College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Enrotron 5 mg/ml oral solution for pigs

Enrotron 25 mg/ml oral solution for cattle

Enrotron 100 mg/ml solution for use in drinking water for chicken, turkeys and rabbits

NL/V/0165/001-003/DC

Created: December 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0165/001-003/DC
Name, strength and pharmaceutical form	Enrotron 5 mg/ml oral solution for pigs Enrotron 25 mg/ml oral solution for cattle Enrotron 100 mg/ml solution for use in drinking water for chicken, turkeys and rabbits
Applicant	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany
Active substance(s)	Enrofloxacin
ATC Vetcode	QJ01MA90
Target species	Pigs (piglets)
Indication for use	<u>Enrotron 5 mg/ml oral solution for pigs:</u> Treatment of infections of the respiratory and alimentary tract caused by enrofloxacin-sensitive microorganisms. In particular: •Treatment of neonatal diarrhoea and septicaemia caused by enrofloxacin-sensitive *E. coli* •Treatment of respiratory infections caused by enrofloxacin-sensitive *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp. •Enzootic pneumonia To be used where clinical experience and/or sensitivity testing indicates enrofloxacin as the drug of choice. <u>Enrotron 25 mg/ml oral solution for cattle:</u> Treatment of infections of the respiratory and alimentary tract caused by enrofloxacin-sensitive microorganisms. In particular: •Treatment of neonatal diarrhoea and septicaemia caused by enrofloxacin-sensitive *E. coli* •Treatment of respiratory infections caused by enrofloxacin-sensitive *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma bovis*.

	To be used where clinical experience and/or sensitivity testing indicates enrofloxacin as the drug of choice. <u>Enrotron 100 mg/ml solution for use in drinking water for chicken, turkeys and rabbits:</u> Treatment of infections caused by the following bacteria susceptible to enrofloxacin: **Chickens** *Mycoplasma gallisepticum,* *Mycoplasma synoviae,* *Avibacterium paragallinarum,* *Pasteurella multocida.* **Turkeys** *Mycoplasma gallisepticum,* *Mycoplasma synoviae,* *Pasteurella multocida*. **Rabbits** For the treatment of infectious diseases due to *Pasteurella multocida* and bacterial enteritis due to infection with *E. coli*. Enrofloxacin should be used where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the active substance of choice.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://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	23 January 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States	Enrotron 5 mg/ml: CY, DE, EL, ES, IE, PT, UK(NI) Enrotron 25 mg/ml: CY, DE, EL, ES, IE, PT, UK(NI) Enrotron 100 mg/ml: CY, DE, FR, IE, PL, UK(NI)

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 slight reactions observed are indicated in the SPC.
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 risk/benefit analysis is in favour of granting a marketing authorisation.

Enrotron is registered via a generic procedure in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The nationally authorized reference products are “BAYTRIL 0,5% ORALE OPLOSSING” (marketing authorisation number in the Netherlands: REG NL 3438, authorised in 1999 and withdrawn in 2016) for Enrotron 5 mg/ml, “BAYTRIL 2,5% ORALE OPLOSSING VOOR KALVEREN” (marketing authorisation number in the Netherlands: REG NL 2912, authorised in 1999 and withdrawn in 2016) for Enrotron 25 mg/ml and “BAYTRIL 100 mg/ml oplossing voor gebruik in drinkwater voor kippen en kalkoenen” (marketing authorisation number in the Netherlands: REG NL 2929, authorized in 2005) for Enrotron 100 mg/ml (rabbits have been added later on for procedural reasons).

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II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains enrofloxacin (5, 25 or 100 mg/ml) and the excipients benzyl alcohol, potassium hydroxide, , diluted hydrochloric acid and purified water. The 5 mg/ml and 25 mg/ml also contain the excipient Hypromellose.

The container/closure system consists of an opaque polyethylene bottle with opaque polyethylene temper evident screw cap and white pump dispenser.

The choice of the formulation is 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 at a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and 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.

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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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.

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.

F. 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.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated, results of pharmacological and toxicological tests are not required. The pharmacological and toxicological aspects of this product are identical to the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that direct contact with the skin should be avoided because of sensitisation, contact dermatitis and possible hypersensitivity reactions.

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

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

A Phase II ERA is required for Enrotron 25 mg/ml and Enrotron 100 mg/ml as the Phase I assessment showed that the initial predicted environmental concentration in soil is greater than 100 µg/kg and no mitigations exist that alter the PEC_{soil}.

Enrotron 5 mg/ml: highest PEC_{soil} value (for weaner pigs): 73.9 µg/kg. The ERA stops in Phase I, as PEC_{soil} values are below 100 µg/kg.

Enrotron 25 mg/ml: PEC_{soil} value for calves: 142.8 µg/kg. A Phase II ERA assessment was provided.

Enrotron 100 mg/ml: highest PEC_{soil} value (for broilers): 443.5 µg/kg. A Phase II ERA assessment was provided.

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Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). The data were considered to be complete and acceptable.

The Phase II assessment was based on data concerning another product, for which the applicant had consent, that have been assessed by the CVMP. According to the assessment of the CVMP it could be concluded that the environmental risk of Enrotron 25 mg/ml and Enrotron 100 mg/ml was acceptable. For more information regarding the Phase II data and assessment, please refer to the EC Decision of 5 May 2009 and the CVMP opinion of 15 January 2009 for Unisol 10 % Oral Solution following an Article 33 Referral.

Residue Studies

No residue depletion studies were conducted, as this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated.

Withdrawal Periods

Based on the data provided a withdrawal period of 7 days for meat and offal in pigs, cattle and chicken, 13 days for turkeys and 15 days for rabbits is justified. Enrotron is not authorised for use in birds producing eggs for human consumption. Enrotron should not be administered to layer replacement birds within 14 days of coming into lay.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of 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 Heads of Vetrinary Medicines 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.

Summary of change	**Section updated**	**Approval date**
New European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph of a new manufacturer. (NL/V/0165/001-003/IA/001)	N/A	30 November 2013
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure (NL/V/0165/003/IA/002)	Indication and withdrawal periods	23 April 2014
Replacement or addition of a manufacturing site of the finished product: - where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products - for primary packaging - for secondary packaging Change to importer, batch release arrangements and quality control testing of the finished product: - of a site where batch control/testing takes place - of a manufacturer responsible for importation and/or batch release, not including batch control/testing (NL/V/0165/IB/001-003/G)	N/A	21 July 2015
New European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph of a new manufacturer (NL/V/0165/001-003/IA/004)	N/A	19 July 2016
Submission of an updated CEP for an active substance from an already approved manufacturer	N/A	17 November 2016

(NL/V/0165/001-003/IA/005)		
Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient. (NL/V/0165/001-003/IA/006)	N/A	12 April 2017
Renewal – NL as RMS (NL/V/0165/001-003/R/001)	N/A	29 August 2017
Submission of an updated CEP for an active substance from an already approved manufacturer. (NL/V/0165/001-003/IA/008)	N/A	6 December 2018
Submission of an updated CEP for an active substance from an already approved manufacturer (NL/V/0165/001-003/IA/009)	N/A	7 January 2021