Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pharmasin 200 mg/ml Solution for Injection for Cattle and Pigs

Date Created: November 2016

Updated: January 2018

PuAR correct as of 26/02/19 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0605/001/DC
Name, strength and pharmaceutical form	Pharmasin 200 mg/ml Solution for Injection for Cattle and Pigs
Applicant	Huvepharma N.V. Uitbreidingsstraat 80 2600 Antwerpen Belgium
Active substance(s)	Tylosin
ATC Vetcode	QJ01FA90
Target species	Cattle and pigs
Indication for use	Infections caused by microorganisms susceptible to tylosin. Cattle (adult): - Treatment of respiratory infections, metritis caused by Gram-positive micro-organisms, mastitis caused by Streptococcus spp., Staphylococcus spp. and interdigital necrobacillosis caused by Fusobacterium necrophorum i.e. panaritum or foot rot. Calves: - Treatment of respiratory infections and necrobacillosis (calf diphtheria caused by Fusobacterium necrophorum). Pigs: - Treatment of enzootic pneumonia caused by Mycoplasma hyopneumoniae, haemorrhagic enteritis (Porcine proliferative haemorrhagic enteropathy due to Lawsonia intracellularis), erysipelas caused by Erysipelothrix rhusiopathiae and metritis.

	- Treatment of arthritis caused by Mycoplasma and Staphylococcus spp.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	A generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21 September 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Belgium and The Netherlands

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended). The reference product is Tylan 200, 200 mg/ml, Solution for Injection authorised in the UK since 1996. The product fulfils the requirements for a waiver from bioequivalence studies in accordance with exemption 7.1.b of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

Pharmasin is indicated for the treatment of infections caused by microorganisms susceptible to tylosin, it is authorised for use in cattle and pigs.

Cattle (adult):
In adult cattle the product is indicated for the treatment of respiratory infections, metritis caused by Gram-positive micro-organisms, mastitis caused by *Streptococcus* spp., *Staphylococcus* spp., and interdigital necrobacillosis caused by *Fusobacterium necrophorum*.

Calves:
In calves the product is indicated for the treatment of respiratory infections and necrobacillosis (calf diphtheria caused by *Fusobacterium necrophorum*).

In cattle, the product is administered by intramuscular injectionat a dose rate of 5-10 mg tylosin/kg bodyweight per day for 3 days (2.5 to 5 ml solution for injection per 100 kg bodyweight). The maximum injection volume per injection site should not exceed 15 ml.

Pigs:
In pigs the product is indicated for the treatment of enzootic pneumonia, caused by *Mycoplasma hyopneumoniae*, haemorrhagic enteritis (Porcine proliferative haemorrhagic enteropathy due to *Lawsonia intracellularis*), erysipelas, caused

by *Erysipelothrix rhusiopathiae,* metritis and the treatment of arthritis caused by *Mycoplasma* and *Staphylococcus* spp.

In pigs, the product is administered by intramuscular injectionat a dose rate of 5-10 mg tylosin/kg bodyweight per day for 3 days (2.5 to 5 ml solution for injection per 100 kg bodyweight). The maximum injection volume per injection site should not exceed 1.3 ml.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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.[1] 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 [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains the active ingredient tylosin 200 mg/ml and the excipients propylene glycol, benzyl alcohol (E1519) and water for injections.

The container/closure system consists of type II colourless glass vials, sealed with a bromobutyl stopper and aluminium cap supplied in a carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of a preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a standard process of mixing, filtering and filling.

Process validation data on the product have been presented in accordance with the relevant European guidelines

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II.C. Control of Starting Materials

The active substance is tylosin is an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. A certificate of suitability was provided.

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.

All excipients are monographed within the European Pharmacopoeia acceptable Certificates of Analysis were provided.

II.C.4. Substances of Biological Origin

Certificates of suitability issued by the EDQM have 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. Neither the active substance nor the excipients are derived from materials of human or animal origin, and no material of animal origin is used during the finished product manufacture.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable

II.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. Control tests on the finished product include identification of tylosin and benzyl alcohol, appearance, clarity, pH, density, impurities and sterility. Batches were stored under VICH[3] conditions of 25°C±2°C /60% RH±5% , 30°C±2°C/65% RH ±5% and 40°C±2°C /75% RH±5% for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

II.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.

[3] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening of the immediate packaging: 28 days. Discard any unused material.
The closures should not be broached more than 15 times. In order to prevent excessive broaching of the stopper, a suitable multiple dosing device should be used.
Protect from light.
Store in the original container.
Do not store above 25°C.
Do not freeze.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and the requirement to demonstrate bioequivalence with the reference product has been waived, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are in line with those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that:

- Care should be taken to avoid accidental self-injection.
- Tylosin may induce irritation. Macrolides, such as tylosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tylosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided.

Therefore the user warnings in the SPC are appropriate:

- If accidental self-injection occurs, seek medical attention immediately.
- In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water.
- Wash hands after use.
- Do not handle the product if you are allergic to ingredients in the product.
- If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

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

Environmental Safety

The applicant has submitted a Phase I and II Environmental Risk Assessment (ERA) in Part III.A.6 of the dossier, which has been carried out in accordance with VICH (CVMP/VICH/592/98-FINAL) and CVMP (EMEA/CVMP/ERA/418282/2005-Rev.1.) guidelines.

Phase I:

In accordance with Question 17 of the Phase I decision tree, the applicant has performed PEC_{soil} calculations using equation 1 of the CVMP guideline. The initial predicted environmental concentration (PEC) in soil is greater than 100 µg/kg and a Phase II ERA was required.

Phase II Tier A:

A Phase II tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physico-chemical properties, environmental fate and effects. Studies were carried out using the active substance tylosin unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	5 g/l at 25°C	Experimental data
Dissociation constants in water pKa	Not specified	7.73	Experimental data
Vapour Pressure	OECD 104	2.64×10^{-35}	Estimated data
n-Octanol/Water Partition Coefficient $logK_{ow}$	OECD 107	pH 5 – 0.36 pH 7 – 1.18 pH 9 – 1.36	Experimental data

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	Kd values ranging between 8 and 62 mg/l	
Degradation in poultry litter	Based on a bespoke method	DT50: 4.9 (days) non-sterile soil	Bespoke study

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test *Anabaena fios-aquae*	OECD 201	EC50	EC50 (growth): 2.2 mg/l EC50 (yield): 0.60 mg/l NOEC: 0.20 mg/l
Daphnia magna. immobilisation	OECD 202	EC50	48-h EC50 value: 680 mg/l NOEC (reproduction): 45 mg/l
Fish, acute toxicity *Oncorhynchus mykiss*	OECD 203	NOEC	100 mg/l
Soil Micro organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	<25% deviation from control at PEC
Terrestrial Plants, Growth Test/*Species*	OECD 208	EC50	EC50: 385.3 mg/kg soil
Earthworm reproduction	OECD 220/222	NOEC	2000 mg/kg

Exposure Calculation

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

	PEC		
	Soil (µg/kg)	**Groundwater (µg/l)**	**Surfacewater (µg/l)**
Highest values	174.8	0.79	0.26

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows.

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	0.193	100	1.93		0.13
Daphnia sp. immobilisation	680	1000	680		0.0004
Fish, acute toxicity	>46	1000	>46		<0.005
Terrestrial Plants, Growth	124.1	100	1241		0.14
Earthworm reproduction	2000	100	20,000		0.009

Nitrogen transformation: ≤25% of control

As all RQ values were <1 the ERA ended at tier A. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the proposed product contains the same active ingredient and excipients as the reference product; in addition the requirement to demonstrate bioequivalence with the reference product has been waived.

MRLs

Tylosin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk. The marker substance is Tylosin A

MRLs are listed below:

Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**
Tylosin A	Cattle Pigs	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidneys Milk	Fat - refers to skin and fat in natural proportions in porcine species

Withdrawal Periods

The withdrawal periods are the same as the reference product.

- Pigs: Meat 9 days
- Cattle: Meat 28 days
- Milk 108 hours.

With cows milked twice daily, milk for human consumption may be taken only from 108 hours, i.e. at the 9th milking) after the last treatment. With other dosing routines, the basis of the veterinary surgeons advice should be that milk may be taken for human consumption only after the same period from the last treatment (i.e. with three times a day milking, milk for human consumption may be taken only from 108 hours, i.e. at the 9th milking).

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1), and the requirement to demonstrate bioequivalence with the reference product has been waived, 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 benefit/risk profile of the product is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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