Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bilovet 200 mg/ml Solution for Injection or Cattle and Pigs

Date Created: 9th March 2015

PuAR correct as of 06/07/2018 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0404/001/DC
Name, strength and pharmaceutical form	Bilovet 200 mg/ml Solution for Injection for Cattle and Pigs
Applicant	Cross Vetpharm Group Ltd. Broomhill Road Tallaght Dublin 24 Ireland
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 cause 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 Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

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	21st October 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Germany, Ireland, Italy, Netherlands, Romania, Spain

I. SCIENTIFIC OVERVIEW

Bilovet 200 mg/ml Solution for Injection for Cattle and Pigs has been developed as a generic of Tylan 200, 200 mg/ml Solution for Injection, which was first authorised in the UK in 1996. The two products are considered essentially similar and bioequivalence with the reference product has been established.

Bilovet contains tylosin and is indicated for use in cattle and pigs to treat conditions associated with bacteria sensitive to tylosin. The product should be administered at a dose of 4 – 10 mg/kg daily in cattle and calves and 2 – 10 mg/kg daily in pigs. The product is contraindicated in chickens and turkeys, and should not be administered to horses or other equines in which injection of tylosin may be fatal. Animals with a known hypersensitivity to tylosin, other macrolides or any of the excipients should not be given the product.

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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains tylosin as active substance, and the excipients are benzyl alcohol, propylene glycol, sodium hydroxide, hydrochloric acid and water for injection.

The container/closure system consists of 100 ml Type II amber glass vials closed with a bromobutyl runner bung and aluminium overseal, packaged in a cardboard 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 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 product is manufactured by mixing the tylosin and benzyl alcohol to propylene glycol until dissolved. The water for injections is added and the pH adjusted as necessary. The product is then filled into the glass vials. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is tylosin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). A Ph. Eur. Certificate of Suitability has been provided for the active substance manufacturer. 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.

All of the excipients are manufactured in accordance with the relevant Ph. Eur. monograph. Certificates of analysis have been provided.

II.C.4. Substances of Biological Origin

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

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. The tests include those for identification and assay of the active substance, identification and assay of the preservative, pH, impurities and sterility.

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.

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. The retest period for the active substance is 3 years as specified by the Ph. Eur. Certificate of Suitability.

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. Data were provided for batches stored at 25°C/60% relative humidity (RH) for 18 months and at 40°C/75% RH for 6 months. A shelf life of 18 months was established for the finished product.

In-use stability studies were also provided. An in-use shelf life of 28 days is supported.

G. Other Information

Shelf life of the finished product as packaged for sale is 18 months.
Shelf life after first opening the immediate packaging is 28 days.
Do not store above 25°C.
Protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of pharmacological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of pharmacological tests are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure are dermal through spillage onto skin, inhalation, ocular by hand to eye transfer or parenteral through accidental self-injection. However, it was concluded that as the product will only be administered by professionals the risk to the user is low and the risks are the same as the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Care should be taken to avoid accidental self-injection.
- 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.
- 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.
- 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

Environmental Safety

An environmental risk assessment (ERA) has been conducted in accordance with VICH and CVMP guidelines. A Phase I and Phase II assessment was provided.

Phase I:
The product is intended for use in food-producing animals and will be used to treat groups of animals in a herd. As the product will be administered to intensively reared animals which are housed indoors, there is potential for the tylosin to be excreted by the housed animals and incorporated in the manure/slurry. This active residue can reach the environment when the manure/slurry from the housing is spread onto land. In addition, as the product is for use in cattle, tylosin also has the potential to be released into the environment through excretion by field-reared animals directly onto pasture. Further, secondary exposure to an aquatic environment could occur through leaching to groundwater, runoff to surface water and infiltration through soil.

The $PEC^{3}_{soil\ initial}$ is less than 100 µg/kg for dairy cattle, calves and fattening pigs. However, the initial PEC in soil is greater than 100 µg/kg for weaner pigs. Therefore 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 (at 25°C) (mg/l)	OECD 105	5000	Published source
Melting Point/Melting Range (°C)	OECD 102	128 - 132	Published source
Vapour Pressure (Pa)	OECD 104	2.65×10^{-32}	Published source
n-Octanol/Water Partition Coefficient $logP_{ow}$	Broadly in accordance with OECD 107	1.63	Indicates low affinity for sorption to organic matter

[3] PEC – Predicted Environmental Concentration

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	3509 K_{oc}	Indicates that tylosin is slightly mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} = 76 days	Indicates that tylosin is persistent in soil

Environmental effects

Study type	Guideline	Endpoint	Result
Cyanobacteria, Growth Inhibition Test/ *Anabaena sp*	OECD 201	EC_{50}[4] 72 h	0.0605 mg/l
Daphnia sp. immobilisation	OECD 202	EC_{50}	680 mg/l
Fish, acute toxicity/ *Oncorhyncus mykiss*	OECD 203	LC_{50}[5]	101 mg/l
Soil Micro organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	5.05% (Tylosin concentration = 1.3033 mg/kg)
Terrestrial Plants, Seedling emergence and growth in two monocotyledonous species (ryegrass and maize) and four dicotyledonous species (soybean, oilseed rape, tomato and radish) over 21 days.	OECD 208	EC_{50}	206 mg/kg
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC[6]	3000 mg/kg

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.

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surface water (µg/l)
Calf	85.68	N/A	N/A
Dairy cow	48.17	N/A	N/A
Cattle (0 - 1 year)	75.56	N/A	N/A

[4] EC_{50} – Half the maximal effective concentration
[5] LC_{50} – The concentration that kills half a sample population
[6] NOEC – No observable effect concentration

Target animal	PEC		
Cattle (> 2 years)	87.43	N/A	N/A
Pasture reared Dairy Cow	42.00	N/A	N/A
Pasture reared Beef Cattle	62.70	N/A	N/A
Weaner pig (to 25 kg	130.33	0.525	0.175
Fattening pig (25 - 125 kg)	88.40	N/A	N/A
Sow (with litter)	31.38	N/A	N/A

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

Test organism	End point (mg/kg or l)	AF	PNEC (µg/kg or l)	PEC (µg/kg or l)	RQ
Cyanobacteria, Growth Inhibition	72 h EC_{50} (growth)= 0.0605	100	0.605	0.175	0.289
Daphnia sp. immobilisation	48 h EC_{50} = 680	1000	680	0.175	0.000257
Fish, acute toxicity	EC_{50} = 101	1000	101	0.175	0.00173
Soil Micro organisms	No effect on activity (1.303 mg/kg)	N/A	N/A	130.33	No unacceptable risk
Terrestrial Plants,	EC_{50} = 260	100	2060	130.33	0.0633
Earthworm reproduction	NOEC = 3000	10	300000	130.33	0.000434

As all RQ values were <1, the ERA ended at Tier A and the product is not expected to pose a risk for the environment when used as recommended. The following environmental information is included on the SPC and product literature.

- Tylosin is persistent in some soils.

III.B.2 Residues documentation

Residue Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of residues studies are not required.

Withdrawal Periods

The withdrawal periods are the same as those for the reference product. As bioequivalence has been demonstrated this is acceptable.

Pig
Meat and offal: 9 days
Cattle
Meat and offal: 28 days
Milk: 5 days

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of pharmacological tests are not required.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of tolerance studies are not required.

IV.II. Clinical Documentation

Laboratory Trials

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, results of laboratory trials are not required.

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(s) 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.

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

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.

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