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

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs

Created: April 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0142/001/DC
Name, strength and pharmaceutical form	Centidox 100%, powder for use in drinking water or milk / milkreplacer for calves and pigs
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel the Netherlands
Active substance(s)	Doxycycline hyclate
ATC Vetcode	QJ01AA02
Target species	Calves, pigs
Indication for use	Calves and pigs: Treatment and metaphylaxis of respiratory diseases caused by *Pasteurella multocida* and *Mycoplasma* spp. susceptible to doxycycline.

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

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).

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

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	29th April 2010
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Germany, Denmark, Spain, France, Italy, Poland and Slovakia.

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, any 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. Qualitative and quantitative particulars

The product contains doxycycline hyclate (quantitative) .

The container/closure system are:

The packs consists of one of the following laminates:
- Sachet with outside a white layer, inside different transparent layers, a sub-layer of aluminium and an inner layer of polyethylene.
- Sachet with an outer layer of polyester, middle layers of polyethylene and aluminium and an inner layer of an ionomer (Surlyn).
- Sachet with an outer layer of polyethylene terephtalic acid, middle layers of aluminium and polyamide and an inner layer of polyethylene.

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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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 stability after reconstitution is based on the demonstration of stability for a batch broached and stored 36 months at 40°C.

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

G. Other Information

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

Shelf life after first opening the immediate packaging: 6 months.

Shelf life after dilution or reconstitution according to directions:
Solutions in water: 4 hours.
Milk solutions: 6 hours.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a 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

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 and toxicological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a 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 due to sensitisation and contact dermatitis one should avoid direct contact with the skin and inhalation when handling the product. Therefore a dust mask and gloves should be worn
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

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	PECsoil [µg doxycycline.kg_{soil}^{-1}]
calves	**248**
weaner pig	**378**
fattening pig	**256**
sow+litter	91

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 <not> considered to be complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	Low	stated as slightly soluble in water
		312 mg/l	at 25°C, estimated for doxycycline
		630 mg/l	
		745 mg/l	At environmentally relevant pH of 5 at 25°C in a NaCl-HCl solution of 1.0 M.
		1300 mg/l	At environmentally relevant pH of 5 at 25°C in a $NaNO_3$-HNO_3 solution of 1.0 M
		626 mg/l	At 25°C with no $NaNO_3$-HNO_3 or NaCl-HCl at unknown pH.

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Dissociation constants in water pKa	OECD 112	pKa = 3.5	20°C
		pKa= 7.7	20°C
		pKa= 9.5	20°C
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107 or 117 or 123	$logD_{ow}$ at pH 2.5 = -0.2	
		$logD_{ow}$ at pH 7 = 0.0	
		$logD_{ow}$ at pH 9 = -1.6	

Environmental fate			
Soil Adsorption/	OECD 106	Koc = 187793 l/kg	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	31.0	µg/l	*Pseudokirchneriella subcapitata*
Daphnia sp. immobilisation	OECD 202	EC50	> 87	mg/l	*Daphnia magna*
Fish, acute toxicity/*species*	OECD 203	LC50	> 13.5	mg/l	*Oncorhynchus mykiss*
Terrestrial Plants, growth test	OECD 208	EC50	57	mg/kg	6 species: (list names) *Brassica napus*
Earthworm/ reproduction	OECD 220/222	NOEC	≥ 139	mg/kg	

*add information on analytical verification of test substance (nominal (n) or measured (m)), on exposure (e. g. semi-static, flow-through, sediment spiked, etc.), on test substance (salt, base), and on test medium (e. g. Corg content)

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 Algae: 0.31 Crustacea: 0.87 mg/l Fish: 0.14 mg/l	µg/l Calves: 0.007 Weaner pig: 0.010 Fattening pig: 0.007	<u>Algae</u> Calves: 0.023 Weaner pig: 0.032 Fattening pig: 0.023 <u>Crustacea</u> Calves: <0.001 Weaner pig: <0.001 Fattening pig: <0.001 <u>Fish</u> Calves: <0.001 Weaner pig: <0.001 Fattening pig: <0.001
groundwater	Crustacea: > 0.87 mg/l	µg/l Calves: 0.020 Weaner pig: 0.030 Fattening pig: 0.021	Crustacea: Calves: < 0.001 Weaner pig: < 0.001 Fattening pig: < 0.001
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	Mg/kg Micro-organisms:	µg/kg Calves: 300 Weaner pig:	<u>Micro-organisms:</u>

	Earthworms: ≥ 13.9 Plants: 0.57	457 Fattening pig: 310	Calves: n.r Weaner pig: n.r. Fattening pig: n.r. <u>Earthworms</u> Calves: 0.022 Weaner pig: 0.033 Fattening pig: 0.022 <u>Plants</u> Calves: 0.53 Weaner pig: 0.80 Fattening pig: 0.54

n.r.= not relevant

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.

- The RQ for green algae does not indicate a risk for surface water. However since the risk assessment should have been performed with a cyanobacteria. A final conclusion will be drawn after submission of a test with cyanobacteria.
- The risk for the other non-target species is considered acceptable.
- For the risk to surface water no final conclusion can be made since a toxicity test with cyanobacteria is not available

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Log Dow = -1.6 to 0	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$		(v)P
Toxicity	NOEC or CMR	Log Dow = -1.6 to 0	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

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.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 16 days for meat and offal in calves and 8 days 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.

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.

Summary of change	**Section updated**	**Approval date**
Change in the immediate packaging of the finished product considering the quantitative and qualitative composition (NL/V/0142/001/IA/001)	Module 3 II.A	22nd November 2012
Change in the QPPV and in the contact details of the QPPV (NL/V/xxxx/IA/006/G)	NA	6th March 2013
Update of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer and a new European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. form a new manufacturer. (NL/V/xxxx/IA/008/G)	NA	9th September 2013
Renewal – NL as RMS (NL/V/0142/001/R/001)	NA	31st July 2015
Update of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer. (NL/V/xxxx/IA/015/G)	NA	10th January 2016
Deletion of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. (NL/V/xxxx/IA/018/G)	NA	27th October 2016
Update of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer. (NL/V/xxxx/IA/025/G)	NA	8th March 2018

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs	NL/V/0142/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

Change in the QPPV and/or QPPV contact details and/or back-up procedure (NL/V/xxxx/IA/033/G)	NA	11th January 2019