AGENCE NATIONALE DU
MEDICAMENT VETERINAIRE

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Maycetam 400 mg/ml solution for use in drinking water (BG, FR, DK, ES, PL, PT, RO)
Maycetam 400 mg/ml solution for use in drinking water for pigs (DE)

DATE :
27 April 2022

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	N° FR/V/0436/001/DC
Name, strength and pharmaceutical form	Maycetam 400 mg/ml solution for use in drinking water (BG, FR, DK, ES, PL, PT, RO) Maycetam 400 mg/ml solution for use in drinking water for pigs (DE)
Applicant	Laboratorios Maymó, S.A. Via Augusta, 302 08017 Barcelona (Spain)
Active substance(s)	Paracetamol
ATC Vetcode	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.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website https://www.anses.fr/en/thematique/veterinary-medicine-anmv

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	9 feb 2022
Concerned Member States for original procedure	BG, DE, DK, ES, 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. Composition

The product contains paracetamol (400.0 mg/mL) and the excipients colorant E124, dimethyl sulfoxide and macrogol 300.
The packaging of the finished product is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.
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 described in the European 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

Not applicable.

F. 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 sites have been provided demonstrating compliance with the specification.

G. Stability

A re-test period for the active substance is set in the certificates of suitability issued by EDQM.

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.
An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

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

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

The product is bioequivalent to the reference products, **PRACETAM 20 % SOLUTION FOR USE IN DRINKING WATER** and **PRACETAM 40% MG SOLUTION FOR USE IN DRINKING WATER**, which are authorised and marketed in France.

Toxicological Studies

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

The toxicological of this product are identical to those of the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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

Ecotoxicity

The applicant provided a phase I and a phase II environmental risk assessment in compliance with the relevant guideline.

Phase I:

The Phase I assessment showed that the initial predicted environmental concentration in soil is greater to 100 µg/kg. Therefore, a phase II ERA is required.

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.

Physical-chemical properties		
Study type	**Test protocol**	**Result**
Water solubility	OECD 105	12 g/L at 20°C
Dissociation constants in water pKa	OECD 112	pKa = 9.48
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	logK_{ow} = 0.5

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc = 67, 39, 29, 62, 32 K_d = 2, 1, 1, 1, 1	Clay, Silt loam, Loam, Silt, Loamy sand
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50\ pc*}$= 0.25, 0.291, 0.0326, 0.238 $DT_{50\ pc,\ geo.\ mean}$ =0.154d $DT_{50\ pc+\ NER}$= 1140, 2600, 548, 1140	Sandy loam, Silt loam, Loam, Clay

* pc: parent compound ; NER: Non Extractable Residue

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

	protocol				
Algae, growth inhibition test/ *Pseudokirchneriella subcapita*	OECD 201	EC50	>209.7	mg/l	
Daphnia sp. immobilisation	OECD 202	EC50	9.2	mg/l	
Daphnia sp. reproduction	OECD 211	NOEC	5.72	mg/l	Kim et al. (2012)
Fish, acute toxicity/*species*	OECD 203	LC50	> 9.2	mg/l	Limit test
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25% difference in N transformation	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	> 900	mg/kg dw	Avena sativa, Zea mais, Beta vulgaris, Glycine mas, Helianthus annuus, Cucumis sativus
Earthworm reproduction	OECD 222	NOEC	308.6	mg/kg dw	

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 Tier A	9.2 µg/L	103.4 µg/L	11
Refined surface water Tier A (FOCUS)	9.2 µg/L	1.31 ng/L	<1
groundwater		<0.1 µg/L	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	> 9 mg/kg	1.3 mg/kg	<0.14

The risk characterisation resulted in risk quotients (RQs) below 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.

PBT assessment

PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	BCF	logKow < 4	not B
Persistence	DT50, compartment, 12 °C	0.62 day	not P
Toxicity	NOEC or CMR	NOEC Daphnia, D21= 5.72 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

The outcome of the environmental risk assessment indicates that the use of the product is not expected to pose a significant concern to the environment.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted.

MRLs

The active substance, paracetamol, is included in table 1 of the annex of the Commission Regulation (EU) No. 37/2010, as follows,

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Not applicable	Porcines	No MRL required	Not applicable	For oral use only	No entry	37/2010 of 22.12.2009

The acceptable daily intake of paracetamol is 50 µg/kg bw, *i.e.* 3 mg/person.

The composition of the generic product is acceptable according to the European regulation (EC) No 470/2009.

Withdrawal Periods

The withdrawal periods agreed for the reference product can be applied to the new product, as follows:
Meat and offal: zero days.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology
Pharmaceutical form

The test and the reference products have the same pharmaceutical form: solution for use in drinking water.

Active substance qualitative and quantitative composition
The test and reference products have the same qualitative and quantitative composition in active substance: 400 mg of paracetamol per mL.

Bioequivalence studies
No study was provided.
The reference and candidate products can be considered bioequivalence according to the section 7.1 and the annexe I of the bioequivalence GL (EMA/CVMP/016/2000-Rev.3).

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, tolerance data are not required. The excipients of the tested product are safe and extensively used in veterinary medicine.

IV.B Clinical Studies

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 are acceptable.