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

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens

Created: April 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0141/001/DC
Name, strength and pharmaceutical form	Soludox 500 mg/g, powder for use in drinking water for pigs and chickens
Applicant	Eurovet Animal Health, Bladel, The Netherlands
Active substance(s)	Doxycycline hyclate : 500 mg per g.
ATC Vetcode	QJ01AA02
Target species	Pigs and chickens (broiler, pullet, breeder)
Indication for use	Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by Actinobacillus pleuropneumoniae, Pasteurella multocida, and Mycoplasma hyopneumoniae susceptible to doxycycline Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by Pasteurella multocida or to reduce morbidity and lesions in respiratory infections caused by Ornithobacterium rhinotracheale (ORT)

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	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).

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	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, Germany, Estonia, Greece, Spain, Finland, France, Italy, Latvia, and 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; 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 500 mg/g (quantitative) and the excipients Tartaric acid

The container/closure system consist of one of the following laminates:

- Polyester / polyethylene / aluminium / polyethylene and an inner layer of polyethylene
- Polyester / polyethylene / aluminium and an inner layer of ionomer (surlyn).
- Polyethylene terephtalic acid / aluminium / polyamide and an inner layer of polyethylene.

Pack sizes of 100g, 250g, 500g, 1 kg and 10x 100g in a carton box

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.

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

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.

Process validation data on the product have been presented in accordance with the 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.

G. Other Information

- Shelf-life of the veterinary medicinal product as packaged for sale: 3 years
- Shelf-life after first opening the immediate packaging: 9 months
- Shelf-life after dilution or reconstitution according to directions: 24 hours

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

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.

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.

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 direct contact with the skin and inhalation should be avoided when handling, processing and /or using the product. Dust mask and gloves are mandatory.
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/equal to 100 µg/kg and no mitigations exist that alter the PECsoil.

Target animal	PECsoil [µg doxycycline.kg_{soil}^{-1}]
Broiler	**614**
Replacement layer	**136**
Broiler breeder	39

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

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	experimental value for doxycycline
		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 NaNO3-HNO3 solution of 1.0 M.
		626 mg/L	At 25°C with no NaNO3-HNO3 or NaCl-HCl at unknown pH.
Dissociation constants in water pKa	OECD 112	pKa = 3.5	20°C
		pKa = 7.7	20°C
		pKa = 9.5	20°C

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc =187793 L.kg	

Effect studies

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	31.0	µg/l	
Daphnia sp. immobilisation	OECD 202	EC50	>87000	µg/l	
Fish, acute toxicity/*species*	OECD 203	LC50	>13500	µg/l	*Oncorhynchus mykiss*
Terrestrial Plants, growth test	OECD 208	EC50	57000	µg/kg	6 species: (list names) *Brassica napus*
Earthworm/*Enchytraeidae* reproduction	OECD 220/222	NOEC	≥ 139000	µg/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	Algea: 0.31 µg/L Crustaceans: >0.87 mg/L Fish: > 0.14 mg/L	µg.L Broiler: 0.016 Replacement layer: 0.004	<u>Algea:</u> Broiler: 0.052 Replacement layer: 0.013 <u>Crustaceans:</u> Broiler: <0.001 Replacement layer: <0.001 <u>Fish:</u> Broiler: <0.001 Replacement layer: <0.001

groundwater		µg.L Broiler: 0.049 Replacement layer: 0.011	Since the calculated $PEC_{groundwater}$ lower than 0.1 $\mu g.L^{-1}$, no further refinement of $PEC_{groundwater}$ is warranted.
soil microorganisms: Nitrogen transformation test	<>25% difference in N transformation	NA	NA
soil	Micro-organisms: n.d. Earthworms: ≥ 13.9 mg/kg Plants: 0.57 mg.kg	µg.kg Broiler: 742 Replacement layer: 164	Micro-organisms: Broiler: n.r. Replacemet layer: n.r Earthworms: Broiler: 0.053 Replacement layer: 0.012 Plants: Broiler: 1.3 Replacement layer: 0.29

n.r: not relevant

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water, groundwater, 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	Since log D_{ow} of doxycycline is -1.6 to 0, the bioaccumulation potential is considered to be low and therefore a risk for secondary poisoning is not expected	(v)B/not B
PBT-statement :	The compound is not considered as PBT nor vPvB		

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because the application is made in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of essential similarity, it is not required to provide documentation on residues.

Withdrawal Periods

Based on the data provided above, a withdrawal period in chickens for :

- Meat and offal: 3 days, for the treatment of Pasteurellosis with a maximum of 10 mg/kg body weight for a maximum of 4 days,

- Meat and offal: 9 days, for the treatment of ORT with a maximum of 20 mg/kg body weight for a maximum of 4 days, and a withdrawal period for meat and offal in pigs for 4 days, is 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**
Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a referral procedure. (NL/V/0141/001/IA/001)	NA	25th August 2011
Change in immediate packaging of the finished product (NL/V/0141/001/IA/003)	Module 3 II.A	28th October 2012
Change in the QPPV and in the contact details of the QPPV (NL/V/xxxx/IA/006/G)	NA	6th March 2013
Change of QPPV to Dr Francesca Holland Change of contact details for QPPV		19 April 2013
Change to the withdrawal period to 9 days (previously 12 days) for chicken meat and offal at a high dose. (UK/V/xxxx/WS/006)	Module 3 III.B	21st August 2013
Update of European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer and addition of a new European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from a new manufacturer. (NL/V/xxxx/IA/008/G)	NA	9th September 2013

Soludox 500 mg/g, powder for use in drinking water for pigs and chickens	NL/V/0141/001/DC
Eurovet Animal Health,	DCP
	Publicly available assessment report

Renewal – NL as CMS (NL/V/0141/001/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 from a manufacturer of the active substance (NL/V/xxxx/IA/018/G)	NA	27th October 2016
Minor change in the manufacturing process of the finished product and change in the batch size up to 10-fold compared to the originally approved batch size. (NL/V/xxxx/IA/022/G)	NA	22nd February 2017
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
Change in the QPPV and/or QPPV contact details and/or back-up procedure (NL/V/xxxx/IA/033/G)	NA	11th January 2019