Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amoxy Active CTD 697 mg/g Powder for Use in Drinking Water for Chickens, Turkeys and Ducks

Date Created: February 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0645/001/DC
Name, strength and pharmaceutical form	Amoxy Active CTD 697 mg/g Powder for Use in Drinking Water for Chickens, Turkey and Ducks
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance	Amoxicillin 697 mg/g (As amoxicillin trihydrate) 800 mg/g
ATC Vetcode	QJ01CA04
Target species	Chickens, turkeys and ducks
Indication for use	Treatment of infections caused by bacteria 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	19th December 2019
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Romania, Spain

I. SCIENTIFIC OVERVIEW

This was an application for a generic 'hybrid' product, Amoxy Active CTD 697 mg/g Powder for Use in Drinking Water for Chickens, Turkeys and Ducks.

The reference product is Amoxinsol 100% w/w Powder for Oral Solution, authorised in the UK since August 1996. The reference product was authorised via an informed consent application, with the parent product being Amoxinsol 50% w/w Powder for Oral Solution, authorised in the UK since July 1990, and has been through the review procedure. A variation was approved in 1996 to change the formulation to 100% active substance. The quantitative and qualitative composition of the candidate product differs from that of the reference product. Therefore, the application for a marketing authorisation is submitted in

accordance with Article 13 (3) of Directive 2001/82/EC, as amended by 2004/28/EC (a 'hybrid' application). Essential similarity with the reference product was accepted by means of dissolution studies.

The product is indicated for use in chickens, turkeys and ducks, for the treatment of infections caused by bacteria 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 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 697 mg/g amoxicillin, (as amoxicillin trihydrate 800 mg/ml), and the excipients sodium carbonate and sodium citrate.

The container/closure system consists of either a securitainer: a white cylindrical polypropylene container, covered with a low-density polyethylene closure. The securitainer contains 100 g, 250 g, 500 g or 1 kg of product, or a white polypropylene bucket provided with a polypropylene closure. The bucket contains 1, 2.5 or 5 kg of product.

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. In order to demonstrate that the excipients did not influence the bioavailability of the proposed product as compared to the reference product, a comparative dissolution study was performed at three pH values. Essential similarity was established and bioequivalence accepted.

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 process of mixing and filling. Process validation

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

data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is amoxicillin, an established active substance. 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 for all product components, where relevant.

Both excipients comply with requirements, and packaging materials comply with EU Regulation 10/2011 and its amendment.

II.C.4. Substances of Biological Origin

Suitable data were provided in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, which confirmed that the only component of animal origin, lactose, (used by one active substance manufacturer to prepare 6-amino penicillanic acid), is sourced from healthy cattle under the same conditions as milk collected for human consumption.

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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, reconstitution time, packaging content, identification and assay of active substance, pH, water purity, related substances of amoxicillin and microbiological quality.

II.F. Stability

Stability data on the active substance and finished product 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

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening of the immediate packaging: 1 month.
Shelf life after reconstitution in drinking water: 12 hours.
Store below 25 ºC.
Store in a dry place.
Store in tightly closed original container to protect from moisture.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the application, pharmacological and toxicological data were not required. A user risk assessment and environmental risk assessment were submitted.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- Penicillins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may cause cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
- People with known hypersensitivity to beta-lactam antibiotics should avoid handling the product.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- This product may cause skin and eye irritation. Avoid contact with skin and eyes.
- Do not smoke, eat or drink while handling the product.
- During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear gloves and either a disposable half mask respirator conforming to European Standard EN149 or a non-disposable respirator conforming to European Standard EN140 with a filter to EN 143 when mixing and handling the product. Wash hands after use.
- In case of contact with eyes or skin, wash immediately with water.

- 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.

Environmental Safety

The applicant provided the same ERA data that were submitted for the DCP for Amoxy Active 697 mg/g Oral Powder for Pigs and Chickens, also with the same MAH. This includes a Phase I and Phase II ERA and supporting references. In addition to this, the applicant has provided a brief Phase I and Phase II ERA for the proposed product that includes product specific predicted environmental concentration (PEC) values. The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The target species are usually reared in housing, potentially exposing the environment to amoxicillin or its degradation products is the spreading of manure. The aquatic environment may also be exposed. The initial predicted environmental concentration (PEC) for the amoxicillin degradation product amoxicillin penocilloic acid (APA) in soil is greater than 100 µg/kg in all but broiler breeders, and a Phase II ERA was required. (The ERA for amoxicillin ended at Phase I, as the trigger value was not reached).

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.

Studies were carried out using APA. All data were from referenced material.

Physic-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	84 g/l at 20°C	Indicates APA soluble in water
Dissociation constants in water Pak	OECD 112	pKA1 = 7.8 pKB1 = 6.2* pKA2 = 9.9 pKB2 = 4.1* *calculated	
Melting Point/Melting Range	OECD 102	~285oC	No melting before decomposition
Vapour Pressure	OECD 104	Not determinable	

Study type	Guideline	Result	Remarks
n-Octanol/Water Partition Coefficient log $_{Pow}$	OECD 117	Log K_{now} -2.00	Know <4, not bio accumulative

Environmental fate

Study type	Guideline	Result	Remarks
Soil sorption behaviours	OECD 106	Adsorption KOC 38.5 – 99.2 ml/g (mean: 74.2 ml/g)	APA is mobile in soil. The worst case Koch value was used in the assessment.
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} 0.3 – 1 days (geometric mean 0.7 days)	APA is a non-persistent molecule in soil

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test Anabena *flos-aquae*	OECD 201	EC_{50}	163 mg/l
Daphnia magna immobilisation	OECD 202	EC_{50}	757 mg/l
Fish, acute toxicity *Danio rerio*	OECD 203	LC_{50}	95 mg/l
Soil Micro-organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	Nitrate production <25% of control at 28 days
Terrestrial Plants, Growth Test: *Avena sativa* *Allium cepa* *Beta vulgaris* *Brassica alba* *Lactuca sativa* *Phaseolus aureus*	OECD 208	EC_{50}	>946 mg/kg dwt
Earthworm *Eisenia fetida* subacute/reproduction	OECD 220/222	NOEC	≥229 mg/dwt
Dung beetle larvae	OECD draft	EC_{50}	

Exposure assessment (Predicted exposure concentration)

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. Exposure to APA will be less from use of the proposed product when compared to the already authorised product. However, for the sake of completeness, PECs in groundwater and surface water were presented. The following PEC values were calculated.

PEC		
Soil (µg/kg)	**Groundwater (µg/l)**	**Surfacewater (µg/l)**
609	205	68

Risk Characterisation (Risk Quotient)

An updated risk characterisation was provided for the proposed product. Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values as follow:

Test organism	**End point**	**AF**	**PNEC (µg/kg or l)**	**PEC (µg/kg or l)**	**RQ**
Algae, Growth Inhibition	EC_{50} = 163 mg/l	100	1630	68	0.04
Daphnia sp. immobilisation	EC_{50} = >757 mg/l	1000	757	68	0.09
Fish, acute toxicity	LC_{50} = >95 mg/l	1000	95	68	0.72
Soil Micro-organisms:	<25% difference in N transformation (28 days)	NA	-	-	-
Terrestrial Plants, Growth	EC_{50} = >946 mg/kg	100	9460	665	0.07
Earthworm reproduction	NOEC ≥229 mg/kg	10	22900	665	0.03

As all RQ values were less than one, 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

No residue depletion studies were conducted because bioequivalence to the reference product was accepted.

MRLs

Amoxicillin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues.

MRLs (µg/kg) are listed below:

	All food species	Other provisions
Muscle	50	Fin fish: Muscle MRL relates to 'muscle & skin in natural proportions. MRLs for fat, liver & kidney do not apply. For porcine & poultry species: Fat MRL relates to 'skin & fat in natural proportions' Not for use in animals from which eggs are produced for human consumption
Liver	50	
Kidney	50	
Fat / skin	50	
Milk	4	

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified:

Chickens: meat and offal: 1 day.

Turkeys: meat and offal: 5 days.

Ducks: meat and offal: 9 days.

Not authorised for use in birds producing eggs for human consumption.

Do not use within 4 weeks before the onset of the laying period.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, no data were submitted for this section of the dossier. The SPC cites appropriate pharmacodynamic and pharmacokinetic data.

Pharmacodynamics

Amoxicillin is a time-dependent bactericidal antibiotic belonging to the semisynthetic penicillin group. It has a broad spectrum of activity against Gram positive and Gram negative bacteria, and its activity is due to the inhibition of the development of the peptidoglycan network structure in the bacterial cell wall.

Pharmacokinetics

Amoxicillin is well absorbed following oral administration and it is stable in the presence of gastric acids. Excretion of amoxicillin is mainly in the unchanged form via the kidneys to give high concentration in renal tissue and urine. Amoxicillin is well distributed in body fluids.

Studies in birds have indicated that amoxicillin is distributed and eliminated more rapidly than in mammals. Biotransformation appeared a more important route of elimination in birds than in mammals.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application.

Resistance

An overview resistance to the active substance was provided, and suitable advice appears in the SPC.

IV.II. Clinical Documentation

Due to the legal basis of the application, no data were required for this section.

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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