Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MOXAPULVIS 500 mg/g Powder for Use in Drinking Water

Date Created: May 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0652/001/DC
Name, strength and pharmaceutical form	MOXAPULVIS 500 mg/g powder for use in drinking water
Applicant	VMD NV Hoge Mauw 900 2370 Arendonk Belgium
Active substances	Amoxicillin trihydrate 574 mg (equivalent to Amoxicillin 500 mg)
ATC Vetcode	QJ01CA04
Target species	Chickens, ducks, turkeys, pigs.
Indication for use	Treatment of infections in chickens, turkeys and ducks caused by bacteria susceptible to amoxicillin. Pigs: For the treatment of pasteurellosis caused by *Pasteurella multocida* susceptible to amoxicillin.

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 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	31st January 2018
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Bulgaria, Croatia, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Spain

I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid application for Moxapulvis 500 mg/g Powder for Use in Drinking Water. This was determined a generic 'hybrid' application because changes to the active substance with regard to the reference medicinal product have been made. The reference product is Amoxinsol 50% w/w Powder for Oral Solution, marketed in the UK since July 1990. Exemption was claimed from the requirement for bioequivalence studies under 7.1.c) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

The product is indicated for the treatment of infections in chickens, turkeys and ducks caused by bacteria susceptible to amoxicillin, and in pigs, for the treatment of pasteurellosis caused by *Pasteurella multocida* susceptible to amoxicillin.

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 used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 574 mg/g amoxicillin trihydrate, equivalent to 500 mg/g amoxicillin, and the excipients silica (colloidal anhydrous), sodium carbonate monohydrate and lactose monohydrate.

The container/closure system consists of a multi-layer laminated bag made of polyester/aluminium and foil/polyethylene. The product is also available as round, white HDPE jars that are closed by a polypropylene lid with a cardboard/aluminium/PE inner-layer.

Pack size: 1 kg bag, 100 g jar, 1 kg jar.

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. A dissolution study and a palatability study confirmed that the reference product and proposed product were essentially similar.

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 a simple mixing of the components.

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

II.C. Control of Starting Materials

The active substance is amoxicillin trihydrate, an established active 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. Acceptable Certificates of Suitability were provided. Satisfactory Certificates of Analysis were provided for each excipient.

Suitable data were provided confirming the appropriateness of the packaging.

II.C.4. Substances of Biological Origin

Satisfactory transmissible spongiform encephalopathy (TSE) information was provided. Compliance with the guideline was accepted.

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, pH, water content, uniformity of filling mass, identification and assay of amoxicillin, identification of carbohydrates and lactose monohydrate, microbiological quality.

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 when stored under the approved conditions.

G. Other Information

Bag:

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

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

Shelf life after reconstitution according to directions: 24 hours.

Jar:

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

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

Shelf life after reconstitution according to directions: 24 hours.

Bag:
This veterinary medicinal product does not require any special storage conditions.

Jar:

Store below 25 °C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application, no pharmacological or toxicological data were required. Bioequivalence was claimed under 7.1.c of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products, (EMA/CVMP/016/00-Rev 2).

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the product is safe to use when used as directed in the SPC and product literature.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The following applicant's user recommendations are appropriate:

- 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 reactions to these substances may occasionally be serious.
- Do not handle this product if you know you are sensitised or if you have been advised not to work with such preparations.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- 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 with breathing are more serious symptoms and require urgent medical attention.
- 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.
- Wear gloves during preparation and administration of medicated water.
- Wash any exposed skin after handling the product or medicated water.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The initial predicted environmental concentration (PEC) in soil is greater than 100 µg/kg, (excluding ducks and turkeys as minor species), and a Phase II ERA was required. Phase I PEC_{soil} studies were carried out using amoxicillin trihydrate (ATH). Amoxicillin penicilloic acid (APA), (the transformation product of amoxicillin), was used in Phase II studies, as, due to mitigating results, there was no further requirement to assess amoxicillin trihydrate.

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. A number of the results from the various species showed PEC_{soil} as being in excess of 100 µg/kg. Phase II studies were therefore required. A series of calculations for $PEC_{groundwater}$ and $PEC_{surfacewater}$ showed that there was no risk to these compartments.

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 physico-chemical properties, environmental fate and effects.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	84.0 g/l
Dissociation constants in water pKa	OECD 112	9.9
UV-Visible Absorption Spectrum	OECD 101	Peak: 230 nm (diode array) Peak: 258 nm (UV-vis spectrum
Melting Point/Melting Range	OECD 102	No melting before decomposition (at approximately 285°C
Vapour Pressure	OECD 104	Not determinable. As the substance is not volatile,
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	Log P_{OW} -2.0 (main component) Log P_{OW} -0.465-0.374

Results were acceptable.

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption (APA)	OECD 106	Mean K_{OC} value 74.2 (Mobile in soil)
Aerobic and Anaerobic Transformation in Soil (APA)	OECD 307	Mean DT_{50} 0.8 (Does not persist in soil)

Results were acceptable.

PNEC calculations
The applicant has calculated PNECs at Tier A according to VICH Phase II guidance as follows:

Species	Endpoint (mg/kg)	Reference	AF	PNEC (µg/kg or l)
Soil microorganisms	19.7	3a-saf\lit-p3-saf-s.pdf	NA	19 700
Plant	EC_{50} = > 1000 mg APA-Na/kg	3a-saf\lit-p3-saf-s-z.pdf	100	>10 000
Earthworm	NOEC = ≥ 1000 mg APA Na/ kg	3a-saf\lit-p3-saf-l-s.pdf	10	≥100 000
Cyanobacteria	EC_{50} = 172.54 mg APA-Na/l	3a-saf\lit-p3-saf-s-z	100	1725.4
Daphnia magna	EC_{50} = >800 mg APA-Na/l	3a-saf\lit-p3-saf-l-s	1000	>800
Fish	LC_{50} > 100 mg APA-Na/l	3a-saf\lit-p3-saf-s-z	1000	100

All risk quotient (RQ) values were less than 1, (PEC[3]/PNEC[4]), where the PEC_{soil} was 839.29 and $PEC_{surfacewater}$ for aquatic organisms was 43.24. No undue risk was identified for soil and aquatic organisms.

Risk characterisation

PEC (µg/kg or l)	Species	PNEC (µg/kg or l)	PEC/PNEC (RQ's)
Soil = 839.29	Soil microorganisms	19 700	<1
	Plant	10 000	<1
	Earthworm	100 000	<1
Surface water = 43.24	Cyanobacteria	1725.4	<1
	Daphnia magna	800	<1
	Fish	100	<1

[3] PEC – Predicted Environmental Concentration.
[4] PNEC – Predicted No Effect Concentraion.

As all RQ values were <1, the ERA ended at tier A. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

Due to the legal basis of the application residue depletion studies were not provided. This approach was considered acceptable. The same meat withdrawal periods as authorised for the reference product were agreed. In line with the reference product, the test product is contraindicated for use in birds producing eggs for human consumption. The proposed withdrawal periods are considered sufficient to ensure the safety of the consumer.

Withdrawal Periods

Based on the data provided, the following withdrawal periods were approved:

Chickens (meat & offal):	1 day
Ducks (meat & offal):	9 days
Turkeys (meat & offal):	5 days
Pigs (meat & offal):	2 days

Not for use in birds producing or intended to produce eggs for human consumption.

IV CLINICAL DOCUMENTATION

IV.II. Clinical Documentation

As the reference product were shown to be essentially similar, no further studies were required.

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 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.

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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.

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