



ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES

**Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

**Enroxil 100 mg/ml Solution for Injection for Cattle and Pigs (AT, IE,
NL, UK)**

Enroxal 100 mg/ml Solution for Injection for Cattle and Pigs (DE)

**PuAR correct as of 29/01/2018 when RMS was transferred
to IE. Please contact the RMS for future updates.**

MODULE 1

PRODUCT SUMMARY

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| EU Procedure number | UK/V/234/02/MR |
| Name, strength and pharmaceutical form | Enroxil 100 mg/ml Solution for Injection for Cattle and Pigs |
| Applicant | KRKA, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia |
| Active substance | Enrofloxacin |
| ATC Vetcode | QJ01MA90 |
| Target species | Cattle, Pigs, |
| Indication for use | <p>Cattle: Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of <i>Pasteurella multocida</i>, <i>Mannheimia haemolytica</i> and <i>Mycoplasma</i> spp. Treatment of acute severe mastitis caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>. Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>. Treatment of septicaemia caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>. Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of <i>Mycoplasma bovis</i> in cattle less than 2 years old.</p> <p>Pigs: Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of <i>Pasteurella multocida</i>, <i>Mycoplasma</i> spp. and <i>Actinobacillus pleuropneumoniae</i>. Treatment of infections of the urinary tract caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>. Treatment of post-partum dysgalactiae syndrome, PDS (MMA syndrome) caused by enrofloxacin susceptible strains of <i>Escherichia coli</i> and <i>Klebsiella</i> spp.</p> |

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| | <p>Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>.</p> <p>Treatment of septicaemia caused by enrofloxacin susceptible strains of <i>Escherichia coli</i>.</p> |
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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

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| Legal basis of original application | Mutual Recognition application in accordance with Article 13 (1) of Directive 2001/82/EC as amended. |
| 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 |
| Concerned Member States for original procedure | Austria Germany Ireland Netherlands |

I. SCIENTIFIC OVERVIEW

This product is a solution for injection containing enrofloxacin 100 mg/ml for use as a synthetic, broad-spectrum bactericidal antimicrobial to treat respiratory and alimentary tract diseases of bacterial and mycoplasmal origin in cattle and pigs. Refer to the SPC¹ 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 100 mg/ml Solution for Injection mg/ml for cattle and pigs 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

¹ SPC – Summary of Product Characteristics.

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 (PHARMACOTOXICOLOGICAL)

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 100 mg/ml Solution for Injection has been shown to be essentially similar to Baytril 10 % Injection.
- Enroxil 100 mg/ml Solution for Injection 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 10 % Injection is an authorised product and as such environmental safety is considered to be acceptable.
- The environmental safety of Enroxil 100 mg/ml Solution for Injection will be identical to that of the reference product.
- Disposal advice is the same for the two products:

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

Milk: 3 days.

Following subcutaneous injection: Meat and offal: 12 days.

Pigs: Meat and offal: 13 days.

IV CLINICAL ASSESSMENT (EFFICACY)

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 benefit/risk 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 Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed