

The choice of the formulation and the presence of preservative are 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 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 paracetamol, 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.

Scientific data and 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*

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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

The re-test period of the active substance is specified on the Ph. Eur. CEP

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.

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III. SAFETY AND RESIDUES ASSESSMENT

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the user warnings proposed by the applicant address the identified risks of the product and have been updated in order to reflect the conclusions of the URA.

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. **Phase I:**

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PEC_{soil} initial = 1303 µg/kg) is greater to 100 µg/kg and no mitigations exist that alter the PEC_{soil}.

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 (EMA/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	Ph. Eur. 6.0	10,000-33,333 mg/l	Higher solubility used in the ERA
Dissociation constants in water pKa	OECD 112	pKa = 9.65	

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Physical-chemical properties			
Study type	Test protocol	Result	Remarks
n-Octanol/Water Partition Coefficient logP _{ow}	OECD 107	logP _{ow} = 0.34	HPLC method

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Soil 1 Koc = 124.2 l/kg Soil 2 Koc = 57,347.6 l/kg Soil 3 Koc = 31,1190.5 l/kg Soil 4 Koc = 172.9 l/kg Soil 5 Koc = 269.9 l/kg	Soil 1 pH 4.7, 23.4% Clay, 4.93 % OC Soil 2 pH 6.5, 19.2% clay, 1.17% OC Soil 3 pH 6.9, 16.7% clay, 1.33% OC Soil 4, pH 6.4, 6.5% clay, 1.69% OC Soil 5 pH 6.6, 9.3% clay, 1.52% OC
Aerobic and Anaerobic Transformation in Soil	OECD 307	Soil 1: DT50 0.427 days Soil 2: DT50 0.227 days Soil 3: DT50 0.172 days Soil 4: DT50 0.326 days	Soil 1: 22%clay, 6.4 pH, 1.1% OC Soil 2: 11% clay, pH 7.6, 0.23% OC Soil 3: 29% clay, pH 5.3, 4.1% OC Soil 4 31% clay, pH 7.5, 1.2% OC

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Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Cyanobacteria, growth inhibition test <i>Pseudokierchneriella subcapitata</i>	OECD 201	EC50	493,000 (growth) 73,000 (yield)	µg/l	
Cyanobacteria, growth inhibition test <i>Pseudokierchneriella subcapitata</i>	OECD 201	NOEC	10,000 (yield)	µg/l	Tier B
<i>Daphnia</i> sp. immobilisation	OECD 202	EC50	7,760	µg/l	
Fish, acute toxicity <i>Cyprinus carpio</i>	OECD 203	LC50	> 1000,000	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	15% effect at D28 (PECsoil x 767)	--	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	NOEC	300,000	µg/kg	Due to the lack of effect, no EC50 could be derived. The worst case NOEC will be used in the Risk Assessment <i>Zea mays, Triticum aestivum, Sinapis alba, Helianthus annuus, Cucumis sativus, Vigna radiata</i>
Terrestrial Plants, growth test	OECD 208	NOEC	250,000	µg/kg	Oat, tomato, garden cress
Earthworm reproduction	OECD 222	NOEC	221,700	µg/kg	

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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 (EMA/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	7.76 ug/l	0.09113 ug/l	0.0117
groundwater	--	< 0.1 ug/l	No risk
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	No risk
soil	3000 ug/kg	1303.33 ug/kg	0.43

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended. The exposure in groundwater is under the trigger value (0.1 ug/l), hence no risk is expected in the groundwater compartment.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this application is for a hybrid product, submitted in accordance with Article 13(3) of Directive 2001/82/EC and bioequivalence with a reference product has been demonstrated.

MRLs

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

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Paracetamol	Not applicable	Bovine, Porcine	No MRL required	Not applicable	For oral use only

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The excipients:

	Included in Table 1 of Commission Regulation (EU) No 37/2010
Dimethyl acetamide	Yes. As no MRL required for all food producing species.
Benzyl alcohol	Yes. As no MRL required for all food producing species.
Saccharin sodium	Yes. As no MRL required for all food producing species.
Azorrubine (E-122)	Yes. As no MRL required for all food producing species.
Purified water	No. Included as substance not falling within the scope of Regulation (EC) No. 470/2009, with regard to residues of VMP EMEA/CVMP/519714/2009- Rev.35) as aqua purificata.
Macrogol 300	Yes. As no MRL required for all food producing species.

Withdrawal Periods

The proposed meat and offal withdrawal period for the PIRESOL 300 mg/ml is zero days, the same as for the reference product.

PIRESOL 300 mg/ml has the same pharmaceutical form and the same active substance as the reference product but has different strength in active substance and different composition in terms of excipients, however the bioequivalence with the reference product has been demonstrated.

IV. CLINICAL ASSESSMENT (EFFICACY)

For generics, insert in the relevant sections as appropriate:

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.

In addition, the applicant conducted a palatability study in order to demonstrate the adequate uptake of water, according to GL EMA/CVMP/EWP/206024/2011. The study demonstrated that the water consumption between test and reference product was equivalent according to the guideline requirements.

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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.

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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 veterinary Heads of Agencies website (www.hma.eu).

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