FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
AGENCE NATIONALE DU MEDICAMENT VETERINAIRE
8 rue Claude Bourgelat –
Parc d'activités de la grande Marche –
Javené – CS 70611 –
35306 FOUGERES

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tylosine Ceva 200 mg/ml solution for injection for cattle and pigs [FR]

Tyljet 200 mg/ml solution for injection for cattle and pigs [BE NL HR CZ EE FI LV LT MT SK SI SE UK]

Tyljet [NO]

DATE: 20/12/2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0325/001/DC
Name, strength and pharmaceutical form	Tylosine Ceva 200 mg/ml solution for injection for cattle and pigs
Applicant	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne, France
Active substance(s)	Tylosin
ATC Vetcode	QJ01FA90
Target species	Cattle, Pigs
Indication for use	For the treatment of specific infections (listed below) caused by microorganisms susceptible to tylosin. Cattle (adult): -Respiratory infections, metritis caused by Gram-positive microorganisms, mastitis caused by *Streptococcus spp*, *Staphylococcus spp* and interdigital necrobacillosis, i.e. panaritium or foot rot. Calves: -Respiratory infections and necrobacillosis. Pigs: -Enzootic pneumonia, haemorrhagic enteritis, erysipelas and metritis. -Arthritis caused by *Mycoplasma spp*. and *Staphylococcus spp*. For information regarding swine dysentery see section 4.5.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://mri.medagencies.org/veterinary/

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	21/11/2018
Concerned Member States for original procedure	BE NL HR CZ EE FI LV LT SK SI SE UK NO

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 reactions that may be observed are indicated in the SPC, with information on the frequency.
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 overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 200 000 IU/ml of tylosin and the following excipients: benzyl alcohol, propylene glycol and water for injections.

The product is packed in plastic vials. The particulars of the containers and controls performed are provided and conform to the regulation.
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 tylosin, 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. 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.

G. 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.
An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT

III.A Safety Testing

Pharmacological Studies

Based on exemption 7.1. b) of the "Guidelines on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/00-Rev.2), it is accepted that the test product is bioequivalent to the reference product TYLAN 200 marketed by LILLY FRANCE and authorized in France since 15/12/1980. 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 aspects of this product are identical to those of the reference product.

Toxicological Studies

The toxicological aspects of this product are identical to those of the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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

Ecotoxicity

A phase I and a phase II Environmental Risk Assessment (ERA) has been performed according to VICH Phase I Guideline CVMP/VICH/592/98-final, VICH Phase II Guideline CVMP/VICH/790/03-final and the supporting CVMP Guideline EMEA/CVMP/ERA/ 418282/2005-rev1.

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 130 µg/kg) is greater to 100 µg/kg and no mitigations exist that alter the PECsoil.

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	17.8 to 177.7 g/L	
Dissociation constants in water pKa	OECD 112	pKa = 7.65	

n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107 and 117	$logP_{ow}$ = -1.08 at pH 3.5 0.33 at pH 5.4 0.5 at pH 6.9 0.43 at pH 7.0 0.97 at pH 9.2 0.94 at pH 10.6	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc = 3200 l/kg	
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50 (geometric mean) = 25 days	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	160	µg/l	
Daphnia sp. immobilisation	OECD 202	LC50	>100	mg/l	
Fish, acute toxicity/*species*	OECD 203	LC50	>100	mg/l	
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	116.7	mg/kg	Avena sativa, Lepidium sativum, Raphanus sativus, Brassica oleracea, Brassica rapa
Earthworm/*Enchytraeidae* reproduction	OECD 220/222	EC50	543.4	mg/kg	No OECD compliance

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	1.6	0.19	0.12
groundwater		0.57 FOCUS : < 0.1	
soil microorganisms: Nitrogen transformation test	< 25 %	NA	NA
soil	1167	130	0.11

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water and 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		not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	190 days	vP
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is considered as Persistent		

III.B Residues documentation

Residue Studies

No residue depletion studies were required, based on exemption 7.1. b) of the “Guidelines on the conduct of bioequivalence studies for veterinary medicinal products” (EMA/CVMP/016/00-Rev.2) and in accordance with the CVMP guideline “Approach towards harmonisation of withdrawal periods” (EMEA/CVMP/036/95).

MRLs

The active substance tylosin is listed in table 1 of Council Regulation 37/2010. The marker substance is Tylosin A.

MRLs are listed below:

Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**

Tylosin A	All food producing species	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg 200 µg/kg	Muscle Fat Liver Kidneys Milk Eggs	For fin fish the muscle MRL relates to « muscle and skin in natural proportions ». MRLs for fat, liver and kidney do not apply for fish. For porcine and poultry species, the fat MRL relates to "skin and fat in natural proportions".	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009

The MRL status of excipients is indicated in the following table:

Excipient	MRL status
Benzyl alcohol	Table1, no MRL required
Propylene glycol	Table1, no MRL required
Water for injection	Out of scope

Withdrawal Periods

The same withdrawal periods as the reference product are accepted:

Cattle:
Meat – 28 days
Milk – 108 hours

Sheep and Goat:
Meat – 42 days
Milk – 108 hours

Pigs:
Meat – 14 days

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated based on exemption 7.1. b) of the "Guidelines on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/00-Rev.2), efficacy studies are not required.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography regarding the susceptibility or resistance to tylosin for pathogens but also for commensal bacteria, provided in a context of prudent use of antimicrobials and responsible attitude of the applicant, is difficult to interpret in the absence of recognised break points for tylosin.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

The efficacy claims for this product are equivalent to those of the reference product and take also into account the decision taken by the European Commission in a referral on oral products containing tylosin to be used in pigs.

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 are acceptable.