MINISTERIO DE SANIDAD Y CONSUMO
agencia española de medicamentos y productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

RHEMOX PREMIX 100 mg/g premix for medicated feeding stuff for pigs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0129/001/DC
Name, strength and pharmaceutical form	RHEMOX PREMIX 100 mg/g premix for medicated feeding stuff for pigs
Applicant	Industrial Veterinaria, S.A. Esmeralda, 19 08950 Espluges de Llobregat (Barcelona), Spain
Active substance(s)	Amoxicillin trihydrate
ATC Vet code	QJ01CA04
Target species	Pigs (after weaning)
Indication for use	Treatment and prevention of infectious processes caused by *Streptococcus suis* susceptible to amoxicillin in pigs after weaning. The presence of disease in the herd should be established before treatment.

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	Decentralised application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25/02/2009
Date product first authorised in the Reference Member State (MRP only)	
Concerned Member States for original procedure	BE, CY, CZ, EE, EL, HU, IT, LT, LV, NL, PL, PT, RO and SK

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.

II. QUALITY ASPECTS

A. Composition

The product contains amoxicillin trihydrate (100 mg/g) and excipients (non-crystallising liquid sorbitol, light liquid paraffin and corncob).

The container/closure system consists of 3 and 24 kg bags formed by a triple paper/aluminium/polyethylene layer closed by heat welding. The particulars of the containers and controls performed are provided and conform to the regulation.

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 from a licensed manufacturing site.

The manufacturing process consists of a blend of the components of the product. The flow chart of the manufacturing process has been included.

Process validation data on 3 bulk batches of the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is amoxicillin tryhidrate, an established active substance described in the current edition of the European Pharmacopoeia monograph 0260. 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.

A copy of the certificate of suitability No. R2-CEP 1995-034-Rev 02 has been included.

Non-crystallising liquid sorbitol and light liquid paraffin comply with the Eur. Ph. monograph 0437 and 0240, respectively.

Specifications and control methods for corncob have been provided.

Certificates of analysis have been included for each excipient.

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

Lactose, the only starting material of animal origin for the production of amoxicillin tryhidrate, complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products according to the declaration of the supplier.

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.

G. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 (2 years) when stored under the approved conditions (Store below 25ºC and protect from moisture).

The claim of 3 months stability after first opening the container is based on the demonstration of stability for six batches broached and stored 3 months at 20-30ºC/50%-60% RH.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Additional quality requirements such as incorporation of the premix to the feed, homogeneity, compatibility and stability in the feed have been included

III. SAFETY AND RESIDUES ASSESSMENT

This application is submitted in accordance with the article 12(3) of Directive 2001/82/EC like a known active substance.

Rhemox Premix 100 mg/g is a premix for medicated feeding stuff of pigs. It contains amoxicillin base as trihydrate. Amoxicillin is an antibiotic of the β-lactamic group, one of the groups most widely used in veterinary medicine.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that amoxicillin acts by inhibition of the biochemical processes of bacterial cell wall synthesis by selectively and irreversible blocking different enzymes involved in such processes. It has bactericidal activity and acts against Gram-positive and Gram-negative microorganisms.

The applicant has also provided bibliographical data which show that amoxicillin is readily and completely absorbed after oral or parenteral administration, it has good tissue diffusion, it is partially metabolised in the liver and it is mainly excreted via renal.

Toxicological Studies

The applicant has provided bibliographical data which show that amoxicillin has low toxicity. Toxic effects have only been observed at very extreme doses. The most important adverse effect is hypersensitivity reaction. Amoxicillin is not mutagenic and carcinogenic substance.

- Single Dose Toxicity

SPECIES	**administration route**	**LD50**
Rat	Oral	> 15,000 mg/kg
	Intraperitoneal	2,870 mg/kg
	Subcutaneous	> 8,000 mg/kg
Mice	Oral	> 25,000 mg/kg
	Intraperitoneal	3,590 mg/kg
	Subcutaneous	> 20 mg/kg
Rabbit	Oral	> 12,500 mg/kg

Observations in Humans

The applicant has provided bibliographical information which shows that amoxicillin is used in humans to treat infections caused by sensitive germs. Among the side effects derived from administering amoxicillin is found diarrhoea but it is not frecuent.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline and has conducted a risk characterisation for the veterinary medicinal product.
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.
As a part of the Phase I assessment data on degradation of the active substance in manure may be submitted. The protocol of the study submitted satisfies the criteria included in guideline EMEA/CVMP/ERA/418282/2005-corr. The applicant commits itself to submit the results of the study as soon as they are available.

III.B Residues documentation

Residue Studies

A residue depletion study using the final formulation has also been conducted in target specie. Samples of tissues were taken from animals at several time points. The kidney was the tissue with the slowest depletion of the drug by the organism. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period.
The analytical method was HPLC with fluorimetric detection. The method was fully validated.

MRLs

Amoxicillin is listed in Annex I of Council Regulation 2377/90. MRLs are listed below:

Substance	Labelling residue	Species	MRL	Tissues
Amoxicillin	Amoxicillin	All food producing species	50 µg/kg	Muscle, liver, kidney, fat

Withdrawal Periods

A withdrawal period of 4 days for meat in pigs (after weaning) is justified and set by the alternative method to the statistical analysis of the results.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies
Pharmacology

The applicant has conducted studies to provide the value of the MICs.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. All doses were administered by oral route.
Parameters evaluated were the consumption of feed and water, the general condition of the animals, haematology and clinical chemistry analyses and Histology and Pathological Anatomy.

No adverse effects were seen following doses up to 3 times the recommended dose.

Resistance

The information provided suggests that the current situation in Europe is good.

IV.B Clinical Studies

Field Trials

The applicant has conducted field studies which show that amoxicilina 10% premix administered orally as a premix of medicated feed is an effective treatment.

The field study was conduced under GCP; the design of the study, a double blinded, randomized and controlled was adequate to the objective. 301 animals were involved. The inclusion criteria seem relevant and ensured, by bacteriological analysis as well as clinical observations, that the pigs suffered infection by S. suis. The statistical analysis of the primary and secondary variables concluded that there were no significant differences between treatments in the efficacy assessment and the non-inferiority was demonstrated.

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.

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	