IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

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

PRODUCT SUMMARY

EU Procedure Number	IE/V/0456/001 (formerly UK/V/0624/001)
Name, Strength, Pharmaceutical Form	Enrocare 25 mg/ml Oral Solution for Pet Rabbits, Rodents, Ornamental Birds and Reptiles
Active Substances(s)	Enrofloxacin
Applicant	Ecuphar NV, Legeweg 157-I, 8020 Oostkamp, Belgium
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target Species	Pet rabbits, rodents, ornamental birds and reptiles.
Indication For Use	Pet rabbits 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. Rodents, reptiles and ornamental birds 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.
ATC Code	QJ01MA90
Date of conclusion of the decentralised procedure	27 March 2017 (UK) 26 May 2017 (IE)
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Ireland (now RMS) UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Enrocare 25 mg/ml Concentrate for Oral Solution for Pet Rabbits, Rodents, Ornamental Birds and Reptiles, submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The reference product is Baytril 2.5% Oral Solution, which has been nationally authorised in the UK since November 1993. Cattle, included in the indication for the reference product are not included in the proposed product. This is acceptable.

The proposed product is indicated for use in pet rabbits, for the treatment of infections of the digestive and respiratory tracts caused by enrofloxacin-susceptible strains of *Escherichia coli*, *Pasteurella multocida* and *Staphylococcus* spp., or for the

treatment of skin and wound infections caused by enrofloxacin susceptible strains of *Staphylococcus aureus*. In rodents, reptiles and ornamental birds, the product may be used for the 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. The Summary of Product Characteristics (SPC) provides detail on dosage for the different species indicated.

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, which should be referred to for the recommended dosing regimens. 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. QUALITY ASPECTS

II.A. Composition

The product contains 25 mg/ml enrofloxacin and the excipients potassium hydroxide, benzyl alcohol, hypromellose and purified water.
The container/closure system consists of 20 and 100ml amber polyvinyl chloride bottles with a polypropylene self-sealing syringe adaptor and a child resistant polyethylene screw cap.
The 20ml presentation is packaged in a carton containing a 3ml polypropylene syringe and the 100ml presentation is packaged in a carton containing a 10ml polypropylene syringe.. 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 a stirring and dissolution process, followed by filling and labelling the containers.

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). 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. A certificate of suitability was provided.

All excipients are monographed in the Ph. Eur. Certificates of suitability or in-house specifications were provided for the packaging materials, as appropriate.

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, relative density, pH, identification of the active substance, benzyl alcohol identification, microbiological purity and fill volume.

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. A retest period of 3 years for suitably stored material was provided by the manufacturer.
Stability of the finished product was demonstrated appropriately, in accordance with VICH[1] guidelines.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 30 months
Shelf life after first opening the immediate packaging: 90 days.
Shelf life after dilution: Any medicated liquid remaining 24 hours after preparation must be discarded.
The bottle is to be stored in the carton.

[1] VICH – International Cooperation on the Harmonisation on Technical Requirements for Registration of Veterinary Medicinal Products.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the application, pharmacological and toxicological data were not required.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which claims that the proposed and reference products are essentially similar. This was accepted.
Warnings and precautions as listed on the product literature, updated in line with an Article 35 referral which affected the reference product, are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- This product may cause allergic reactions in those that are sensitive.
- People with known hypersensitivity to (fluoro)quinolones or to any of the excipients should avoid contact with the product.
- The undiluted product is strongly alkaline and may cause irritation if it comes into contact with the skin or eyes.
- Avoid skin and eye contact.
- Wear impermeable gloves when administering the product.
- Rinse any splashes from skin or eyes immediately with water.
- If irritation persists, seek medical advice.
- Wash hands and exposed skin after use.
- Do not smoke, eat or drink when handling the product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.
The product will only be used in individual non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

The product is intended for use in non-food producing pet rabbits, rodents, ornamental birds and reptiles. Residues documentation was not requited.

Withdrawal Periods

The SPC and product literature states 'Do not use in animals producing food intended for human consumption.'

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Two enzymes essential for DNA replication and transcription in the target bacteria are inhibited by fluoroquinolones. The active substance is effective against many bacterial species, as cited in the SPC and product literature. The mode of action of enrofloxacin is bactericidal, and bactericidal activity is concentration dependent.

Pharmacokinetics

The pharmacokinetic properties of enrofloxacin are such that both oral and parenteral administration leads to similar serum levels. Enrofloxacin possesses a high distribution volume. Tissue levels 2-3 times higher than found in the serum, have been demonstrated in laboratory animals and target species. Organs in which high levels can be expected are the lungs, liver, kidney, skin, bone and lymphatic system. Enrofloxacin also distributes into the cerebrospinal fluid, the aqueous humour and the foetus in pregnant animals.

Tolerance in the Target Species

No tolerance studies were required due to the nature of the application. However, data in the SPC were updated accordingly, in accordance with an Article 35 referral which affected the reference product:

- The product should not be used for prophylaxis.
- Do not use in cases of confirmed or suspected resistance to quinolones, since a high degree or cross resistance between enrofloxacin and other quinolones exists.
- Do not use in cases of hypersensitivity to fluoroquinolones or to any of the excipients.
- Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Resistance

No resistance studies were required due to the nature of the application. However, data in the SPC were updated accordingly, in accordance with an Article 35 referral which affected the reference product:

- The product should not be used for prophylaxis.
- Do not use in cases of confirmed or suspected resistance to quinolones, since a high degree or cross resistance between enrofloxacin and other quinolones exists.
- Do not use in cases of hypersensitivity to fluoroquinolones or to any of the excipients.
- Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

It is noted that use of the product deviating from instructions in the SPC may increase the resistance of bacteria resistant to the antimicrobial class, and reduce effectiveness of the product with other quinolones, due to the potential for cross-resistance.

IV.II. Clinical Documentation

Due to the nature of the application, no studies or further data were required for this section.

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.