College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Enrobactin 25 mg/ml Concentrate for Oral Solution for Pet Rabbits, Rodents, Ornamental Birds and Reptiles

Exoflex vet 25 mg/ml Concentrate for Oral Solution for Pet Rabbits, Rodents, Ornamental Birds and Reptiles (DK, FI, NO, SE only)

RMS transfer from UK (UK/V/0561/001/DC) to NL (NL/V/0315/001) on 31 March 2019.

Date Created (by UK): March 2016
Date updated (by NL): July 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0315/001 (former UK/V/0561/001/DC)
Name, strength and pharmaceutical form	Enrobactin 25 mg/ml Concentrate for Oral Solution for Pet Rabbits, Rodents, Ornamental Birds and Reptiles
Applicant	Le Vet Beheer B.V. Wilgenweg 7 3421 TV Oudewater The Netherlands
Active substance(s)	Enrofloxacin
ATC Vetcode	QJ01MA90
Target species	Pet rabbits, rodents, ornamental birds and reptiles
Indication for use	<u>Pet rabbits</u> Treatment of infections of the digestive and respiratory tracts caused by enrofloxacin susceptible strains of: *Escherichia coli, Pasteurella multocida* and *Staphylococcus* spp. Treatment of skin and wound infections caused by enrofloxacin susceptible strains of *Staphylococcus aureus*. <u>Rodents, reptiles and ornamental birds</u> Treatment of infections of the digestive and respiratory tracts where clinical experience, if possible, supported by susceptibility testing of the causal organism, indicates enrofloxacin as the substance of choice.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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	22 July 2015
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands (current RMS), Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

Enrobactin 25 mg/ml Concentrate for Oral Solution has been developed as a generic of Baytril 2.5% oral solution. The reference product was first authorised in the UK in 1993. A biowaiver has been granted, providing an exemption from clinical studies. The biowaiver was permitted on the basis of essential similarity between the test and reference products.

The product is indicated for the treatment of respiratory and alimentary tract infections caused by enrofloxacin sensitive bacteria. The product is for use in pet rabbits, rodents, ornamental birds and reptiles, and is administered orally following dilution. The product is contraindicated in animals that are epileptic or suffer from seizures and should not be given to animals producing food for human consumption.

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. The product is safe for the user, 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains enrofloxacin as the active substance and the excipients benzyl alcohol (E-1519), potassium hydroxide, hydroxyethylcellulose, caramel aroma and purified water.

The container/closure system consists of Type III amber glass bottles closed with a tamper-evident HDPE screw cap with ring and colourless LPDE syringe insert. The 10 ml bottle is supplied with a 1 ml dosing syringe and the 50 ml bottle is supplied with a 5 ml dosing syringe. Each bottle is packaged in an individual 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 manufacturing method consists of dissolving potassium hydroxide and enrofloxacin in the water before mixing the solution with the remaining excipients. Once the correct pH is established, and the excipients are all dissolved in the solution, the bottles are filled with the product. 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 enrofloxacin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). A Ph. Eur. Certificate of Suitability has been supplied 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 the excipients, apart from caramel aroma, are described in a pharmacopoeia and manufactured in accordance with their respective Ph. Eur. monograph. Data were provided for caramel aroma. Certificates of analysis have been provided for all excipients.

II.C.4. Substances of Biological Origin

Scientific data and/or 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.

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. Control tests on the finished product include: identification and assay of the active substance, identification and assay of excipients, identification of impurities, appearance, clarity, pH, viscosity and microbiological purity.

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.

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 the batches stored at 25°C/60%RH for 36 months and 40°C/75%RH for 24 months. A 3 year shelf life has been established.

In-use stability data were also provided. Following broaching of the container, a batch was stored at 25°C/60%RH for 28 days. An in-use shelf life of 28 days has been determined.

G. Other Information

Shelf life
Shelf life of the finished product as packaged for sale is 3 years.
Shelf life after first opening the immediate packaging is 28 days.
Once diluted according to directions, use immediately.

Special precautions for storage
Keep the bottle tightly closed.
Any remaining diluted solution should be discarded immediately after use.

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 the reference product has been established, results of pharmacological studies 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 the reference product has been established, results of toxicological studies are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main route of exposure is dermal, but oral and ocular exposure scenarios were also considered in the risk assessment. The product is not expected to pose a risk when used in accordance with the SPC. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
- Personal protective equipment consisting of impermeable gloves should be worn when handling the veterinary medicinal product.
- Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
- Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Environmental Safety

An Environmental Risk Assessment (ERA) was provided. The ERA was conducted in accordance with VICH and CVMP guidelines.

Phase I:
The product will only be used to treat individual animals not intended for human consumption. As a result environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

The product is only intended for use in non-food animals, therefore residue documentation was not required. A contraindication has been added to the SPC and product literature:

- Do not use in animals producing food for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Enrofloxacin belongs to the fluoroquinolones class of antibiotics. It has a bactericidal effect and works by interacting with the DNA gyrase to affect bacterial replication and altering the permeability of the cell membrane. Enrofloxacin possesses antimicrobial activity against most Gram-negative bacteria, many Gram-positive bacteria and against mycoplasmas.

Pharmacokinetics

The availability of enrofloxacin is similar following either oral or parenteral administration. Enrofloxacin also has a high distribution volume; tissue levels 2-3 times higher than serum levels have been demonstrated in laboratory animals and the target species. High levels of enrofloxacin are often found in the lungs, liver, kidney, skin, bone and lymphatic system. Enrofloxacin is also distributed to the cerebrospinous fluid, aqueous humour and foetus in pregnant animals.

No bioequivalence studies have been performed. A biowaiver is supported on the basis of essential similarity. Therefore, the test product can be considered bioequivalent to the reference product.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been established, tolerance studies are not required. The warnings included on the SPC and product literature for this product are equivalent to those of the reference product.

Resistance

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been established, resistance data are not required. The warnings included on the SPC and product literature for this product are equivalent to those of the reference product.

IV.II. Clinical Documentation

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been established, clinical data is 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(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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

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 product.

Summary of change	**Section updated**	**Approval date**
RMS transfer from UK to NL (NL/V/0315/001)	Cover page, module 1	21 March 2019
Introduction of a new pharmacovigilance system which has been assessed for another product of the same MAH (NL/V/xxxx/WS/021).	N/A	12 July 2019
Minor change in the manufacturing process (NL/V/0315/001/IA/002)	N/A	26 December 2020
Renewal (NL/V/0315/001/R/001)	N/A	27 December 2020