DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

OXYGAN 500 mg/g POWDER FOR USE IN DRINKING WATER

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0379/001/DC
Name, strength and pharmaceutical form	Oxygan 500 mg/g powder for use in drinking water
Applicant	S.P. VETERINARIA S.A. Ctra. Reus – Vinyols, Km. 4,1 RIUDOMS (Tarragona) SPAIN
Active substance(s)	Oxytetracycline (hydrochloride)
ATC Vetcode	QJ01AA06
Target species	Cattle (calf), sheep (lamb), goats (kid), pigs, rabbits, broilers, layer hens, turkeys and ducks.
Indication for use	Treatment and metaphylaxis of septicemia, respiratory infections and digestive infections due to oxytetracycline-sensitive organisms.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23/09/20
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	CMS: HU, IT, PT, RO, BG

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains Oxytetracycline hydrochloride (500 mg) and Citric acid as excipient.

The container/closure system is thermo-sealed polyethylene/aluminium/polypropylene bags of 1 kg and 100 g

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 from 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 Oxytetracycline hydrochloride, 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.

Certificate of suitability issued by the EDQM has 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.

D. Control on intermediate products

Nor 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 has been provided in a Ph. Eur. Certificate of Suitability (Ph. Eur. CEP). A re-test period of 48 months is specified on the Ph. Eur. CEP if the material is stored in a double polyethylene bag, placed in a double paper bag.

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 (24 months) when stored under the approved conditions.

Appropriate data have been provided to support the in-use shelf-life of the product.

G. Other Information

Appropriate data have been provided to support the stability in drinking water of the product.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

This application has been submitted in accordance with article 13.3 of Directive 2001/82/EC, as amended by Directive 2004/28/EC. The product has the same pharmaceutical form as the reference product, equivalent qualitative and quantitative composition of active substances and the same qualitative composition in terms of excipients. It is therefore deemed essentially similar to the reference product. The omission of bioequivalence studies has been justified based on the fulfilment of condition 7.1 c) of the "Guideline on the conduct of bioequivalence studies for veterinary medicinal products" EMA/CVMP/016/00-Rev.2.
Consequently, as details on pharmacodynamics/pharmacokinetics and toxicology have been sufficiently described in the file of the reference product, no further documentation is needed.

User Safety

A user risk assessment broadly in accordance with current guideline EMA/CVMP/543/03-Rev.1 has been submitted.

The tasks and situations that lead to exposure have been properly described. Hazards of allergic and hypersensitivity reactions and local toxicity effects such as irritation have been identified.

Regarding inhalation and dermal exposure, a narrow margin of safety has been estimated.

Therefore, precautional measures are needed to reduce these risks.

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 no mitigations exist that alter the PECsoil (PECsoil initial = 571.2 µg/kg for calf [intensive reared]; PECsoil initial = 868.9 µg/kg for Weaner pig; PECsoil initial = 887.0 µg/kg for broiler; PECsoil initial = 721.2 µg/kg for rabbit; PECsoil initial = 418 µg/kg for beef cattle [extensive reared] and PECsoil initial = 160 µg/kg for sheep).

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.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	1 g/ml (10^6 mg/L)	
Dissociation constants in water pKa	OECD 112	pKa1 = 3.41 ± 0.01 Observed interval = 0.01 pKa2 = 7.23 ± 0.02 Observed interval = 0.03 pKa3 = 8.88 ±0.05 Observed interval = 0.09	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	Log Pow pH7 = -1.09 Log Pow pH2= -1.38 Log Pow pH11= -3.34	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc = 42506 l/kg Koc = 47881 l/kg Koc = 93317 l/kg Koc = 27792 l/kg **mean Koc = 52874 L/kg**	
Soil Adsorption/Desorption	OECD 106	Koc = 177863.64 l/kg Koc = 238954.55 l/kg Koc = 35187.50 l/kg Koc = 24256.41 l/kg Koc = 108320 l/kg Koc = 79440.68 l/kg Koc = 102842.86 l/kg Koc = 30967.74 l/kg Koc = 62538.46 l/kg Koc = 27434.43 l/kg Koc = 58444.44 l/kg **mean Koc = 86022.79 L/kg**	
Soil Adsorption/Desorption	OECD 106	Koc = 153896.1039 l/kg Koc = 20454.54545 l/kg Koc = 192660.5505 l/kg Koc = 14220.18349 l/kg **mean Koc = 95307.85 L/kg**	
		Mean Koc = 78068.09 L/kg	Koc value used in the risk assessment. Mean value by considering the results of the three absorption/desorption studies.
Aerobic and Anaerobic Transformation in Soil	OECD 307	Sandy loam $DT_{50\ soil,\ [SFO],\ [20^aC]}$ = 17	

Environmental fate			
		Sandy loam $DT_{50\ soil,\ [SFO],\ [20^aC]}$ = 11 Clay $DT_{50\ soil,\ [SFO],\ [20^aC]}$ =7 Clay loam $DT_{50\ soil,\ [SFO],\ [20^aC]}$ =65 **geometric mean (20°C): 17.07 d** **$DT_{50\ soil}$ = 25 d**	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Cyanobacteria, growth inhibition test/*P. subcapitata*	OECD 201	EC50 (growth)	261.34	µg a.s/l	Nominal concentration
Daphnia sp. Reproduction test	OECD 211	EC50	45400	µg a.s/l	Nominal concentration. Semi-static.
Fish, acute toxicity/*Brachidanio rerio*	OECD 203	LC50	>100000	µg a.s/l	Limit test. Nominal concentration. Semi-static.
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25%		Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	648730	µg a.s/kg	8 species: (*Brassica napus, Pisum sativum, Helianthus annuus, Beta vulgaris, Cucumis stivus, Zea Mays, Allium cepa, Avena sativa*)
Terrestrial Plants, growth test	OECD 208	NOEC	288	µg a.s/kg	*Tier B* 8 species: (*Brassica napus, Pisum sativum, Helianthus annuus, Beta vulgaris, Cucumis stivus, Zea Mays, Allium cepa, Avena*

					sativa)
Earthworm/*Eisenia foetida* reproduction	-	NOEC	100000	µg a.s/kg	
Earthworm/*Eisenia foetida* reproduction	OECD 222	NOEC(mortality) NOEC(reproduction)	5000000 3000000	µg a.s/kg	

a.s: active substance.

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 (µg/L)**	**RQ**
surface water	2.6134	0.023	No risk
groundwater	--	0.07	No risk
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	6487.3	886.96	No risk

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 following information on environmental properties needs to be included in the product literature Oxitetracycline is persistent in soil.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Log Pow < 4	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	>120d (DT_{50} 12º C = 123.27 d)	P
Toxicity	NOEC	>0.01 mg/L (EC10 = 0.024 mg/l)	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

Since this application has been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as modified by Directive 2004/28/EC (so-called “hybrid” application) through a decentralised procedure and bioequivalence with the reference product has been assumed, it is not necessary to provide residues data. However, the applicant

has conducted studies of depletion of residues in chickens and rabbits in order to reduce the withdrawal periods currently authorised for the reference product in these species. Both studies were conducted following GLPs and meet the requirements of VICH GL48. The analysis of tissue samples was performed using a HPLC LC-UV method previously validated.

Oxytetracycline and its 4-epimer were determined in tissue samples. In chickens, 6 hours after administration values above the MRL of the marker residue were detected in all tissues but concentrations only remained above the MRL 12 hours and 1 day after administration in muscle, which seems to be the withdrawal period determining tissue.

A 3-day withdrawal period for chicken meat has been recommended.

Regarding rabbits, since most residues were below the LOQ in all tissues at all slaughter time points a 1-day withdrawal period for rabbits has been established.

MRLs

The active substance Oxytetracycline is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues
Oxytetracycline	Sum of parent drug and its 4-epimer	All food producing species	600 300 100 100 200	Kidney Liver Muscle Milk Eggs

The excipient anhydrous citric acid is a food additive with a valid E number approved as additive in foodstuffs for human consumption and, as such, included in table 1 of the annex to Commission Regulation (EU) No 37/2010 with the status “No MRL required”

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Meat and offal:

Calves, lambs, kids, pigs, laying hens, turkeys and ducks: 7 days

Broiler chickens: 3 days

Rabbits: 1 day.

Eggs: zero days.

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.

IV.A Pre-Clinical Studies(pharmaceuticals only)

Resistance

The bibliography / information provided suggests that no increased risk of emergence of resistances is expected when the product is used according to the SPC.

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 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 veterinary Heads of 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 (Application number)	Approval date
Addition of a 100 g presentation ES/V/0379/001/A/003	23/06/2022