IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

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Enrox Flavour 50 mg Tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0423/001 IE/V/0423/002 IE/V/0423/003
Name, strength and pharmaceutical form	**Enrox Flavour 15 mg Tablets for Dogs and Cats** **Enrox Flavour 50 mg Tablets for Dogs** **Enrox Flavour 150 mg Tablets for Dogs**
Applicant	KRKA, d.d., Novo mesto
Active substance(s)	Enrofloxacin
ATC Vetcode	QJ01MA90
Target species	Dogs and Cats
Indication for use	Enrox Flavour 15 mg Tablets for Dogs and Cats The product is for use in dogs and cats in the treatment of bacterial infections of the alimentary, respiratory and urogenital tracts, skin, secondary wound infections and otitis externa where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice. Enrox Flavour 50 mg and Enrox 150 mgTablets for Dogs The product is for use in dogs for the treatment of bacterial infections of the alimentary, respiratory and urogenital tracts, skin, secondary wound infections and otitis externa where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice.
Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original decentralised procedure	18 June 2009 (UK) 12 June 2009 (IE)
Concerned Member States for original procedure	Austria Belgium Bulgaria Czech Republic Denmark

	France Germany Greece Hungary Ireland (now RMS) Italy Latvia Lithuania Luxembourg Netherlands Poland Portugal Romania Slovakia Slovenia Spain Added as CMS via RMS change: United Kingdom

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

Enroxil Flavour 15 mg Tablets for Dogs and Cats, Enroxil Flavour 50 mg Tablets for Dogs and Enroxil Flavour 150 mg Tablets for Dogs contains the active substance enrofloxacin. The products are authorised to be used in dogs and cats in the treatment of bacterial infections of the alimentary, respiratory and urogenital tracts, skin, secondary wound infections and otitis externa. The dosage rate of enrofloxacin is 5 mg/kg given orally once daily or as a divided dose twice daily for 5 to 10 days with or without food.

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 and the slight reactions observed are indicated in the SPC. 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 of the product was demonstrated according to the claims made in the SPC.

II. QUALITY ASPECTS

A. Composition

The product contains enrofloxacin as an active substance and mannitol, maize starch, sodium starch glycolate (type A), meat flavour 10022, sodium laurilsulphate, basic butylated methacrylate copolymer, dibutyl sebacate, croscarmellose sodium, magnesium stearate, talc and silica colloidal anhydrous as excipients.
The product is packaged in polyamide/aluminium/polyvinyl chloride film (OPA/Al/PVC), heat sealed with aluminium foil.
The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the formulation is justified.

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, enrofloxacin, is an established active substance and supporting data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.
There are eleven excipients used in the formulation and each has been used previously in veterinary medicines. Mannitol, maize starch, sodium starch glycolate (type A), sodium laurilsulphate, basic butylated methacrylate copolymer, croscarmellose sodium, magnesium stearate, talc and silica colloidal anhydrous have monographs in the Ph. Eur. and each comply with the requirements of the current edition of the Ph. Eur.
No European Pharmacopoeia monograph is available for Dibutyl Sebacate. Acceptably, the applicant applies the monograph of the current USP.
The applicant provided raw material specification for meat flavour 10022, comprising tests of appearance, identity, loss on drying and microbiological quality.

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

The magnesium stearate and meat flavour 10022 are materials that may be sourced from either animal or non-animal sources. A declaration has been provided certifying that the raw materials, ingredients and additives used to produce magnesium stearate and meat flavour 10022 are exclusively of vegetable origin.

E. Control on intermediate products

Not applicable

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. The satisfactory validation data for the analytical methods have been provided.

G. Stability

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. The shelf-life of the veterinary medicinal product as packaged for sale is 3 years. The in-use shelf life of 24 hours is justified.

H. Genetically Modified Organisms
Not applicable
J. Other Information
None

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Pharmacological Studies
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on pharmacodynamics and pharmacokinetics are not required. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability study.
Toxicological Studies
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on toxicology are not required.
User Safety
The following operator warnings are included in the SPC and product literature:

- Wash hands after use.
- In case of contact with the eyes, wash with plenty of clean water.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet to the physician.
- People with known hypersensitivity to fluoroquinolones should avoid contact with the product.

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline.
The assessment ended at Phase I as the products will only be used in dogs and cats and exposure of the environment is not sufficient to require further assessment. The 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

IV.A Pre-Clinical Studies
Pharmacology
Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product.
Pharmacokinetics

In order to demonstrate bioequivalence with the reference product, the applicant conducted pharmacokinetic studies in cats and dogs with the proposed product. A bioequivalence study was conducted in cats using enrofloxacin flavour 15 mg tablets and the reference product. The study was conducted in accordance with GLP. The pharmacokinetic parameters of enrofloxacin and ciprofloxacin (metabolite) for both the test and reference products were calculated and tested for bioequivalence. Another bioequivalence study was conducted in dogs using enrofloxacin flavour 150 mg tablets and the reference product. This study was also conducted in accordance with GLP. These studies demonstrated that the enroxil flavour 15 mg, 50 mg and 150 mg tablets are bioequivalent to the reference product. Another in-vitro bioequivalence study was conducted between enrofloxacin flavour tablets 50 mg and enrofloxacin flavour tablets 15 mg in dogs and enrofloxacin flavour tablets 50 mg in cats. The dissolution studies were conducted in line with the bioequivalence guideline. This study demonstrated that the ratio of the treatment means for AUC and Cmax were contained within the 90% confidence interval of 80-125%, in accordance with the CVMP bioequivalence guidelines.

Tolerance in the Target Species of Animals

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product. The SPC carries suitable warnings.

Resistance

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, resistance data is not required as it has already been presented for the reference product.

Adequate warnings and precautions appear on the product literature. These are:

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly to other classes of antimicrobials. Whenever possible, use of fluoroquinolones should be based on susceptibility testing. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may increase the effectiveness of treatment with other quinolones due to the potential for cross-resistance. Official and local antimicrobial policies should be taken into account when the product is used.

Do not use in case of resistance to quinolones, as there exists almost complete cross resistance to other quinolones and complete cross resistance to other fluoroquinolones.

IV.B Clinical Studies

Laboratory Trials

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of

a reference medicinal product, resistance data is not required as it has already been presented for 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.