Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Awazom 800 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys

Date Created: June 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0688/001/DC
Name, strength and pharmaceutical form	Awazom 800 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys
Applicant	Billev Farmacija Vzhod d.o.o. Parmova Ulica 14 1000 Ljubljana Osrednjeslovenska Slovenia
Active substance(s)	Amoxicillin Trihydrate
ATC Vetcode	QJ01CA04
Target species	Chickens, Ducks, Turkeys
Indication for use	Treatment of infections in chickens, turkeys and ducks 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	13th March 2019
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Slovenia

I. SCIENTIFIC OVERVIEW

This was an application for a generic 'hybrid' product, Awazom 800 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys, submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended by 2004/28/EC (a 'hybrid' application). The quantitative and qualitative composition of the proposed product differs from that of the reference product, therefore, suitable dissolution studies were performed to ascertain bioequivalence.

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, which has been authorised in the UK since July 1990. A variation was approved in 1996 to change the formulation to 100% active substance. The applicant is claiming an exemption from the provision of bioequivalence studies. This is in accordance with section 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 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 800 mg amoxicillin trihydrate, corresponding to 679 mg of amoxicillin, and the excipients sodium carbonate monohydrate, sodium citrate and silica colloidal anhydrous.

The container/closure system consists of thermosealed bags of PET/Al/PE containing 100 g, 250 g, 500 g or 1000 g powder. 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 is 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 a simple dry-blending process, after which a final bulk mixture is assessed and filled into packaging.

Process validation 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 trihydrate, an established active substance described in the European Pharmacopoeia (Ph. Eu). 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. An acceptable Certificate of Suitability was provided.

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

All excipients are monographed in the Ph. Eur. All packaging is authorised by suitable specifications.

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, fill mass, identification and assay of the active substance, clarity of solution, colouration, water content, pH, dissolution speed and 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

- Shelf-life after first opening the immediate packaging:
  100 g pack: 1 month.
  250 g, 500 g and 1000 g packs: 2 months.

- Shelf life after dilution according to directions: 12 hours.

- Once opened, the medicinal product should be stored at temperatures below 25°C.

- In order to protect from moisture, store the product in the original packaging.
- Once opened, keep the bags tightly closed by folding the cut edge of the bag over and securing with a clip.

- Shelf-life as packaged for sale: 3 years.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the application, the applicant was not required to submit pharmacological and toxicological data. A user risk assessment (URA) and environmental risk assessment (ERA) were included.

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 and cephalosprins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross sensitivity 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 care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
- During preparation and administration of the medicated drinking water, avoid skin and eye contact and inhalation of dust particles, as this product may be irritating.
- Wear impervious gloves and an appropriate dust mask (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 EN143) when mixing and handling the product.
- In the event of eye or skin contact, rinse the affected area with large amounts of clean water.
- Do not smoke, eat or drink while handling the product.
- 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 for broilers, replacement layers and turkeys and a Phase II ERA was required. The ERA stopped at phase I for ducks, which are considered a minor species.

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 amoxicillin trihydrate.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	3.16g/l at 20°C ± 1
Dissociation constants in water pKa	OECD 112	pKa1 = 2 pKa2 = 7.7 pKa3 = 10
UV-Visible Absorption Spectrum	OECD 101	259-269 nm (pH 6.2-12.8)
Melting Point/Melting Range	OECD 102	Not determined as test substance decomposed at temperatures above 130°C
Vapour Pressure	OECD 104	≤2 x 10-4 Pa at 25°C
n-Octanol/Water Partition Coefficient $\log P_{ow}$	OECD 107	-1.54 1.08 (pH 5-10)

Environmental fate

Study type	Guideline	Result
Soil Adsorption	OECD 106	K_{OC} 32.62 = high soil mobility
Aerobic and Anaerobic Transformation in Soil	OECD 307	mean DT_{50} = 1.78 hours

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/*Anabena flos-aquae*	OECD 201	EC_{50}	0.043 mg/l
Daphnia magna immobilisation	OECD 202	EC_{50}	>400 mg/l
Fish, acute toxicity	OECD 203	LC_{50}	>1000 mg/l
Soil Micro organisms: Nitrogen Transformation Test (28 days)	OECD 216	≤25% of control	7100 µg/kg dry soil
Terrestrial Plants, Growth Test	OECD 208	EC_{50}	>194.1 mg/kg soil
Earthworm/*Eisenia foetida* subacute/reproduction	OECD 220/222	NOEC	≥245.0 mg/kg soil

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.

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 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

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

MRLs

The MRL status of active substance and excipients are in accordance with the European Regulation 470/2009. Active substance and marker residue: amoxicillin.

MRLs are listed below:

	All food species
Muscle	50 µg/kg
Liver	50 µg/kg
Kidney	50 µg/kg
Fat	50 µg/kg
Milk	4 µg/kg

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.

Withdrawal Periods

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

Chickens (meat and offal): 1 day

Ducks (meat and offal): 9 days

Turkeys (meat and offal): 5 days

The product is not authorised for use in laying birds producing eggs for human consumption and within 3 weeks of onset of laying.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Due to the nature of the application, no additional pharmacodynamic data were required.

Amoxicillin is a time-dependent bactericidal antibiotic belonging to the semisynthetic penicillin group, which acts by inhibiting the synthesis of bacterial cell walls during bacterial replication. It has a broad spectrum of activity against Gram positive and Gram negative bacteria.

There are three main mechanisms of resistance to beta-lactams. One of the most important is the inactivation of penicillin by beta-lactamase enzymes produced by certain bacteria. Cross-resistance is observed between amoxicillin and other penicillins, particularly with aminopenicillins.

Pharmacokinetics

Due to the nature of the application, no additional pharmacodynamic data were required.

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 because bioequivalence with the reference was accepted.

Resistance

Resistance studies were not required because bioequivalence with the reference was accepted.

IV.II. Clinical Documentation

Clinical documentation was not required because bioequivalence with the reference was accepted.

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

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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