IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

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ENROXIL 50 mg/ml solution for injection for calves, pigs and dogs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0422/001
Name, Strength, Pharmaceutical Form	ENROXIL 50 mg/ml solution for injection for calves, pigs and dogs
Active Substances(s)	Enrofloxacin
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto Slovenia
Legal Basis of Application	Mutual Recognition application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Target Species	Calves, Pigs, Dogs
Indication For Use	Calves: Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp. Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

	Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*. Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*. Pigs: Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mycoplasma* spp. and *Actinobacillus pleuropneumoniae*. Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*. Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*. Dogs: Treatment of infections of the alimentary, respiratory and

	urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of *Staphylococcus* spp., *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.
ATC Code	QJ01MA90
Date of completion of the original mutual recognition procedure	27 September 2007
Date product first authorised in the Reference Member State (MRP only)	15 March 2006 (UK) 14 September 2007 (IE)
Concerned Member States for original procedure	Austria Germany Ireland Netherlands

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 product is a solution for injection containing enrofloxacin 50 mg/ml for use as a synthetic, broad-spectrum bactericidal antimicrobial to treat respiratory and alimentary tract diseases of bacterial and mycoplasmal origin in calves and pigs and to treat respiratory, alimentary, urogenital tracts, skin and secondary wound infections in dogs. Refer to the SPC for detailed specification and contraindications related to use of the product.
This application is submitted under Article 13 (1) of the Directive 2001/82/EC as amended by Directive 2004/28/EC. The applicant has confirmed that the formulation of Enroxil Solution for Injection 50 mg/ml for Calves, Pigs and Dogs is a generic of an approved product. For this type of application, applicants are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that a proposed product is a generic veterinary medicinal product, performing in the same manner as an established reference product, i.e. one authorised in the EU for not less than ten years. The generic product is required to have a comparable composition to the reference product, the same pharmaceutical form, and to perform equivalently in treated animals.
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 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 overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance enrofloxacin and excipients n-butyl alcohol, potassium hydroxide and water for injections.
The container/closure system comprises amber glass vials and synthetic rubber closures that comply with appearance and dimensional checks and with tests specified in the relevant monographs of the European Pharmacopoeia for materials

used in injectable products. The particulars of the containers and controls performed are provided and conform to current guidelines.
The choice of the formulation and 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.

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. 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.
Excipients, apart from the preservative, are the subject of monographs in the European Pharmacopoeia. Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these ingredients. In the case of the preservative, butanol (normal butyl alcohol), compliance with the monograph of the United States Pharmacopoeia National Formulary has been accepted as a specification that adequately identifies the material and limits chemical and microbiological contaminants appropriately for its use in an injectable product.
For the packaging, the amber glass vials and synthetic rubber closures comply with appearance and dimensional checks and with tests specified in the relevant monographs of the European Pharmacopoeia for materials used in injectable products.

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

There are no intermediate products.

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 site have been provided demonstrating compliance with the specification.

G. Stability

The stability of enrofloxacin is discussed in the ASMF assessment report. 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.
The claim of a 28 day stability after broaching is based on the demonstration of stability for a batch broached and stored for 28 days at 25°C/60%RH.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 5 years
Shelf-life after first opening the container: 28 days

Special precautions for storage

Do not store above 25°C.
Store in the original package.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

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 studies.

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. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

User Safety

The following operator warnings are included in the SPC and product literature:

- People with known hypersensitivity to fluoroquinolones should avoid any contact with the 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.
- Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Ecotoxicity

The applicant has provided an environmental risk assessment which makes the following points:

- Enroxil Solution for Injection 50 mg/ml has been shown to be essentially similar to Baytril 5% Injection.
- Enroxil Solution for Injection 50 mg/ml will be used in the same way as the reference product, i.e. it is indicated for the same species and given at the same dose.
- Baytril 5% Injection is an authorised product and as such environmental safety is considered to be acceptable.
- The environmental safety of Enroxil Solution for Injection 50 mg/ml will be identical to that of the reference product.
- Disposal advice is the same for the two products:

Any unused product or waste material should be disposed of in accordance with local requirements.

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.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because there are no differences in the formulation of this product, compared with the reference product, that would be liable to alter the residue depletion profile.

MRLs

Enrofloxacin is listed in Annex I of Council Regulation 2377/90. The marker substance is the sum of enrofloxacin and ciprofloxacin.

MRLs are listed below:

	Bovine, ovine, caprine	Porcine, rabbits
Muscle	100 µg/kg	100 µg/kg
Liver	300 µg/kg	200 µg/kg
Kidney	200 µg/kg	300 µg/kg
Fat	100 µg/kg	100 µg/kg
Milk	100 µg/kg	n/a

Withdrawal Periods

Calves: Following intravenous injection, meat and offal: 5 days.
Following subcutaneous injection: Meat and offal: 12 days.
Not authorised for use in animals producing milk for human consumption.
Pigs: Meat and offal: 13 days.

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. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

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, new tolerance data is not required as it has already been presented for the reference product. However, some information of this nature has been provided. The tolerance in the target species is acceptable.

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.

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, this information 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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.