Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Doxylin 433 mg/g, powder for use in drinking water for chickens and turkeys

Date Created: August 2015

PuAR correct as of 30/08/2018 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0522/001/DC
Name, strength and pharmaceutical form	Doxylin 433 mg/g, powder for use in drinking water for chickens and turkeys
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Doxycycline
ATC Vetcode	QJ01AA02
Target species	Chickens (broilers, broiler breeders) Turkeys (broilers, breeders)
Indication for use	Treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 March 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania

I. SCIENTIFIC OVERVIEW

Doxylin 433 mg/g powder for use in drinking water for chickens and turkeys has been produced as a generic hybrid of Doxyprim 40%. The reference product was first authorised in Hungary in July 2001, and pharmaceutical equivalence has been claimed with Pulmodox 500 mg/g granules for oral solution, authorised in the UK since April 2010.

The product is authorised to treat respiratory conditions associated with *Mycoplasma gallisepticum* susceptible to doxycycline in chickens and turkeys. The product is administered via the drinking water. It is contraindicated in animals with hepatic dysfunction and when tetracycline resistance has been detected in the flock due to the potential for cross resistance. The product should not be used in cases of known hypersensitivity to the active substance or any of the excipients.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 433.3 mg doxycycline (500 mg as doxycycline hyclate) as the active substance and the excipients citric acid (anhydrous) and lactose monohydrate.

The container/closure system consists of either a securitainer or a bucket. The securitainer is a white polypropylene container, closed with a low-density polyethylene cap, containing 1 kg of product. The bucket is a white polypropylene container with polypropylene cap and contains 1, 2.5 or 5kg of product. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the active substance and the excipients. The mixture is then filled into the bucket or securitainer. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is doxycycline, an established active substance described in the European Pharmacopoeia. Certificates of suitability were provided for the two manufacturers of the 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.

The excipients are controlled in accordance with their respective Ph. Eur. Monographs. Certificates of analysis have been supplied.

II.C.4. Substances of Biological Origin

[2] Efficacy – The production of a desired or intended result.

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.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. The tests include those for identification and assay of the active substance, appearance, pH and solubility.

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.

II.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. The active substance is controlled according to the Ph. Eur. Certificates of Suitability. A retest period of 3 years has been established for one manufacturer and a retest period of 4 years for the other.

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. Batches of the product were stored in securitainers at 25°C/ 60% RH for 60 months and at 40°C/ 75% RH for 9 months. Product was also stored in buckets at 25°C/ 60% RH for 30 months and at 40°C/ 75% RH for 9 months. A shelf life of 3 years for the securitainer and 2 years for the bucket was determined.

Data on the in-use stability were provided for batches opened and stored for 3 months under real conditions. A 3 month in-use shelf life is accepted. In addition, data were provided for stability following reconstitution with water. A batch from each presentation was used to make a solution and stored for 24 hours.

G. Other Information

Shelf life
The shelf life of the finished product as packaged for sale is 3 years for the securitainer and 2 years for the bucket.
Shelf life after first opening the immediate packaging is 3 months.
Shelf life after reconstitution in drinking water is 24 hours.

Special precautions for storage
Store below 25°C.
Store in tightly closed original container in order to protect from light.
Medicated drinking water should be protected from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the results of pharmacological studies are not required.

Toxicological Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the results of toxicological studies are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main routes of exposure are dermal, oral, ocular or inhalation of the powder. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- During preparation and administration direct contact of the product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
- People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
- Wear protective gloves (e.g. rubber or latex), glasses and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143) when reconstituting or administering the solution. Wash exposed skin after preparation of medicated drinking water. In case of accidental eye contact, rinse with plenty of fresh water.
- Do not smoke, eat or drink when handling the product.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Inflammation of

the face, lips or eyes or respiratory difficulties are the most serious signs which require urgent medical attention.

Environmental Safety

The product contains doxycycline, a broad spectrum tetracycline antibiotic, to be administered to chickens and turkeys via the drinking water. An environmental risk assessment (ERA) has been submitted in support of the application. The ERA is in accordance with VICH and CVMP guidelines. As all animals are housed the only route of environmental exposure is by spreading manure onto land.

Phase I:
A Phase I assessment was supplied. The initial predicted environmental concentration (PEC) was calculated for broilers, broiler breeders and turkeys. The PEC in soil was greater than 100 µg/kg, for broilers and turkeys, therefore a Phase II ERA was required.

Phase II Tier A:
A Phase II tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physico-chemical properties, environmental fate and effects. Studies were carried out using the active substance doxycycline unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	pH 5: 540.3 ± 5.1 mg/l pH 7: 436.1 ± 7.9 mg/l pH 9: 26766 ± 1187 mg/l	Soluble in water.
Dissociation constants in water pKa	OECD 112	pK_{A1}: 3.5 pK_{A2}: 7.7 pK_{A3}: 9.5	Published source.
Melting Point	OECD 102	201°C	Published source.
Vapour Pressure	OECD 104	1.89 x 10^{-18} mPA	Published source.
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	pH 2: -0.16 pH 7: -0.12 pH 10: -1.65	Very low Log K_{OW}, no bioaccumulation potential

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption	OECD 106	K_{OC} = 34603 ml/g	
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} =26 days at 20°C	

Environmental effects

Study type	Guideline	Endpoint	Result	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	EC50	145 µg/l	
Daphnia sp. immobilisation	OECD 202	EC50	>140 mg/l	
Fish, acute toxicity/*Species*	OECD 203	LC50	>84.7 mg/l	
Soil Micro organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	<25%	
Terrestrial Plants, Growth Test/*Species*	OECD 208	EC50	>93.7 mg/kg	
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC	≥ 924 mg/kg	

PEC Calculations

PEC values for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surface water (µg/l)
Broiler	887	0.36	0.121
Broiler breeder	56	0.02	0.008
Turkey	553	0.23	0.075

As initial PECs in groundwater exceeded 0.1 µg/l, a groundwater risk assessment was provided. Using the meta-model provided in the relevant CVMP guidelines, it was demonstrated that appropriate use of the product does not pose a risk to groundwater.

PNEC Calculations and Risk Characterisation

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows. The worst case scenario is included in the table below.

Broilers

Test organism	End point	AF	PNEC	PEC	RQ

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = 145 µg/l	100	1.45 µg/l	0.121 µg/l	<0.083
Daphnia sp. immobilisation	EC_{50} = >140 mg/l	1000	>140 µg/l	0.121 µg/l	<0.00086
Fish, acute toxicity	LC_{50} = >84.7 mg/l	1000	>84.7 µg/l	0.121 µg/l	<0.00143
Soil Micro organisms:	<25% effect in N trans-formation (28 d)	NA	NA	NA	NA
Terrestrial Plants, Growth	EC_{50} = >93.7 mg/kg	100	>937 µg/kg	887 µg/kg	0.95
Earthworm reproduction	NOEC = ≥924 mg/kg	10	≥92400 µg/kg	887 µg/kg	0.0096

As all RQ values were <1 the ERA ended at tier A. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the results of residues studies are not required.

A GLP-compliant residue depletion study using the final formulation has been provided for turkeys. Samples of kidney, liver, fat and skin and muscle tissue were taken from animals at several time points. Results showed that residues depleted to below the MRL in all tissues before the end of the withdrawal period. For every series of test samples analysed a calibration curve and QC samples were also analysed. An ultra-performance liquid chromatography (UPLC) method was used. The method was fully validated.

MRLs

Doxycycline is listed in Commission Regulation 37/2010 and MRLs have been established for edible tissues. The marker substance is doxycycline.

MRLs are listed below:

	Poultry
Muscle	100 µg/kg
Liver	300 µg/kg
Kidney	600 µg/kg
Fat / skin	300 µg/kg

Withdrawal Periods

Based on the data provided, and as bioequivalence with the reference product has been accepted, the same withdrawal period as the reference product is proposed.

Meat and offal of chickens: 5 days
Meat and offal of turkeys: 12 days
Not permitted for use in laying birds producing eggs for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the results of pre-clinical studies are not required.

Bioequivalence studies were not required as an exemption was claimed in accordance with 7.1.c) Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is essentially similar to the reference product and data on the solubility and rate of dissolution were supplied in both soft (low pH) and hard water (high pH). It is concluded that following the addition of the test product and the reference product to drinking water at the same concentration, the absorption and bioavailability will be similar. The biowaiver was accepted and the product can be considered bioequivalent to the reference product.

IV.II. Clinical Documentation

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, the results of clinical studies are not required.

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 benefit/risk profile of the product(s) is favourable

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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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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