Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats

Date Created: May 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0681/001/DC
Name, strength and pharmaceutical form	Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats, Suspension for injection
Applicant	Univet Ltd, Tullyvin, Cootehill, Co. Cavan, Ireland
Active substance(s)	Amoxicillin
ATC Vetcode	QJ01CA04
Target species	Cats Cattle Dogs Pigs Sheep
Indication for use	For the treatment of infections of the alimentary tract, respiratory tract, urogenital tract, skin and soft tissue caused by bacteria susceptible to amoxicillin.

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	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	6th February 2019
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden.

I. SCIENTIFIC OVERVIEW

The application was for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference product is Betamox LA 150 mg/ml Suspension for Injection (Vm 02000/4070), marketed by Norbrook Laboratories (GB) Limited, which has been authorised in the UK since June 1986. The applicant claimed exemption from the requirement for bioequivalence studies in accordance with exemption 7.1.d0 of the Guideline on the Conduct of Bioequivalence Studies.

Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs and Cats contains 150 mg/ml amoxicillin (as amoxicillin trihydrate). The proposed indications in Cattle, Sheep, Pigs, Dogs and Cats are as follows:

In vitro amoxicillin is effective against a wide range of Gram-positive and Gram-negative bacteria, which include:

Escherichia coli
Klebsiella pneumoniae
Proteus species
Salmonella species
Staphylococci and
Streptococci

Not effective against beta-lactamase producing organisms.

Suitable for the control of infections due to susceptible microorganisms in cattle, sheep, pigs, dogs and cats, where a single injection giving prolonged activity is required. It may also protect from secondary bacterial invasion due to sensitive organisms in cases where bacteria are not the initial cause of the disease.

Indications include infections of:
(a) Alimentary tract
(b) Respiratory tract
(c) Skin and soft tissue
(d) Urogenital tract and,
(e) In prevention of post-operative infection (treat before surgery).

The proposed dosage is 15 mg/kg bodyweight, repeatable if necessary after 48 hours. Dose volume is equivalent to 1 ml per 10 kg bodyweight. If the dose volume exceeds 20 ml, it should be divided and injected into two sites.

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 Amoxicillin (as Amoxicillin Trihydrate) and the excipients Butylated Hydroxyanisole, Butylated Hydroxytoluene, Aluminium distearate and Propylene Glycol Dicaprylocaprate.

The container/closure system consists of 50ml, 100ml and 250ml Type II clear glass vials and 100ml and 250ml clear polyethylene terephthalate vials. Vials are sealed with nitrile closures and aluminium overseals. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

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

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 mixing, dry heat sterilising, cooling, filling and testing.

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 Amoxicillin Trihydrate, 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.
Certificates of Suitability were provided for the active substance.

The excipients Butylated Hydroxyanisole, Butylated Hydroxytoluene and Propylene Glycol Dicaprylocaprate comply with monographs in the European Pharmacopeia. Aluminium distearate does not appear in the European Pharmacopeia and is subject to in-house specification and satisfactory certificates of analysis were provided.

Information on the containers for the active substance were stated on the Certificates of Suitability, the containers consist of a double low density polyethylene bag placed either in a fibre or cardboard container, a fibre drum or polyethylene woven bag.

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. 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 those for appearance, fill volume, specific gravity, impurities, syringeability, viscosity, particle size, water content and sterility.

II.F. Stability

Stability data on the active substance have been evaluated by EDQM during the assessment of the applications for the Certificates of Suitability, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 1 year
Shelf life after first opening the immediate packaging: 28 days
Do not store above 25ºC.
Protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological and Toxicological Studies

The application is made in accordance with Atricle 13(1) of Directive 20001/EC, as amended, and adequate justification has been provided for the omission of bioequivalence studies, in accordance with section 7.1.d 9EMA/CVMP/016/00-Rev.2); therefore, data from pharmacological and toxicological studies are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that as the proposed product and the reference product have the same qualitative and quantitative composition, with respect to the active substance (150 mg amoxicillin), and are in the same pharmaceutical form, given at the same dose and route, the tasks and situations that lead to exposure will be the same for both products. Therefore, the risks to the user are expected to

be identical to those posed by the reference product and are mitigated by appropriate advice in the SPC.

The warnings proposed in the SPC are identical to those authorised for the reference product and are as follows:

Care should be taken to avoid accidental self-injection. In the case of accidental self-injection, seek medical advice immediately.
Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
1. Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
2. Handle this product with great care to avoid exposure, taking all recommended precautions.
3. If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.
Wash hands after use.

A warning has been included on the outer carton 'Special Warnings' :

Penicillins may occasionally cause severe allergic reactions.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

A Phase I and II ERA were submitted, written in accordance with appropriate guidance. The applicant used the total residue approach to calculate the $PEC_{soil\ initial}$ for both intensively reared and pasture animals. Cats and dogs were not included in the ERA, as exposure from these animals is considered negligible.

In Phase I PEC_{soil} calculations, the weaner pig PEC_{soil} was greater than the trigger value of 100 µ g/kg, when 50% of the herd receives two treatments. This was considered a worst-case scenario, as the proposed dosing regimen is a single administration; however, the dose may be repeated 48 hours later. Nevertheless, based on the results of the weaner pigs receiving two treatments, a Phase II ERA was required, focusing on intensively reared exposure scenarios.

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 effectsAs 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 product contains the same amount of active substance and is qualitatively identical in terms of excipients to the reference product. It has the same pharmaceutical form and physiochemical properties as the reference product. The product is considered eligible for an exemption from demonstration of bioequivalence with the reference product under section 7.1(d). Therefore, *in vivo* studies are not required to demonstrate the pharmacokinetics and residue depletion, as these can also be considered equivalent to the reference product.

MRLs

The active substance amoxicillin is listed in Table 1 of Regulation 37/2010 of pharmacologically actives substances. MRLs are given for muscle, skin/fat in natural proportions, liver, kidney and milk.

MRLs are listed below:

	All food producing species
Muscle	50 µg/kg
Liver	50 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	4 µg/kg

For fin fish the muscle MRL relates to 'muscle and skin in natural proportions . MRLs for fat, liver and kidney do not apply to fin fish.
For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions.
Not for use in animals from which eggs are produced for human consumption.

Withdrawal Periods

No residue or analytical data were presented. The applicant has justified the omission of residue studies on the basis that the proposed formulation is a generic of the reference product and is qualitatively and quantitatively identical in

terms of active substance and has been exempt from bioequivalence studies under biowaiver 7.1d. The product is to be administered in the same way, with the same maximum injection volumes. Therefore, the same withdrawal periods have been proposed and are acceptable.

Cattle (meat): 28 days
Milk: 84 hours

Sheep and pigs (meat): 19 days

Not for use in sheep producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Owing to the legal basis of the application, no pharmacodynamic data are required.
The applicant has claimed a waiver from the requirement to conduct a bioequivalence study, based on section 7.1d) of the current guideline on bioequivalence (EMEA/CVMP/016/00-Rev.2): *The formulations are identical (identical active substances and excipients as well as physicochemical properties [e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process]).*

Tolerance in the Target Species

Tolerance studies were not required because the proposed product can be considered bioequivalent to the reference product, the safety of the proposed product in the target species can be expected to be no different from that of the reference product, and therefore, no target species tolerance data have been presented.

IV.II. Clinical Documentation

The applicant has claimed a waiver form the requirement to conduct a bioequivalence study, in accordance with criterion 7.1d) of the guideline EMEA/CVMP/016/00-Rev.2. No pre-clinical or clinical data was provided.

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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