College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Doxylin 100%

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0184/001/MR
Name, strength and pharmaceutical form	Doxylin 100%
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Doxycycline hyclate
ATC Vetcode	QJ01AA02
Target species	Calve and pig
Indication for use	Pre-ruminating calves: - Bronchopneumonia and pleuropneumonia caused by *Pasteurella* spp, *Streptococcus* spp, *Arcanobacterium pyogenes*, *Haemophilus somnus* and *Mycoplasma* spp. Pigs: - Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*; - Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*; - Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

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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).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Autogeneric application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	20th November 2013
Date product first authorised in the Reference Member State (MRP only)	6th March 2013
Concerned Member States for original procedure	Belgium, Germany, Denmark, Estonia, Greece, Spain, France, Hungary, Italy, Lithuania, Latvia, Poland and Romania

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; anyreactions 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 Doxycycline hyclate:1000 mg.

The container/closure systems are buckets of three different sizes (1 kg, 2 kg and 5 kg) of white PP and a securitainer of 100 g and 1 kg of white PP.

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 at a licensed manufacturing site.

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The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is doxycycline hyclate, an established active 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.

Certificates of suitability issued by the EDQM 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

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.

The claim of a 3 months stability after broaching is based on the demonstration of stability for a batch broached and stored 3 months at +25°C.
The claim of a 12 hours stability of medicated drinking water is based on the demonstration of stability for a batch stored 24 hours at +25°C.
The claim of a 6 hours stability of medicated milk replacer is based on the demonstration of stability for a batch stored 6 hours at +25°C.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening of the immediate packaging: 3 months.

Shelf life after reconstitution in drinking water: 12 hours.

Shelf life after reconstitution in milk replacer: 6 hours.

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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 are identical to the reference product.

III.A Safety Testing

Pharmacological 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.

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

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that during the handling of the product, skin contact and inhalation has to be avoided, taking into account the risk of sensitisation and contact dermatitis. For that purpose wear gloves and a dust mask.

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 (PECsoil initial = see table) is greater to 100 µg/kg and no mitigations exist that alter the PECsoil.

Target animal	PEC_{soil} [$\mu g\ kg_{soil}^{-1}$]
Calves	**248**
Weaner pig	**378**
Fattening pig	**256**
Sow + litter	91

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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.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	540 mg/L	pH 5; 20 ºC
		436 mg/L	pH 7; 20 ºC
		26766 mg/L	pH 9; 20 ºC
Dissociation constants in water pKa	OECD 112	PKa 1 = 3.30	20 ºC
		PKa 2 = 7.7	20 ºC
		PKa 3= 8.73	20 ºC
Partition coefficient	OECD 107	Log Pow = -0.16 (pH2)	pH 2, 20 ºC
		Log Pow = -0.12	pH 7, 20 ºC
		Log Pow = -1.65	pH 10, 20 ºC

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc = 29199 L/kg	Doxycycline is a difficult substance when performing a sorption study. The substance has a low solubility and a high detection limit. Since only three soils were tested, the lowest of these values is selected for use in the risk assessment. *From the submitted study reliable endpoints could be derived. However, since the substance does not follow Freundlich kinetics, a different endpoint was selected by the RMS: 29199 L kg^{-1}*
	OECD 106	Koc = 71176.9 L/kg	Silt loam
	OECD 106	Koc = 106087.7 L/kg	Clay loam
	OECD 106	Koc = 221722.6 L/kg	

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Effect studies*					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Cyanobacteria, growth inhibition test	OECD 201	EC50	0.198	mg/l	*Anabaena flos-aquae*
Cyanobacteria, growth inhibition test	OECD 201	EC10	0,145	mg/L	*Anabaena flos-aquae*
Daphnia sp. immobilisation	OECD 202	EC50	>151	mg/l	*Daphnia magna*
Fish, acute toxicity	OECD 203	LC50	>84.7	mg/l	*Oncorhynchus mykiss*
Terrestrial Plants, growth test	OECD 208	LC50	>93.7	mg/kg	*Avena sativa, Lactuca sativa* and *Raphanus sativus.*
Terrestrial Plants, growth test	OECD 208	NOEC	>93.7	mg/kg	*Avena sativa, Lactuca sativa* and *Raphanus sativus*
Terrestrial Plants, growth test	OECD 208	EC50	>150	mg/kg	*Brassica rapa, Lepidium sativum* and *Raphanus sativus* in sandy loam
Terrestrial Plants, growth test	OECD 208	NOEC	≥ 150	Mg/kg	*Brassica rapa, Lepidium sativum* and *Raphanus sativus* in sandy loam
Earthworm reproduction	OECD 220/222	NOEC	>924	mg/kg	*Eisenia foetida*
Earthworm mortality	OECD 222	NOEC	>924	mg/kg	*Eisenia foetida*

* all values are expressed as doxylin base.

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:

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Compartment	**PNEC**	**PEC**	**RQ**
surface water	µg/L Cyanobacteria: 1.98 µg/L Crustacea: >0.151 mg/L Fish: 0.0847 mg/L	µg/L Calf: 0.035 Weaner pig: 0.054 Fattening pig: 0.037 Sow + Litter: 0.013	Cyanobacteria: Calf: 0.018 Weaner pig: 0.027 Fattening pig: 0.019 Sow+litter: 0.007 Crustacea Calf: <0.00023 Weaner pig: 0.00036 Fattening pig: 0.00025 Sow+litter: 0.0009 Fish Calf: <0.00041 Weaner pig: <0.00064 Fattening pig <0.00044 Sow+litter: <0.00015
groundwater	The PNEC for *Daphnia magna* representative for the trophic level of aquatic invertebrates is used to calculate the RQ for the groundwater compartment.	µg/kg Calf: 0.11 Weaner pig: 0.16 Fattening pig: 0.11 Sow + Litter: 0.04	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil	µg/kg Micro-organisms: No long term influence on nitrogen	µg/kg Calf: 248 Weaner pig: 378	<u>Micro-organisms:</u> Calves: n.c Weaner pig: n.c.

	transformation in soils Earthworms: ≥92400 Plants: >937	Fattening pig: 256 Sow + Litter: 91	Fattening pig: n.c Sow + litter n.c <u>Earthworms:</u> Calves: <0.0027 Weaner pig: <0.0041 Fattening pig: <0.0028 Sow+litter: <0.001 <u>Plants:</u> Calves:<0.26 Weaner pig: <0.40 Fattening pig:<0.27 Sow +litter: <0.097

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	A BCF value calculated from the log Kow is lower than 2000 L kg^{-1}	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	The compound would not be persistent since the half-life in soil reported by the applicant is 31 days	not P
Toxicity	NOEC	The reported NOECs are < 0.01 mg L^{-1}, and the compound has no endocrine or CMR properties	not T
PBT-statement :	The compound was not considered as PBT nor vPvB		

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III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because The product applied for is identical to the Reference Product Doxycycline hyclaat (REG NL 8917). There is no need to perform additional residue studies.

The withdrawal periods for calves and pigs are in line with those recommended for the reference product.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 14 days for meat and offal in calves and 8 days for meat and offal for pigs are justified.

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.

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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**	**Approval date**
Update of European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer; Deletion of multiple European Pharmacopoeial Certificates of Suitability to the relevant Ph. Eur. Monograph. (NL/V/xxxx/IA/016/G)	NA	25th May 2016
Change in pack size of the finished product concerning the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products (NL/V/0184/001/IB/002)	Module 3 II.A	10th December 2016
New European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. of a new manufacturer. (NL/V/xxxx/IA/023/G)	NA	29th March 2017
Introduction of a re-test period of an active substance supported by real time data. (NL/V/0184/001/IB/004)	NA	26th April 2017
Renewal – NL as RMS. (NL/V/0184/001/R/001)	NA	5th December 2018
Update of European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer. (NL/V/xxxx/IA/038/G)	NA	10th August 2019

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Introduction of a re-test period supported by real time data; Update of European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer. (NL/V/0184/IB/005/G)	NA	17th August 2019