Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 15 mg Tablets for dogs and cats
Enrocill Flavour 50 mg Tablets for cats and dogs
Enrocill Flavour 150 mg Tablets for dogs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0207/001-003/DC
Name, strength and pharmaceutical form	Enrocill Flavour 15 mg Tablets for dogs and cats Enrocill Flavour 50 mg Tablets for cats and dogs Enrocill Flavour 150 mg Tablets for dogs
Applicant	Hifarmax, Lda, Av. Marechal Craveiro Lopes nº96 R/C Dto 2775-696 Carcavelos, Portugal
Active substance(s)	Enrofloxacin
ATC Vet code	QJ01MA90
Target species	Enrocill Flavour 15 mg Tablets for dogs and cats Enrocill Flavour 50 mg Tablets for cats and dogs Enrocill Flavour 150 mg Tablets for dogs
Indication for use	Treatment of infections caused by gram-positive bacteria, gram-negative bacteria and mycoplasmas susceptible to enrofloxacin: Staphylococcus spp., E.coli, Haemophilus spp. Pasteurella spp. and Salmonella spp. The product is indicated for treatment of mono or mixed bacterial infections of the respiratory, digestive and urinary tract, ear, skin and wound infections. If there is no clinical improvement within three days, further susceptibility testing and possibly a change in antimicrobial therapy should be considered.

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MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 27/01/2014
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	PT

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains enrofloxacin 15 mg, 50 mg or 150 mg and excipients Mannitol, Maize starch, Sodium starch glycolate (type A), Meat flavour 10022, Sodium laurilsulphate, Basic butylated methacrylate copolymer, Dibutyl sebacate, Croscarmellose sodium, Silica colloidal anhydrous, Talc and Magnesium stearate.

The container/closure system consists of a Polyamide/Aluminium/Polyvinyl chloride film (OPA/Al/PVC), heat-sealed with aluminium foil containing 10 tablets / blister. Each cardboard carton contains 10 blister packs or 1 blister pack. The particulars of the containers and controls performed are provided and conform to the regulation.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance is enrofloxacin, 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.

Two active substance manufacturers are requested. One of them submits the master file according to the Active Substance Master File procedure. The CEP is included according to the European Pharmacopoeia (EDQM) by the other one.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products (pharmaceuticals)

Not applicable.

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F. 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 sites have been provided demonstrating compliance with the specification.

G. 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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users / the environment.

Since this product is intended for companion animals only, no residue data need to be provided.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, toxicological studies are not required.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not pose an unacceptable risk.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Enrofloxacin is an antibiotic that belongs to the chemical class of fluoroquinolones. The compound exerts bactericidal activity via mechanism of action based on the inhibition of the A subunit of DNA gyrase (topoisomerase II). In Gram positive bacteria the primary target is topoisomerase IV instead of topoisomerase II. With this mechanism enrofloxacin blocks the replication, transcription and recombination of bacterial DNA. Fluoroquinolones also act on on bacterial cells during stationary phase by changing the permeability in the phospholipid cellular membranes. These mechanisms explain the rapid loss of viability of the bacteria exposed to enrofloxacin. Inhibitory and bactericidal concentrations of enrofloxacin are strongly correlated. They are either equal, or differ in 1-2 dilution steps. Enrofloxacin exerts its antimicrobial action at low concentrations. It is effective against most Gram-negative bacteria and many Gram positive bacteria, both aerobes and anaerobes.
Antibacterial spectrum: Staphylococcus spp, Escherichia coli, Haemophilus spp., Pasteurella spp., Salmonella spp., Mycoplasma spp.
Induction of resistance against quinolones can develop by mutations in the gyrase gene of bacteria and by changes in cell permeability towards quinolones.

Pharmacokinetics

Enrofloxacin has relatively high bioavailability after oral administration in almost all of the species studied. In dogs and cats, orally dosed with enrofloxacin, the maximum plasma concentration of enrofloxacin is reached after 1 and 2 hours, respectively. The antibacterial activity is still maintained after 24 hours. Concomitant administration of compounds containing multivalent cations (antacids, milk or milk replacers) decreases the oral bioavailability of fluoroquinolones.
Fluoroquinolones are characterized by extensive distribution to body fluids and tissues, reaching in some concentrations higher than those found in plasma. Fluoroquinolones are widely distributed in skin, bone and semen as well as in the anterior and posterior chambers of the eye; they cross the placenta and brain barrier. High levels are found in phagocytic cells (alveolar macrophages, neutrophils); therefore fluoroquinolones are effective against intracellular microorganisms.
The degree of metabolism varies between species and is around 50-60%. Enrofloxacin is biotransformed in the liver, to an active metabolite ciprofloxacin. In general, metabolism occurs via hydroxylation and oxidation reactions. Other reactions involved are N-dealkylation and glucuronic acid conjugation.
Excretion occurs via the bile and kidney, the latter being predominant. The renal excretion is by glomerular filtration and tubular excretion.
In dogs, orally administered 5 mg / kg enrofloxacin rapid absorption was observed and concentrations of enrofloxacin after 4 h were 0.3 µg / ml in plasma, 3.3 µg / ml in alveolar macrophages and 4.8 µg / ml in lung epithelial fluid. The bioavailability was approximately 80%.

Tolerance in the Target Species of Animals

As this is a generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, tolerance studies in the target species are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

The applicant has submitted a complete bibliographic review of the resistance situation to fluoroquinolones in the target species dogs and cats. The resistance part was satisfactorily documented.

Suitable warning are included on the SPC and product literature.

IV.B Clinical Studies

This is a generic application submitted in accordance with Article 13 (1) of directive 2001/82/EC as amended and bioequivalence with the reference product is claimed. The applicant has submitted bioequivalence in vivo studies in dog and cats, in compliance with the relevant guideline which show that the test and reference products are bioequivalent and therefore results of clinical 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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 veterinary Heads of 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.

None

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