IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

OXTRA DD 100 mg/ml solution for injection for cattle, sheep, pigs, horses, dogs and cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0521/001/DC
Name, strength and pharmaceutical form	Oxtra Duo
Active substances(s)	Oxytetracycline hydrochloride
Applicant	FATRO S.p.A., Via Emilia, 285 - 40064, Ozzano Emilia, Bologna, Italy
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Date of completion of procedure	03//06/2020
Target species	Cattle, sheep, pigs, horses, dogs and cats.
Indication for use	For the treatment of infections caused by organisms susceptible to oxytetracycline in horses, cattle, sheep, pigs, dogs and cats.
ATCvet code	QJ01AA06
Concerned Member States	AT, BE, DE, DK, EL, ES, IT, NL, PL, PT, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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; 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product is a solution for injection containing 100 mg/ml of the active substance oxytetracycline (as oxytetracycline hydrochloride). The product contains the following excipients: povidone K12, ethanolamine, magnesium oxide light, sodium formaldehyde sulfoxylate, hydrochloric acid (10% diluted) and water for injections. The product is presented in amber, Type II glass vials containing 20 ml, 50 ml, 100 ml or 250 ml. The product is also presented in amber polyethylene terephthalate (PET) vials containing 100 ml or 250 ml of product. The vials are closed with a chlorobutyl rubber stopper and a flip-off aluminium cap fitted with a tamper-evident polypropylene seal. The absence of a preservative is 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. Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance oxytetracycline hydrochloride is 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 has 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

Not 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 has been provided. Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has 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 in-use shelf-life of the broached product is supported by the data provided.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended, and an exemption from the requirement to demonstrate *in vivo* bioequivalence with a reference product has been satisfactorily justified, results of safety and residue tests are not required. The reference product cited by the applicant is Engemycin 10% DD Solution for Injection (Intervet Ireland Limited, VPA 10996/071/001) which was first authorised in the RMS on 01/10/1988 in accordance with a full application dossier and for which the marketing authorisation remains valid. The reference product has been authorised for in excess of ten years and can therefore be accepted as a valid reference product in this generic application.
The safety aspects of this product are considered to be identical to that of the reference product.
Warnings and precautions as listed on the product literature include those of the reference product and are adequate to ensure safety of the product to users, the consumers of foodstuffs from treated animals and for the environment.

III.A Safety Testing

Pharmacological Studies
This application was submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended (a generic application) and therefore data on pharmacodynamics and pharmacokinetics are not required.

The applicant claimed an exemption from the requirement to provide *in vivo* bioequivalence studies in accordance with waiver 7.1b of the guideline on the conduct of bioequivalence studies for VMPs. Paragraph 7.1b of the guideline permits exemption from the requirement for bioequivalence studies where; '*products intended for intramuscular, subcutaneous or systemically*

acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance.'
Based on the argumentation and quality data provided by the applicant, the criteria of biowaiver 7.1b were fulfilled and bioequivalence was accepted.

Toxicological Studies
This application was submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended (a generic application). Based on the argumentation/quality data presented, it was accepted that exemption from the requirement to conduct an *in vivo* bioequivalence study was justified and that the test product can be considered bioequivalent to the reference product. Accordingly, the applicant is not required to provide the results of toxicological studies.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not present any greater risk to the user than that presented by the reference product. 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 was required as the Phase I assessment showed that the PEC_{soil} exceeded the trigger value of 100 µg/kg for calf, cattle 0-1 year, weaner pig and fattening pig.

Phase II
A Phase II Tier A assessment was conducted, the results of which are summarised below.

Physico-chemical properties	
Study type	**Result**
Vapour pressure	1.21×10^{-20}
Water solubility	92 g/L
Dissociation constants in water pKa	pKa = 3.26; 7.54; 8.71
n-Octanol/Water Partition Coefficient $logP_{ow}$	$logP_{ow}$ in water = -1.41 $logP_{ow}$ in water = -0.96 $logP_{ow}$ in water = -1.00 $logP_{ow}$ in water = -3.13

Environmental fate	
Soil Adsorption/Desorption	Koc = 24,256 L/kg
Aerobic and Anaerobic Transformation in Soil	$DT_{50,\ 25°C}$ = 56 days $DT_{50,\ 12°C}$ =192 days

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Anabaena flos-aquae*	EC_{50}	0.261	mg/l
Daphnia sp. immobilisation	EC_{50}	0.17	mg/l
Fish, acute toxicity/ *Oncorhynchus mykiss*	LC_{50}	100	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Terrestrial Plants, growth test	EC_{50}	648.73	mg/kg
Earthworm/*Eisenia andrei* reproduction	NOEC	256	mg/kg

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.

Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.

The risk characterisation resulted in risk quotients 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.

PBT Assessment

An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.

The log Kow of oxytetracycline was demonstrated to be <4.0. The compound is not considered to be either PBT or vPvB.

Conclusion

Based on the data provided the product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

Milk residue depletion studies were conducted for the 24 hourly dosage regimen, one in cattle and one in sheep. Results showed that residues depleted to below the MRL in cattle and sheep milk before the end of the withdrawal periods.

No other residue depletion studies were conducted. The omission of injection site residue depletion studies was accepted on the grounds that bioequivalence with the reference product was supported and the formulation of the candidate and reference products were demonstrated to be sufficiently similar to permit extrapolation of withdrawal periods from the reference to the candidate product.

MRLs

Oxytetracycline is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All food producing species
Muscle	100 µg/kg
Liver	300 µg/kg
Kidney	600 µg/kg
Milk	100 µg/kg

Withdrawal Periods

Based on the information provided above, the following withdrawal periods are justified.

24-hour dosage regime

		i.m. use	i.v. use
Cattle:			
	Meat and offal	35 days	35 days
	Milk	72 hours	72 hours
Sheep:			
	Meat and offal	53 days	53 days
	Milk	120 hours	120 hours
Pigs:			
	Meat and offal	14 days	14 days
Horses:			
	Meat and offal	6 months	6 months
	Not authorised for use in horses producing milk for human consumption.		

Prolonged action dosage regimen

		i.m. use
Cattle:		
	Meat and offal	35 days

Sheep:		
	Meat and offal	18 days
Pigs:		
	Meat and offal	13 days

The prolonged dosage regimen is not authorised for use in animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT

As this is a generic application, submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, and as bioequivalence with a reference product is accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

In addition, it is considered that the risk to the target species will be similar for both the test and the reference products. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.
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 veterinary medicinal product.

Changes:

Summary of change (Application number)	Supporting information	Approval date
Change in cattle and sheep milk withdrawal periods (IE/V/0521/001/A/001/G	Proprietary residue depletion studies	08/03/2024