College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Revozyn RTU 400 mg/ml suspension for injection for cattle

Created: August 2019

Revozyn RTU 400 mg/ml suspension for injection for cattle	NL/V/0210/001/DC
Eurovet Animal Health BV	DCP
	Publicly available assessment report

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0210/001/DC
Name, strength and pharmaceutical form	Revozyn RTU 400 mg/ml suspension for injection for cattle
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel Netherlands
Active substance(s)	Penethamate hydriodide
ATC Vetcode	QJ01CE90
Target species	Cattle
Indication for use	Treatment of clinical and subclinical mastitis in lactating cows, caused by staphylococci and streptococci susceptible to penicillin.

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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).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 May 2017
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	DE, UK

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.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product is an oil-based suspension for parenteral administration. The product contains 400 mg penethamate hydriodide per ml of suspension and ethyl oleate and lecithin as excipients.

The primary packaging consists of a multi-dose uncoloured 50 ml glass Type II vials with a fluoropolymer coated type I rubber stopper, secured with an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and absence 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.

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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 penethamate hydriodide, an established active substance, which is not described in the European/British Veterinary 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. For the active substance an ASMF has 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

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 adequately justified.

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.

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.

The claim of a 28 days stability after broaching is based on the demonstration of stability for batches broached and stored 28 days at 30°C/65% RH.

G. Other Information

Not applicable.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a hybrid application submitted according to Article 13(3) of Directive 2001/82/EC as amended by Directive 2004/28/EC. Bioequivalence with the reference product (Mamyzin, powder for suspension for injection for cattle (REG NL 8652) from Boehringer Ingelheim B.V.) has been demonstrated, results of safety tests, resistance trials or clinical trials are not required, as are pre-clinical trials.

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

III.A Safety Testing

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the major risk is sensitization to penethamate.
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. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will be used to treat a small number of animals in a flock or herd. 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

Residue depletion studies using the final formulation have been conducted in dairy cattle. Samples of injections site tissue were taken from animals at several time points. Results show that residues depleted to below the MRL in the injection site and surroundings before the end of the withdrawal period. The analytical method was the LC-MS/MS method. The method was fully validated.

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MRLs

Penethamate is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Marker residue	Animal Species	MRL (µg/kg)	Target Tissues	Other provisions
Benzyl penicillin	all mammalian food-producing species	50 50 50 50 4	Muscle Fat Liver Kidney Milk	For porcine species the fat MRL relates to 'skin and fat in natural proportions'

The MRL status of the excipients of 'Revozyn RTU 400 mg/ml suspension for injection for cattle' is indicated in the following table:

Excipient	MRL status
Ethyl oleate	Table 1, no MRL required
Lecithin (E223)	Table 1, no MRL required

Withdrawal Periods

Based on the data provided above, a withdrawal period of 10 for meat in cattle and 4 days for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

This is a hybrid application according to Article 13(3), and bioequivalence with the reference product (Mamyzin) has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using the target dose in the target species. An authorised reference product containing the same active substance was used as a control. All doses were administered by intramuscular injection on 2 (controls) and 4 (tested product) occasions.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography / information provided suggests that resistance to penicillin is not uncommon and isolation and identification of udder pathogens in herds suffering from subclinical agents is essential to select t he most effective antimicrobial agent.
Adequate warnings and precautions appear on the product literature.

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IV.B Clinical Studies

Field Trials

The applicant has conducted field studies which show that the tested product is bioequivalent based on the geometric mean ratio of the AUC values and a similar tolerance in the target species of the test product and 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.

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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 Veterinary 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 (Application number)	**Section updated in Module 3**	**Approval date**
Change in the QPPV (NL/V/xxxx/IA/033/G)	N/A	11 January 2019
Updated ASMF of the active substance penethamate hydriodide (variations included: Up to 10-fold increase in batch size compared to the originally approved batch size of active substance; Deletion of a nonsignificant specification parameter of an active substance; 2x Change in container closure system of the active substance) (NL/V/xxxx/WS/018)	N/A	3 April 2019
Addition of a manufacturer responsible or batch release, not including batch control/testing (NL/V/xxxx/IA/047/G)	N/A	30 October 2020
Changes to the closed part of the ASMF (NL/V/xxxx/WS/039)	N/A	13 December 2021
Renewal (NL/V/0210/001/R/001)	N/A	30 March 2022
One-off alignment of the product information with version 9.0 of the QRD template (NL/V/xxxx/A/068)	N/A	1 December 2022