IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

ENRODEXIL 100 mg/ml solution for injection for cattle and pigs

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0264/001/DC
Name, strength and pharmaceutical form	ENRODEXIL 100 mg/ml Solution for Injection for Cattle and Pigs
Active substance(s)	Enrofloxacin
Applicant	Industrial Veterinaria S.A. C/Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	23/02/2011
Target species	Cattle and pigs
Indication for use	**Cattle** 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* in cattle less than 2 years old. **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 urinary tract caused by enrofloxacin susceptible strains of *Escherichia coli*. Treatment of post-partum dysgalactiae syndrome, PDS (MMA syndrome) caused by enrofloxacin susceptible strains of *Escherichia coli* and *Klebsiella 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*.
ATCvet code	QJ01MA90
Concerned Member States	AT, BE, DE, EL, ES, HU, IT, NL, PL, PT, RO, UK

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

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 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

A. Qualitative and Quantitative Particulars

The product contains the active substance enrofloxacin (100 mg/ml) and excipients benzyl alcohol, potassium hydroxide, glacial acetic acid, disodium edetate and water for injections.

The container/closure system consists of Type II amber glass vials of 250 ml with pink bromobutyl rubber stoppers.

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 at 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.

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. ***D.***

Control on Intermediate Products

Not applicable.

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.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance enrofloxacin has 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.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

See part IV.

Toxicological Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. Based on information provided in support of this application the applicant claims that the test product is bioequivalent to the reference product (Baytril 10% Solution for Injection). Consequently, specific toxicological data relating to the active substance are not presented.

Note that the safety of the final formulation in the target animal is commented on in Part IV of this report.

User Safety

Given that the product concerned by the present application is a generic of an authorised reference product, it is accepted that there will be no difference between test and reference products in terms of the risk posed by exposure to the active substance. With regard to the excipients, they are widely used in the pharmaceutical and food industries and, at the quantities included in the formulation, are regarded as safe. Consequently, it is considered that the test product will not pose any greater risk to the user than the reference product. The risk mitigating measures proposed for inclusion on the SPC of the test product are in line with those that appear on the SPC for the reference product and can be accepted.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant has provided a comprehensive set of data needed to conduct a full risk assessment according to the VICH and CVMP guidelines. Some of the data are new studies in compliance with GLP and relevant OECD guidelines. Other data are taken from peer reviewed articles published in the open literature. From this data set, it is evident that enrofloxacin does not pose a risk to fresh water invertebrates, fish, algae, soil micro-organism, plants and soil invertebrates. Higher tier modelling has furthermore revealed a negligible risk for ground water contamination.

Based on the available data, it can be concluded that the product when used in accordance with label recommendations will not present an unacceptable risk to the environment.

III.B Residues Documentation

Residue Studies

This application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application).

Based on the data presented (see Part 4), it is accepted that the test and reference products can be considered bioequivalent in cattle (both intravenous and subcutaneous administration) and pigs (intramuscular route). Given that bioequivalence can be assumed, it is reasonable to expect that there should be no difference between products with respect to residue depletion from the primary target tissues. However, as the product is to be administered by the subcutaneous route in cattle and by the intramuscular route in pigs, injection site residue depletion studies would normally be required (in line with current guidance) to demonstrate that the product formulation does not display significantly different residue depletion kinetics from the site of injection when compared with the withdrawal period claimed for the product.

The withdrawal periods were harmonised with the reference product in accordance with Commission Decision C(2014) 6268 Final, following an Article 35 referral.

MRLs

Enrofloxacin is listed in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010 (O.J 20.1.2010, L15/30). The marker substance is the sum of enrofloxacin and ciprofloxacin.

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Bovine	100µg/kg 100µg/kg 300µg/kg 200µg/kg 100µg/kg	Muscle Fat Liver Kidney Milk
		Porcine	100µg/kg 100µg/kg 200µg/kg 300µg/kg	Muscle Skin and fat in natural proportions Liver Kidney

Withdrawal Periods

The following withdrawal periods were accepted for this product:

Cattle: Subcutaneous use:
meat & offal: 12 days

milk: 96 Hours

Cattle: Intravenous use:
meat & offal: 5 days
milk: 72 Hours

Pigs: meat & offal: 13 days.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The product is intended for use in cattle (intravenous and subcutaneous administration) and pigs (intramuscular administration).

The test and reference product have the same qualitative and quantitative composition in terms of active substance. In addition, the applicant argues that the formulations can be considered 'equivalent':

Both are aqueous solutions for parenteral administration

The SPC of the reference product indicates that it contains 100 mg/ml of the active substance, 30 mg/ml of the preservative, butanol, with potassium hydroxide and water for injection as other excipients. Dissolution of the active substance requires an alkaline pH, and so potassium hydroxide is used as the pH adjuster.

The test product has been formulated to include 100 mg/ml of the active substance, 7.8 mg/ml of benzyl alcohol as preservative, with sodium EDTA, glacial acetic acid, potassium hydroxide and water for injection as other excipients.

Based on comparative analysis, the physico-chemical properties (appearance, density, pH) and impurity profiles of both the test and reference product were shown to be similar.

Given the similarity in formulations, it is argued that the test and reference products can be considered equivalent. Further, the applicant argues that the differences between products with respect to excipients will not significantly impact on absorption of the active substance. This was confirmed by conducting *in vivo* bioequivalence studies in both target species.

Crossover bioequivalence study of a single dose of Enrofloxacin 100 mg/ml Solution for Injection (test formulation) and Baytril 10% (reference formulation) Solution for Injection in calves.

Study status:	GLP
Test animals:	22 crossbreed calves
Design:	Cross-over bioequivalence study, with a washout period of 7 days between phases.
Treatment:	Either the test or reference product was administered subcutaneously to calves on a single occasion at a dose of 5 mg/kg.
Results:	The 90% confidence intervals for the ratios between the geometric means of AUC, AUC_t and C_{max} of the test formulation with respect to the reference were as follows:

90% CI of the test item vs reference item				
	Enrofloxacin		Ciprofloxacin	
	Upper limit	Lower limit	Upper limit	Lower limit
AUC	1.04	0.85	1.04	0.92
AUC_t	1.02	0.82	1.02	0.90
C_{max}	0.96	0.80	0.99	0.84

For the pivotal parameters for both enrofloxacin and ciprofloxacin, the 90% confidence intervals were within the acceptable limits of 0.80 to 1.25. I

Conclusions: The extent and rate of absorption of enrofloxacin as well as the extent and rate of formation of ciprofloxacin were equivalent after subcutaneous administration of both products (reference and test formulations) to calves.

Crossover bioequivalence study at single dose of Enrofloxacin 100 mg/ml Solution for Injection for Cattle and Pigs (test formulation) and Baytril 10% Solution for Injection in Pigs.

Study status: GLP

Test animals: 24 crossbreed pigs

Design: Cross-over bioequivalence study, with a washout period of 7 days between phases.

Treatment: Either the test or reference product was administered by the intramuscular route to pigs on a single occasion at a dose of 2.5 mg/kg.

Results: The 90% confidence intervals for the ratios between the geometric means of AUC, AUC_t and C_{max} of the test formulation with respect to the reference were as follows:

90% CI of the test item vs reference item				
	Enrofloxacin		Ciprofloxacin	
	Upper limit	Lower limit	Upper limit	Lower limit
AUC	1.08	0.94	1.05	0.93
AUC_t	1.08	0.93	1.03	0.93
C_{max}	1.15	0.83	1.05	0.94

For the three parameters for both enrofloxacin and ciprofloxacin, the 90% confidence intervals were within the acceptable limit of 0.80 to 1.25.

Conclusions: The extent and rate of absorption of enrofloxacin as well as the extent and rate of formation of ciprofloxacin were equivalent after intramuscular administration of both products (reference and test formulations) to pigs.

In conclusion, based on the data package provided, the following is accepted:

Given the nature of the formulation (solution for injection) and the fact that the test and reference products are the same in terms of active substance content, bioequivalence following intravenous administration in cattle can be assumed (in accordance with paragraph 4a of guideline EMEA/CVMP/016),

Based on the findings of the in vivo study in calves, bioequivalence following subcutaneous administration in cattle has been demonstrated, and

Based on the findings of the in vivo study in pigs, bioequivalence following intramuscular administration in pigs has been demonstrated.

Tolerance in the Target Species of Animals

Based on data/information presented above, it is accepted that the test and reference products can be considered equivalent. Therefore, it is considered that the test product does not present any greater risk to the target species than the reference product.
Based on the evaluation of local tolerance conducted as part of the bioequivalence study in cattle, it is noted that local reactions associated with the administration of both the test and reference item were common and persisted in some animals for between 7 and 14 days. The potential for such effects is detailed in the SPC of the reference product. Similar information is proposed for inclusion on the SPC of the test product. This is considered appropriate and acceptable.
Resistance

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). As such no data are required.

In line with the SPC guidance document relating to fluoroquinolones, the following standard statements are proposed for inclusion in section 4.5 (Special precautions for use in animals) of the SPC:

Official and local antimicrobial policies should be taken into account when the product is used.

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, fluoroquinolones should only be used 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 decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance.

The following statement is proposed for inclusion in Section 4.9 (Amounts to be administered and administration route) of the SPC:

To ensure correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

IV.B Clinical Studies

This application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). It is argued that the efficacy profile of both the test and reference product will be the same.

It should be noted that the proposed indications and posology for the test product reflect the authorised indications and posology of the reference product in the RMS.

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.

VI 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 HPRA website.

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.

Changes:

Safety/Efficacy Changes

Summary of change (Application number)	**Approval date**
Change in the Summary of Product Characteristics, Labelling and Package Leaflet intended to implement the outcome of a Union referral procedure concerning: in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for "Baytril 2.5% injectable, Baytril 5% injectable, Baytril 10% injectable and associated names", and related veterinary medicinal products, which contain the active substance "Enrofloxacin" (Decision number: C (2014) 6268 Final). (IE/V/0264/01/IA/06/G)	18/11/2014