ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Norotril Max 100 mg/ml Solution for Injection for Cattle
(all other CMS)
Enrotril Max 100 mg/ml Solution for Injection for Cattle
(Ireland and Portugal)
Enrotril 100 mg/ml Solution for Injection for Cattle
(Germany, Italy and Spain)
Enrofloxacin N-vet
(Sweden)
Respytril 100 mg/ml Solution for Injection for Cattle
(France)

PuAR correct as of 20/11/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0351/001/DC
Name, strength and pharmaceutical form	Norotril Max 100 mg/ml Solution for Injection for Cattle.
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry County Down Northern Ireland BT35 6JP
Active substance(s)	Enrofloxacin
ATC Vetcode	QA01MA90
Target species	Cattle
Indication for use	Indicated for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma* spp. where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice.

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

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.
Date of completion of the original decentralised procedure	28th July 2010.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This application for a generic product was submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. Bioequivalence was claimed with the reference product, Baytril Max 10% Solution for Injection. Norotril Max 100 mg/ml Solution for Injection for Cattle is a solution for injection containing 100 mg/ml enrofloxcin.

Norotril Max 100mg/ml Solution for Injection for Cattle is intended for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica, Pasteurella multicoda, Histophilus somni* and *Mycoplasma* spp. The recommended dose is 7.5 mg/kg bodyweight, (7.5 ml per 100 kg bodyweight).

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 slight reactions observed are indicated in the SPC[1]. 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.

[1] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains 100 mg/ml enrofloxacin and the excipients benzyl alcohol (E1519), arginine, n-butyl alcohol and water for injection.

The container system consists of amber Type 1 glass vials closed with bromobutyl bungs and aluminium collars. The capacity of the vials is 100 ml, 250 ml and 500 ml. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservatives 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 (GMP) from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines.

Arginine and enrofloxacin are dissolved in water for injections, followed by the addition of n-butyl alcohol and benzyl alcohol. The pH of the solution is adjusted if necessary using potassium hydroxide, and the batch is made up to a final volume with water. After sterilisation and re-mixing, the product is placed in vials and the vials sealed. The vials are then sterilised. In-process controls include tests for completeness of dissolution, pH and product appearance. A report of the validation of one batch was provided, this was satisfactory.

C. Control of Starting Materials

The active substance is enrofloxacin, an established active substance described in a Supplement of 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. Batch analysis data from three consecutive batches showed consistency with the Active Substance Manufacturer's specifications.

For the excipients, the requirements of the monographs of the European Pharmacopoeia were applied for the specifications for benzyl alcohol, arginine and water for injections. The monograph in the United States Pharmacopoeia National formulary for Butanol was applied for n-butyl alcohol.

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. A UK format 3 TSE declaration was provided.

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 site have been provided demonstrating compliance with the specification. Tests on the finished product include the following: appearance, fill volume, pH, presence of derivatives of the active substance during shelf-life, n-butyl alcohol assay, benzyl alcohol assay, syringeability and sterility.

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. Data were provided from three batches of product, stored inverted in the 100 ml vial, and for three batches stored in the 500 ml vial. Two batches were stored in both the 100 ml and 500 ml packs. Results were provided after eighteen months storage at 25°C/60% RH and after six months at 40°C/75%RH. The claim of a twenty-four month shelf-life, for product stored at a temperature not exceeding 25°C was justified.

In-use stability testing was performed at 25°C/60%RH over 28 days from two batches. One batch was filled into the 100 ml vial and one batch into the 500 ml via. Aliquots were removed from the vials in order to simulate the intended use of the product. No changes were recorded in the liquid for specified parameters, for either vial.

J. Other Information

Following first withdrawal of the product from the vial, the product must be used within twenty-eight days. Any unused material must be discarded. Do not store

above 25°C, do not freeze. Store in the original package in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, results of pharmacological and toxicological tests were not required. The reference product is Baytril Max 10% Solution for Injection.

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

This was an application for a Marketing Authorisation presented in accordance with Article 13 (1) of Directive 2001/82/EC (as amended), for a generic product. Therefore, no data were required for this section.

Toxicological Studies

This was an application for a Marketing Authorisation presented in accordance with Article 13 (1) of Directive 2001/82/EC (as amended), for a generic product. Therefore, no data were required for this section.

Observations in Humans

Not applicable.

User Safety

The applicant provided a user risk assessment which proposed the same user safety warnings as were provided for the reference product. After additions to reflect more recent developments involving enrofloxacin injectables, the following precautions are displayed in the Summary of Product Characteristics:-

- The product is an alkaline solution.
- Wear glasses and gloves when handling the product.
- Take care to avoid accidental self injection.
- Any spillage onto the skin should be washed off immediately with water.
- In the event of accidental splash into the eye, rinse with copious amounts of clean water. If irritation occurs, seek medical advice.
- In case of accidental self injection, seek medical advice and show the label to the doctor.
- Persons with known hypersensitivity to the fluoroquinolones should avoid contact with the product.
- Do not eat, drink or smoke when handling the product

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline, which showed that no further assessment was required. The assessment concluded that the product is indicated for large numbers of cattle as a treatment for respiratory disease. The dosage is 7.5 mg /kg body weight, given as a single injection. The active substance is not extensively metabolised, and will enter the soil via the excreta of treated animals or via slurry spreading. Calculation of the PEC_{soil}[2] for target groups of cattle have been performed in accordance with CVMP[3] requirements:-

Target animal	Husbandry	PEC_{soil} (ug/kg)
Calf	Intensive	21.42
Dairy cow		12.04
Cattle 0-1 year		18.89
Cattle > 2 years		21.86
Dairy cow	Pasture	10.50
Beef cattle		15.68

PEC_{soil} levels were satisfactory. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. Enrofloxacin Max 10% Solution for Injection is not expected to pose a risk to the environment when used directed in the SPC.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted as the posology for the product was the same as that currently authorised for the reference product.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 14 days for meat and offal and 84 hours for milk, (the same withdrawal periods as those given for the reference product), are justified.

[2] PEC_{soil} – Predicted Environmental Concentration (soil).
[3] CVMP – The committee for Medicinal Products for Veterinary Use.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC (as amended), and bioequivalence with a reference product has been effectively claimed, efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

There was no requirement to provide new data for this section.

Pharmacokinetics

Both product and reference product have the same qualitative and quantitative composition of active substance, and have the same route of administration to the target animal. Therefore, there was no requirement to provide data from bioequivalence studies.

Tolerance in the Target Species of Animals

As Norotril Max 100 mg/ml is identical to the reference product, no new target species tolerance data were required.

Resistance

As Norotril Max 100 mg/ml is identical to the reference product, no new target species resistance data were required. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

As this was a generic application in accordance with Article 13 (1) of Directive 2001/82/EC (as amended), no results of efficacy laboratory trials were required.

Field Trials

As this was a generic application in accordance with Article 13 (1) of Directive 2001/82/EC (as amended), no results of efficacy field trials were required.

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)