MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

agencia española de
medicamentos y
productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ENROFLOXACIN UNIVERSAL 100 mg/ml
Oral solution for chickens and rabbits

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0145/001/MR
Name, strength and pharmaceutical form	LEVOFLOK 100 mg/ml Oral solution for chickens and rabbits (EL, IT, PT) ENROFLOXACIN UNIVERSAL 100 mg/ml Oral solution for chickens and rabbits (ES)
Applicant	UNIVERSAL FARMA, S.L. Gran Vía Carlos III, 98 – 7ª 08028 – BARCELONA Spain
Active substance(s)	Enrofloxacin
ATC Vet code	QJ01MA90
Target species	Chickens (broilers) Rabbits
Indication for use	CHICKENS (BROILERS): Treatment of infections due to *E.coli*, *Salmonella spp*. and *Mycoplasma spp*. RABBITS: Treatment of respiratory infections due to *P.multocida*.

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	Mutual Recognition application in accordance with Article 13.2 (b) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 29/07/2009
Date product first authorised in the Reference Member State (MRP only)	20/12/2006
Concerned Member States for original procedure	EL, IT, PT

I. SCIENTIFIC OVERVIEW

The product is an oral solution containing 10% enrofloxacin. It is presented as essentially similar to a product granted in Spain since 1992 (Hipralona Enro-S), with the same quantitative and qualitative composition in active substance, as well as the same pharmaceutical form. The product is an oral solution to be administered by oral route via drinking water.
The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

II. QUALITY ASPECTS

A. Composition

The product is a clear, yellow solution containing 10% m/v enrofloxacin and benzyl alcohol, potassium hydroxide and purified water as excipients.

It is packaged in white high-density polyethylene container of 1 litre and 5 litres capacity. Containers are closed with a white screw cap of the same material, with induction disc. The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The product has been considered exempt of bioequivalence studies according to section 4.e) of guideline EMEA/CVMP/016/00-FINAL because:
- It is an oral solution containing the active substance in the same concentration as the reference.
- It does not contain inactive substances that can affect significantly the absorption of the active substance

B. Method of Preparation of the Product

The applicant proposed two different manufacturing sites for the product, one of them authorized by a variation after the initial authorisation in Spain. The manufacturing process for both sites is performing according GMP rules.

The manufacturing process validation performed on three commercial bulk batches is presented for both manufacturers.

C. Control of Starting Materials

The active substance is Enrofloxacin, an established active substance not described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The quality of the active ingredient Enrofloxacin is documented by a Drug Master File. A letter of access has been included. 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.

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

Declarations are provided confirming that no materials of ruminant origin are used in manufacture of the active or excipients. Certificates of each component are attached to certify the absence of TSE risks.

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.

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.

An in-use shelf life of 3 months following first opening of the container is justified by the data.

II.H. DATA IN RELATION TO ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING GMOs

A certificate is attached conform none of the starting materials used in this product contain modified organisms.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

As this is a generic application according to Article 13, and bioequivalence studies are not necessary according to exemption e) of guideline EMEA/CVMP/016/00, results of safety and residue tests are not required.

The safety and residue aspect of this product are identical to the reference product.

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 and consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13, results of pharmacological tests are not provided because evidences were already proved for the reference product.

Enrofloxacin is an antibacterial agent belonging to the chemical group of fluoroquinolones. This compound carries out a bactericide activity by means of an action mechanism based on inhibiting subunit A of bacterial DNA-gyrase (topoisomerase II), thus preventing negative axial rotation of DNA molecule.

Enrofloxacin has relatively high oral, intramuscular and subcutaneous bioavailability in almost all tested species.
Fluoroquinolones are characterised by being broadly diffused in corporal fluids and tissues, reaching greater concentrations there than in plasma.
The metabolism degree varies in relation to species, and it is about 50-60%.
Excretion takes place through biliary and renal routes, being the later the most common elimination route.

Toxicological Studies

As this is a generic application according to Article 13, results of toxicological tests are not provided because evidences were already proved for the reference product.

Enrofloxacin has low acute toxicity, is not teratogenic and is not carcinogenic.

User Safety

As this is a generic application according to Article 13, a user safety assessment is not required.

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 further assessment in Phase II was required. The assessment concluded that the product has an acceptable risk for the environment.

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 this is a generic application according to Article 13 and results of residue tests were already proved for the reference product.

MRLs

Enrofloxacin is listed in Annex I of Council Regulation 470/2009. The marker substance is enrofloxacin plus ciprofloxacin.

MRLs are listed below:

Active substance	Marker residue	Animal specie	Target tissue	MRL (µg/kg)
Enrofloxacin	Enrofloxacin+Ciprofloxacin	Rabbits	Muscle	100
			Fat	100
			Liver	200
			Kidney	300
		Poultry	Muscle	100
			Skin and fat	100
			Liver	200
			Kidney	300

Enrofloxacin is not permitted for use in animals from which eggs are produced for human consumption.

Withdrawal Periods

The withdrawal periods are the same as stated in the reference product:

Meat: Chickens (broilers): 4 days.
Rabbits: 2 days.

Eggs: Not permitted for use in laying birds producing eggs for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence studies are not necessary according to exemption e) of guideline EMEA/CVMP/016/00, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13, results of pharmacological tests are not provided because evidences were already proved for the reference product.

The medicinal product in this application is a solution to be administered by oral route in drinking water, containing 100 mg of enrofloxacin per ml. It is indicated for the treatment of infections caused by E.coli, Salmonella and Mycoplasma in chickens and Pasteurella multocida in rabbits.

Enrofloxacin is an antibacterial agent belonging to the chemical group of fluoroquinolones. This compound carries out a bactericide activity by means of an action mechanism based on inhibiting subunit A of bacterial DNA-gyrase (topoisomerase II), thus preventing negative axial rotation of DNA molecule.

Enrofloxacin has relatively high oral, intramuscular and subcutaneous bioavailability in almost all tested species.
Fluoroquinolones are characterised by being broadly diffused in corporal fluids and tissues, reaching greater concentrations there than in plasma.
The metabolism degree varies in relation to species, and it is about 50-60%.
Excretion takes place through biliary and renal routes, being the later the most common elimination route.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, results of tolerance tests in the target species of animals are not provided because evidences were already proved for the reference product.

Resistance

It is not necessary to submit any evidence to prove its efficacy as far as antimicrobial resistances are concerned because evidences were already proved for the reference product.

However, the applicant carried out a study in order to confirm the *in-vitro* sensitivity to enrofloxacin of 30 *Escherichia coli*, 30 *Salmonella spp* and 22 *Mycoplasma spp* strains isolated from poultry.

IV.B Clinical Studies

As this is a generic application according to Article 13, results of clinical tests are not provided because evidences were already proved 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.

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