College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Altidox 500 mg/g Powder for Use in Drinking Water for Pigs, Chickens and Turkeys

Date Created: November 2016

Updated: August 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0277/001
Name, strength and pharmaceutical form	Altidox 500 mg/g Powder for Use in Drinking Water for Pigs, Chickens and Turkeys
Applicant	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel The Netherlands
Active substance	Doxycycline hyclate
ATC Vetcode	QJ01AA02
Target species	Pigs, Chickens and Turkeys
Indication for use	Pigs: treatment of clinical respiratory infections caused by *Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to doxycycline. Chickens and turkeys: 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 Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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	27th July 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Croatia, France, Germany, Hungary, Ireland, Italy, The Netherlands, Poland, Portugal and Spain

I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid' application submitted in accordance with Article 13 (3) of Directive 2001/82/EC (as amended). The reference product is Pulmodox 500 mg/g granules for oral solution for pigs, chickens and turkeys, authorised in the UK since 2010. The product fulfils the requirements for a waiver from bioequivalence studies in accordance with exemption 7.1.c of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

Pigs
The product is indicated for the treatment of clinical respiratory infections caused by *Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to doxycycline, at a dose rate of 20 mg doxycycline per kg body weight daily (equivalent to 46 mg product per kg body weight), administered in the drinking water for 5 consecutive days.

Chickens
The product is indicated for the treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline, at a dose rate of 20 mg doxycycline per kg body weight daily (equivalent to 46 mg product per kg body weight), administered in the drinking water for 5 consecutive days.

Turkeys
The product is indicated for the treatment of clinical respiratory infections associated with *Mycoplasma gallisepticum* susceptible to doxycycline, at a dose rate of 25 mg doxycycline per kg body weight daily (equivalent to 58 mg product per kg body weight), administered in the drinking water for 5 consecutive days.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 500 mg of doxycycline hyclate, equivalent to 433 mg doxycycline, and citric acid anhydrous.

The container/closure system consists of a bag with an outer layer of polyethylene terephthalic acid, middle layers of aluminium and polyamide and an inner layer of low density polyethylene (PET/ALU/PA/LDPE). The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are 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 manufacturing method consists of a simple mixing then filling by weight method.

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. 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 excipient is monographed within the European Pharmacopoeia, acceptable Certificates of Analysis were provided. Packaging was suitably verified for use.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product. A signed and dated TSE declaration is provided from the applicant stating compliance with the *Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMA/410/01 rev.3).*

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. 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. Control tests on the finished product include identification and assay of doxycycline hyclate, appearance, weight, solubility, microbial quality. Further control tests of the therapeutic solution are pH, clarity and colour.

II.F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product. 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 were stored under VICH[3] conditions of 25°C/60% RH and 40ºC/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution or reconstitution according to directions: 24 hours.

Keep the bag tightly closed after first opening in order to protect from moisture. This veterinary medicinal product does not require any special temperature storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

[3] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

As this is a generic application according to Article 13 (3) and bioequivalence with a reference product has been established results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are in line with those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the potential risks are inhalation of dust and dermal exposure.

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

- Do not smoke, eat or drink while handling the product.
- Take measures to avoid producing dust when incorporating the product into water. Avoid direct contact with skin and eyes when handling the product to prevent sensitisation and contact dermatitis.
- People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product. During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) 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 applying the product.
- In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.
- If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.

Environmental Safety

A Phase I and Phase II Environmental Risk Assessment (ERA) for doxycycline hyclate has been submitted and conducted in accordance with VICH and CVMP[4] guidelines.

Phase I:

As the initial predicted environmental concentration (PEC) of doxycycline hyclate in soil is greater than 100 µg/kg for weaner pigs, fattening pigs, sows with a litter,

[4] The Committee for Medicinal Products for Veterinary Use

broilers, replacement layers, layer chickens and turkeys, a Phase II assessment is required. In the environment the hyclate will not be present; however on this occasion, the values were accepted as it is acknowledged that the hyclate values will be higher and will represent a worst case approach

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 physicochemical properties, environmental fate and effects. Studies were carried out using the active substance doxycycline hyclate (with endpoints corrected to account for doxycycline only) unless indicated otherwise.

Physicochemical properties

Study type	Result	Remarks
Water solubility	Freely soluble in water	Published data
Dissociation constants in water pKa	3.5, 7.7 and 9.5 at 20°C	Published data
Melting Point/Melting Range	Chars without melting at 201°C	Published data
Vapour Pressure	$<10^{-15}$	Calculated method
n-Octanol/Water Partition Coefficient logP_{ow} (OECD 117, HPLC method)	pH 2.5: -0.2 logK_{ow} pH 7.0: 0.0 logK_{ow} pH 9.0: 1.6 logK_{ow}	Bespoke study logK_{ow} <4, indicates low bioaccumulative potential

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	K_{oc} of 11 576.25	Non mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	A range of degradation rates were observed which were dependent on the soil type and test conditions (sterile and non-sterile) DT_{50} = 1.4 to 69 days	Readily to fairly degradable in soil

Environmental effects

Study type	**Guideline**	**Endpoint**	**Result**
Algae Inhibition Test*:* *Pseudokirchneriella subcapitata* *Synechococcus leopoliensis* *Anabaena flos-aquae*	OECD 201	NOEC	6.95 µg at 72 hours (growth rate and yield) 11.2 µg at 48 hours (growth rate and yield) 22.4 µg at 72 hours (growth rate) 6.5 µg at 72 hours (yield)
Daphnia magna immobilisation	OECD 202	NOEC	≥100 mg at 48 hours
Fish, acute toxicity: *Oncorhynchus mykiss*	OECD 203	NOEC LOEC	42.8 mg at 96 hours 82.0 mg at 96 hours No mortality in any test groups
Soil Microorganisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	No long term effects on nitrogen and carbon transformation in soils at a dose ≥ 10 mg/kg dry wt.
Terrestrial Plants, Growth Test in 6 species: *Brassica napus,* *Glycine max,* *Helianthus annuus,* *Cucumis sativus,* *Avena sativa,* *Allium cepa*.	OECD 208	EC_{50}	66.3 mg/kg (*Brassica napus)* No effects on germination
Earthworm reproduction: *Eisenia fetida*	OECD 222	NOEC	160 mg/kg

Exposure assessment

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 PEC values were calculated using broiler chickens corrected to doxycycline from the hyclate salt. As the initial $PEC_{groundwater}$ is above the threshold of 0.1 µg/l, further refinement was conducted using FOCUS PEARL modelling which demonstrated that appropriate use of the product will not pose a risk to drinking water.

The following PEC values were calculated.

Outputs	Value	Source
PEC_{soil} (µg/kg)	887	CVMP Equation 1
$PEC_{groundwater}$ (µg/l)	1.05	CVMP Equation 32
Refined $PEC_{groundwater}$ (µg/l)	<0.01	FOCUS PEARL
$PEC_{surface\ water}$ (µg/l)	0.35	CVMP Equation 36

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.

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} 22 µg/l	100	0.195 µg/l	0.35 µg/l	>1 (1.79)
Daphnia sp. immobilisation	EC_{50} >100 mg/l	1000	>86.6 µg/l		<1 (0.004)
Fish, acute toxicity	LC_{50} >220 mg/l	1000	>191 µg/l		<1 (0.002)
Terrestrial Plants, Growth	EC_{50} >66 mg/kg	100	>572 µg/kg	887 µg/kg	Brassica napus >1 (1.55)
Earthworm reproduction	NOEC >160 mg/kg	10	>13.9 mg/g		<1 (0.064)

Nitrogen: 28 days <25% of control at maximum PEC_{soil}

At Tier A the RQ values for algae and for terrestrial plants was calculated by the applicant to be >1, therefore further Tier B tests were required.

Phase II Tier B:

A Tier B another plant toxicity study according to OECD 208 was conducted using *Brassica napus* and two additional species of Brassicaceae, satisfying the requirements of VICH Tier B.

The applicant used the NOEC values from the algae (already available) and additional plant studies to calculate a revised PNEC for comparison with the PEC as shown below.

Test species	Test result	AF	PNEC (expressed as doxycycline)	PEC (expressed as doxycycline)	RQ
Green algae	NOEC 6.95 µg/l	10	0.695 µg/l	0.35 µg/l	<1
Plants	NOEC 10 mg/kg	10	1000 µg/kg	887 µg/kg	<1

At Tier B the RQ values for algae and for terrestrial plants were demonstrated to be <1; indicating an acceptable risk, and therefore, no further studies were required.

It is concluded that the risk to the environment from the use of the product is acceptable when used as recommended in the SPC.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the product contains the same active substance and excipients and is in the same physical form, making it essentially similar to the reference product.

MRLs

The active substance doxycycline hyclate is listed in table I of the Commission Regulation 37/2010 and MRLs have been established for edible tissues. The marker substance is doxycycline.

MRLs are listed below:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissue	Other provision
Doxycycline hyclate	Doxycycline	All food producing species	600 µg/kg	Kidney	
			300 µg/kg	Liver	
			100 µg/kg	Muscle	
			300 µg/kg	Fat and skin	Skin and fat in natural proportions

Withdrawal Periods

Bioequivalence has been established with the reference product, therefore the same withdrawal periods apply, as follows:

Meat and offal of pigs: 4 days.
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

As this is a generic application according to Article 13 (3) and bioequivalence with a reference product has been established efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

The bibliography provided suggests that there are no data to suggest an emerging resistance problem to doxycycline. Adequate warnings and precautions appear on the product literature.

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 is favourable.

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 Veterinary 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.

•	30 August 2018	Change in RMS from UK to NL.
•	11 April 2018	Submission of an updated Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer.
•	19 July 2021	Renewal