Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Perlium Amoxival 100 mg/g Premix for Medicated Feeding Stuff for Pigs
(DE/HU/IT/PL/PT/ES/UK)

Amoxivet 100 Premix for Medicated Feeding Stuff for Pigs (FR)

Dokamox 100 mg/g Premix for Medicated Feeding Stuff for Pigs (BE/NL)

PuAR correct as of 15/03/2018 when RMS was transferred to NL. Please contact the RMS for future updates

Date Created: September 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0612/001/DC
Name, strength and pharmaceutical form	Perlium Amoxival 100 mg/g Premix for Medicated Feeding Stuff for Pigs
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance(s)	Amoxicillin (as Amoxicillin trihydrate)
ATC Vetcode	QJ01CA04
Target species	Pigs
Indication for use	Preventive treatment of respiratory diseases due to *Streptococcus suis*, limited to reducing mortality. The presence of the disease in the herd should be established before the preventive treatment.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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	15/07/2010.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	AT, BE, BG, CZ, DK, EE, FI, EL, HU, IE, IT, LV, LT, LU, NL, NO, PL, PT, RO, SK, ES, SE, UK

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Amoxival Amoxicilline 100 Prémélange Médicamenteux Porc 100mg, authorised in France since August 1994. Bioequivalence to the reference product has been accepted by way of an *in vivo* bioequivalence study and a comparative dissolution study. The original Reference Member State (RMS) for this product was France, with the EU procedure number FR/V/0194/001/DC. However, the product has since been expired in France and the UK has taken on the role of RMS.

The product is intended to be used as preventive treatment of respiratory diseases due to *Streptococcus suis*, limited to reducing mortality. The presence of the disease in the herd should be established before the preventive treatment. The dose rate is 20 mg of amoxicillin /kg body weight a day for 5 consecutive days, in feed. For a feed intake of 40 g/kg, this dose regimen corresponds to 500 ppm in medicated feed. In order to respect the dose regimen and to take into account the real food intake, the incorporation rate can be increased, which leads to a higher concentration in food. The product can be incorporated in pelleted feed preconditioned with steam for 15 minutes at a temperature of 78°C. The product should not be used in liquid feed.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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

[1] SPC – Summary of product Characteristics.

used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was accepted according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains amoxicillin (as amoxicillin trihydrate) (100 mg) and excipients soya-bean oil and corn cob granules.

The container/closure system consists of a low density polyethylene/paper/paper bag of 10 kg and 25 kg. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the active substance being added to the corn cob granules which have been sprayed with soya-bean oil, mixed, and sprayed with more soya-bean oil. The product is then drained and transferred into bags.

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

II.C. Control of Starting Materials

The active substance is amoxicillin trihydrate, an established substance described in the European Pharmacopoeia (Ph. Eur). 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. Appropriate certificates of suitability were provided.

Soya oil refined is an established substance described in the Ph. Eur. Corn cob granules is produced according to an internal monograph. Certificates of analysis were provided for both excipients demonstrating compliance with the specifications.

[2] Efficacy – The production of a desired or intended result.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for appearance, loss on drying, impurity, sieving, microbiological tests, amoxicillin identification and assay.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance. A re-test period of 6 years or 4 years was accepted for the two different active substance suppliers, respectively.

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 3 month shelf life after incorporation into meal and pelleted feed is accepted based on the stability results provided.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 1 year
Shelf life after first opening: use immediately after first opening
Shelf life after incorporation into meal and pelleted feed: 3 months

Do not store above 25°C
Store in a dry place
Keep the bag tightly closed in order to protect from moisture

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

The product is bioequivalent to the reference product and therefore it is considered that both products have similar toxicological properties. Bibliographic

data concerning amoxicillin were presented in order to support the toxicological properties of the product.

III.A Safety Documentation

Toxicological Studies

Single Dose Toxicity

Bibliographic data were presented which showed that single administrations of amoxicillin given orally in mice and rats gave LD50 values in excess of 5000 mg/g. No deaths or signs of toxicity were observed. The results show that amoxicillin does not cause signs of toxicity even when administered at very high doses.

Repeated dose toxicity

Bibliographic data including a sufficient number of animals demonstrated that amoxicillin causes very little toxicity when given as repeated doses. In rats, amoxicillin 200, 500, 800 or 2000 mg/kg per day, administered orally for 6 months did not cause mortality or signs of toxicity. In dogs, no adverse effects were observed in doses of up to 500 mg/kg over 14 days and 6 months. In cats, amoxicillin 750 mg per cat was given daily for 5 days, or 5 days a week for 28 days at a dosage of 100, 300 or 500 mg per cat. No mortality or adverse effects were observed.

Reproductive Toxicity, including Teratogenicity

Bibliographic data showed that in laboratory studies there has been no evidence of teratogenic, embryotoxic or maternotoxic effects of amoxicillin. However, as no study has been performed in the target species during pregnancy or lactation, the SPC includes advice that the product should be used only accordingly to the benefit/risk assessment by the responsible veterinarian.

Observations in Humans

Amoxicillin is a penicillin antibiotic. A CVMP summary report stated that penicillins, including amoxicillin, show little toxicity but at therapeutic doses may cause hypersensitivity reactions in humans. The committee concluded that at the recommended therapeutic dose and providing the withdrawal period has been observed, it is highly unlikely that the small amounts of amoxicillin that could be found in edible tissues could induce allergic reactions in humans.

User Safety

Reports showed that up to 10% of patients treated with penicillin experience hypersensitivity to the drug. Symptoms range from minor rash to fatal anaphylaxis. User exposure and risk to the user was discussed. It was concluded that when the product is used as intended the risk to humans is

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

- When feed is being prepared, avoid skin contact.
- Whilst handling the product, wear a mask, coveralls, protective goggles and gloves at all times.
- Avoid inhalation of dust. Wear either a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143.
- To rule out any risk of ingestion it is recommended not to eat, or drink while using the product and to wash the hands after use.
- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.
  1. Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
  2. Handle this product with great care to avoid exposure taking all recommended precautions.
  3. If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Environmental Safety

An environmental risk assessment (ERA) was conducted in accordance with VICH and CVMP[3] guidelines.

Phase I:

The initial predicted environmental concentration (PEC) in soil is greater than 100 µg/kg for weaner pigs, fattening pigs and sows with a litter:

Type of animal	PECsoil (µg/kg)
Weaner pigs (to 25 kg)	868.9
Fattening Pigs (25 - 125 kg)	589.3
Sow (with litter)	209.2

A Phase II ERA was therefore required.

Phase II Tier A:

A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines, including studies on physicochemical properties, environmental fate and effects.

[3] Committee for Medicinal Products for Veterinary Use

Studies were carried out using the active substance amoxicillin trihydrate unless indicated otherwise.

Physicochemical properties

Study type	Result	Remarks
Water solubility	4.0 mg/ml (as trihydrate)	Published data
Dissociation constants in water pKa	In water at 22°C Pka1 = 2.4 (COOH) Pka2 = 7.4 (NH2) Pka3 = 9.6 (OH)	Published data
UV-Visible Absorption Spectrum	0.1M HCl: max at 229, 272 and 278 nm 0.1M KOH: max at 248, 291 and 325 nm	Published data
Melting Point/Melting Range	Loss of water (trihydrate) from 50°C to 150°C Decomposition at 160°C	Published data
Vapour Pressure	4.69 x 10 to 17 mm Hg at 25°C	Published data
n-Octanol/Water Partition Coefficient logP_{ow} (OECD 117, HPLC method)	1.6 at 25°C (pH 5.0)	Bespoke study logK_{ow} <4, indicates low bioaccumulative potential

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption (	OECD 106	Worst case scenario (loamy sand) Koc = 8	Mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	Worst case scenario (loamy sand) Amoxicillin trihydrate: DT_{50} = 2.02 hours APA: DT_{50} = 72.62 hours	Non-persistent in soil and rapidly degrades to the primary product penicilloic acid of amoxicillin (APA)

Environmental effects

Study type	Guideline	Endpoint and Result
Algae, Growth Inhibition Test *Anabena flosaquae*	OECD 201	Growth rate EC_{50} = 39.0 µg/l NOEC <1.7 µg/l Yield EC_{50} = 2.03 µg/l NOEC <1.7 µg/l
Daphnia sp. Immobilisation *Daphnia magna*	OECD 202	Number of immobile organisms after 24 and 48 hours NOEC ≥ 234 mg amoxicillin trihydrate /l NOEC ≥204 mg amoxicillin/l
Fish, acute toxicity *Oncorhynchus mykiss*	OECD 203	Mortality NOEC ≥800 mg amoxicillin trihydrate /l NOEC ≥697 mg amoxicillin/l
Soil microorganisms: Nitrogen Transformation Test (28 days)	OECD 216	Effect (≤25% to control).NOEC ≥10.5 mg amoxicillin trihydrate/kg NOEC ≥9.15 mg amoxicillin/kg
Terrestrial Plants, Growth Test *Brassica napus* *Glycine max* *Heliathus annuus* *Cucumis sativus* *Avena sativus*	OECD 208	Germination, fresh weight, mortality and phytotoxicity NOEC ≥500 mg amoxicillin trihydrate /kg NOEC ≥436 mg amoxicillin/kg
Earthworm reproduction and growth *Eisenia fetida*	OECD 222	Mortality, weight change, feeding activity and reproduction rate NOEC ≥100 mg amoxicillin trihydrate /kg NOEC ≥87 mg amoxicillin/kg

Exposure assessment

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated:

Outputs	Value	Source
PEC_{soil} (µg/kg)	868.9	CVMP Equation 1
$PEC_{groundwater}$ (µg/l)	839.3	CVMP Equation 32
Refined $PEC_{groundwater}$ (µg/l)	0.000	FOCUS PEARL
$PEC_{surface\ water}$ (µg/l)	279.8	CVMP Equation 36
Refined $PEC_{surface\ water}$ (µg/l)	0.000	FOCUS SWASH

As the initial PEC for groundwater exceeded the 0.1 µg/l drinking water standard that has been established in the EU, it was refined using the groundwater model FOCUS PEARL. Results demonstrated that the 80th percentile annual average concentration of amoxicillin in leachate was 0.000 µg/l for all soils; confirming that appropriate use of the product will not pose a risk to drinking water. Using FOCUS SWASH modelling, $PEC_{surfacewater}$ concentrations for amoxicillin were calculated to be equal to 0.000 µg/l.

Risk Characterisation

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for the target animals, as follows:

Test organism	End point	AF	PNEC	PEC	RQ
			(µg/kg or l)		
Cyanobacteria,	EC_{50} = 2.03 µg/l	100	0.0203	0.000	<1
Daphnia sp.	NOEC = 204 000 µg/l	1000	204	0.000	<1
Fish	NOEC = 697 000 µg/l	1000	697	0.000	<1
Soil Microorganisms:	<25% difference in N transformation (28 days)	NA			
Plants	NOEC = 436 000 µg/kg	100	4360	839	0.19
Earthworm	NOEC = ≥87 000 µg/kg	10	8700	839	0.10

As all RQ values are <1, the ERA ends without further refinement required. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

As this is a generic application where bioequivalence has been accepted with the reference product, the applicant was not required to submit residues depletion studies. However, the applicant provided some bibliographical data, supporting the approved withdrawal period. The additional data provided enabled the withdrawal period for the proposed product to be set at 5 days for meat and offal.

MRLs

Referenced publications were provided and the MRL status of amoxicillin was cited according to the MRL regulation 2377/90/CEE as follows:

MRLs are listed below:

	Pigs
Muscle	50 µg/kg
Liver	50 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	4 µg/kg

Withdrawal Periods

Based on the data provided, a withdrawal period of 5 days for meat and offal from treated pigs is justified.

IV CLINICAL DOCUMENTATION

An *in vitro* dissolution study and a bioequivalence study were presented, the results of which supported the conclusion that the product is equivalent to the reference product by way of essential similarity. The applicant conducted comparative dissolution studies of the proposed product and the reference product at 3 different pH conditions and at 2 different concentrations representative of the expected active substance concentrations in the target species. Results showed that for both the proposed product and the reference product 85% of the active substance dissolved completely in less than 15 minutes, supporting the conclusion that the products are essentially similar.

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been accepted by way of essential similarity, further efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species

Amoxicillin is generally well tolerated. Adverse effects consisting of gastrointestinal signs (diarrhoea) may sometimes be observed. Penicillins may cause allergic reactions after administration of the product which may be severe (anaphylaxis). The product literature accurately reflects the type of adverse effects which might be expected.

Resistance

The product should be used in individual animals with distinctive clinical signs of streptococcosis only and should be based on susceptibility testing taking into account official and local antimicrobial policies. The product should not be used when resistance to amoxicillin is known. Inappropriate use of the product may

increase the prevelance of bacterial resistant to amoxicillin. 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 benefit/risk profile of the product(s) is favourable.

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)