College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500 3531 AH Utrecht The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DFV Doxivet 500mg/ml powder for administration via drinking water for chickens and pigs

January 2020

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0152/002/DC
Name, strength and pharmaceutical form	DFV Doxivet 500mg/ml powder for administration via drinking water for chickens and pigs
Applicant	Cyton Biosciences Ltd. Hyland Mews 21 High Street Clifton Bristol, BS8 2YF United Kingdom
Active substance(s)	Doxycycline hyclate
ATC Vetcode	QJ01AA02
Target species	Chicken / Pig
Indication for use	Pigs: Treatment of infections caused by microorganisms that are susceptible to doxycycline such as: • Atrophic rhinitis caused by *Pasteurella* spp. and *Bordetella bronchiseptica*; • Bronchial pneumonia caused by Pasteurella multocida, Streptococcus suis and Mycoplasma hyorhinis; Pleuropneumonia caused by Actinobacillus pleuropneumoniae. Chickens: • Pasteurellosis caused by *Pasteurella multocida*; Respiratory infections caused by *Ornithobacterium rhinotracheale* (ORT).

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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).

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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	27th July 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Greece, Spain, Hungary, Irelnd, Italy, Lithuania, Norway, Poland, Portugal, Romania, Sweden, Slovakia, 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.

The safety and efficacy aspects of this product are based on bioequivalence with the reference product DOXY ORT 50%, 500 mg/g, powder for oral solution which has been authorized in the Netherlands on 27 July 1991. The marketing authorisation holder of the reference product is Eurovet Animal Health.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains Doxycycline hyclate 500 mg (quantitative) and the excipients (qualitative) Silica colloidal anhydrous Citric acid anhydrous.

The container/closure system contains package sizes from 100, 1000 and 2500 g and the bags are formed by polyester, aluminium and polyethylene.

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The choice of the formulation 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 at a licensed manufacturing site.
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.

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.

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G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

Shelf-life after first opening the immediate packaging: 12 months.

Shelf-life after dilution or reconstitution according to directions: 24 hours after dilution in drinking water.

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.

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that direct contact with skin and inhalation should be avoided during the preparation or handling and/or administration.
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 is greater to 100 µg/kg and 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 considered to be complete and acceptable.

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Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
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	pH 9; 20 ºC
Dissociation constants in water pKa	OECD 112	pKa 1= 3.30	20 ºC
		pKa 2= 7.5	20 ºC
		pKa 3= 8.73	20 ºC
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	logD_{ow} at pH … = -0.16	pH 2; 20 ºC
		logD_{ow} at pH … = -0.12	pH 7; 20 ºC
		logDow at pH … = -1.65	pH 9; 20 ºC

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
cyanobacteria, growth inhibition /*species*	OECD 201	EC50	1.98	µg/l	*species Anabaena flos-aquae*
Daphnia sp. immobilisation	OECD 202	EC50	> 151 mg L	µg/l	Daphnia magna.
Fish, acute /*species*	OECD 203	LC50	> 84.7	mg/l	Oncorhynchus mykiss
Terrestrial Plants, growth test	OECD 208	EC50	> 93.7	mg/kg	6 species: (list names) Avena sativa and Raphanus sativus.

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Earthworm/ reproduction	OECD 220/222	NOEC	≥ 924	mg/kg	Eisenia foetida

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 Cyanobacterium: 1.98 Crustacea: > 0.151 mg/l Fish: > 0.0847 mg/l	n.c	Since the PECsurface water cannot be calculated due to a lack of valid log KOC data, risk to surfacewater cannot be assessed
groundwater		n.c	Since the PECgroundwater cannot be calculated due to a lack of valid log KOC data, risk to groundwater cannot be assessed
soil microorganisms: Nitrogen transformation test	<>25% difference in N transformation	NA	NA

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soil	µg/kg Micro-organisms: n.c Earthworms: ≥ 92400 Plants: > 937	µg/kg Weaner pig: 301 Fattening pig: 204 Sow + litter: 72.5 Broiler: 615 Laying hen: 71.8 Replacement layer: 136 Broiler breeder: 38.7	Microorganisms: Weaner pig: n.c Fattening pig: n.c. Sow + litter: n.c. Broiler: n.c. Laying hen: n.c. Replacement layer: n.c. Broiler breeder: n.c Earthworms: Weaner pig: ≤0.0033

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			Fattening pig: ≤0.0022 Sow + litter: ≤0.001 Broiler: ≤0.0067 Laying hen: ≤0.001 Replacement layer: ≤0.0015 Broiler breeder: 0.001 Plants: Weaner pig: <0.32 Fattening pig: <0.22 Sow + litter: <0.077 Broiler: <0.66 Laying hen: 0.077 Replacement layer: <0.15 Broiler breeder: <0.041

n.c: not calculated

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.

III.B Residues documentation MRLs

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

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	Poultry **(µg/kg)**	Porcine **(µg/kg)**
Muscle	100	100
Liver	300	300
Kidney	600	600
Fat / skin	300	300

Withdrawal Periods

Based on the data provided above, a withdrawal period of 5 days for meat in pig
3 days for chicken at a dosage of 10 mg per kg of live weight and 12 days for chicken at a dosage above 10 mg per kg of live weight 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.

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**

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Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure (no new data required) (NL/V/0152/002/IB/001)	NA	17th February 2012
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure (new data required) (NL/V/0152/002/II/002)	NA	6th December 2013
Change in the invented name of the nationally authorised product from 'Doxivet 500mg/ml' to 'DFV Doxivet 500mg/ml' (NL/V/0152/002/IB/003)	Module 1	14th March 2014
Renewal – NL as RMS (NL/V/0152/002/R/001)	NA	18th June 2016
Update of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer and deletion of European Pharmacopoeial Certificates of Suitability to the relevant Ph. Eur. Monograph. (NL/V/0152/IA/004/G)	NA	15th October 2016

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