College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Baycubis 325 mg/g

Created : May 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0154/001/DC
Name, strength and pharmaceutical form	BAYCUBIS
Applicant	Bayer BV- Animal Health Division Energieweg 1 3641 RT Mijdrecht
Active substance(s)	Potassium phenoxymethylpenicillin 325mg/g
ATC Vetcode	QJ01CE02
Target species	Chickens
Indication for use	Prevention of mortality at a group level from necrotic enteritis in chickens caused by Clostridium perfringens susceptible strains susceptible to phenoxymethylpenicillin

Product name: Baycubis 325 mg/g	Application number: NL/V/0154/001/DC
Applicant: Bayer BV- Animal Health Division	DCP
	Publicly available assessment report

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	Informed consent application in accordance with Article 13c of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	19th April 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Germany, France, Italy

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 risk/benefit analysis is in favour of granting a marketing authorisation.

The quality / safety / efficacy aspects of this product are identical to Phenoxypen WSP. The initial application for Phenoxypen WSP was assessed before there was a requirement to have a public assessment report; therefore no details in this section are available.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains Potassium phenoxymethylpenicillin 325 mg/g and the excipients Lactose monohydrate

There are two types of container/closure systems:

- white PP cylindrical container, with white HDPE/LDPE closure, with thumb-tab for opening. Two different sized containers (650 ml, 2000 ml) with content of 250g, 1000 g product respectively.
- Composite can: Rectangular container consisting of three layers, carton base with an inlay of aluminium foil. The container contains 1kg of the product.

The choice of the formulation are justified.

The product is a 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 Potassium phenoxymethylpenicillin, an established active substance described in the European 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.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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.

The claim of a stability after reconstitution is based on the demonstration of stability for a batch broached and stored 48 months at +25°C.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale:

Securitainer: 60 months.

Composite can: 3 years

Shelf life after first opening the immediate packaging: 3 months.

Shelf life after reconstitution in drinking water according to directions: 24 hours

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The pharmacological and toxicological aspects of this product are identical to the reference product Phenoxypen WSP.

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 / consumers.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that the administration of the product at a dose of 15 mg/kg BW by the oral route, show that penicillin is well absorbed, with a bioavailability of 69%. in each target species.

Toxicological Studies

The applicant has provided bibliographical data which show that Information on the acute toxicity of penicillin for the chicken is very limited, but indicate a low toxicity. Regarding the data for mammals, it is concluded that the acute toxicity of penicillin for the chicken is low.

- Repeated Dose Toxicity

No information is available on the repeat dose toxicity of penicillin for the chicken. Regarding the data for mammals, it is concluded that the repeat dose toxicity of penicillin for the chicken must be low as well.

- Reproductive Toxicity, including Teratogenicity/ mutagenicity

Up to now no teratogenic, mutagenic or carcinogenic effects have been recorded for penicillin

Other Studies

The applicant has provided bibliographical data which show that the administration of penicillin can affect the gut flora.

Hypersensitivity reactions due to penicillin administration have been observed in animals; however, such reactions have never been reported to occur in the chicken.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that Phenoxymethylpenicillin may cause hypersensitivity reactions after injection, inhalation, oral ingestion or skin contact. Hypersensitivity to Phenoxymethylpenicillin may lead to cross-sensitivity to other penicillins and cephalosporins, and vice versa. Allergic reactions caused by these substances can sometimes be serious. Avoid contact with this substance in known hypersensitivity to penicillins and cephalosporins, or after you have been advised not to handle these substances.

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:

The initial predicted environmental concentration in soil (PECsoil, initial =83.1 µg/kg) is less than 100 µg/kg and A phase II is not deemed necessary.

III.B Residues documentation

Mis en forme : Français (France)

Residue Studies

The applicant has conducted residue depletion studies two residue studies with the candidate formulation were submitted by the applicant for establishment of a withdrawal period. The second study (Van Wijk, 2002) is a radiolabel study. All residue levels were found to be below 12.5 µg/kg from a 24 hour timepoint onwards.

MRLs

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

	Poultry
Muscle	25 µg/kg
Liver	25 µg/kg
Kidney	25 µg/kg
Fat / skin	25 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 2 days for meat and offal in chickens and zero days for eggs is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

Baycubis is identical to the Phenoxypen WSP and the marketing authorisation holder of the original product has given consent to refer for part IV of the dossier of Phenoxypen WSP.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that penicillins, including phenoxymethyl penicillin, is considered as a well known active substance. The mode of action is considered as known. Penicillin shows good activity against Gram+ aerobic and anaerobic bacterial species.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species. All doses were administered by drinking water. Medicated drinking water was offered twice daily in the morning and in the evening and prepared freshly each time.

Parameters evaluated were water and feed consumption, body weight and feed conversion. Animals were observed for behaviour (drinking and eating), defecation pattern and faecal consistency, plumage.

No minimal adverse effects were seen following doses up to 5 times the recommended dose.

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

Resistance

The bibliography provided suggests that bacterial resistance for penicillin is widespread. Production of beta-lactamases is the major resistance mechanism. R-plasmids code for the formation of beta-lactamases. Resistance is achieved only after several steps and cross-resistance with other beta-lactam antibiotics occurs.

Adequate warnings and precautions appear on the product literature.

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 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	**Section updated**	**Approval date**
Updated of an European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. from an already approved manufacturer (NL/V/0154/001/IA/001)	NA	15th May 2012
Extension of the shelf life of the finished product, as packaged for sale (supported by real time data) (NL/V/0154/001/IB/002)	Module 3 II.G	12th September 2012
Change in the withdrawal period for eggs. (NL/V/0154/001/II/003)	Module 3 III.B	5th March 2014
Change in the name of the marketing authorisation holder in France (NL/V/0154/001/IA/004)	NA	17th April 2014
Renewal – NL as RMS (NL/V/0154/001/R/001)	NA	9th March 2016
Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH) (NL/V/0154/001/IA/005)	NA	29th May 2016
Deletion of manufacturing site for an active substance (NL/V/0154/001/IA/006)	NA	11th June 2016
Extension of the shelf life of the finished product as packaged for sale and after dilution or reconstitution (supported by real time data) (NL/V/0154/IB/007/G)	Module 3 II.G	13th October 2016

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Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product and change in batch size up to 10-fold compared tot the originally approved batch size (NL/V/0154/IA/008/G)	NA	4th August 2017
Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH. (NL/V/xxxx/IA/028/G)	NA	10th October 2018