Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Biocillin 1000 mg/g Powder for use in drinking water for chickens, ducks and turkeys [CZ, DE, DK, EL, FI, HR, IE, PL, RO, SK, UK]
Belacillin 1000 mg/g Powder for use in drinking water for chickens, ducks and turkeys [SE]

Date: October 2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V0182/001/DC/
Name, strength and pharmaceutical form	Biocillin 1000 mg/g Powder for use in drinking water for chickens, ducks and turkeys
Applicant	Bela-Pharm GmbH & Co. KG Lohner Straße 19 49377 Vechta Germany
Active substance(s)	Amoxicillin trihydrate 1000 mg (equivalent to 871 mg Amoxicillin)
ATC Vetcode	QJ01CA04
Target species	Chickens, ducks and 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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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	30th March 2016.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Croatia, Czech Republic, Denmark, Finland, Greece, Ireland, Poland, Romania, Slovakia, Sweden, United Kingdom

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 was Amoxinsol 100% Powder for Oral Solution, which has been marketed in the UK since 1996. The proposed product is indicated for use in chickens, turkeys and ducks, for the treatment of infections caused by bacteria susceptible to amoxicillin. An exemption from bioequivalence studies was claimed and accepted as the proposed product was confirmed as being identical to the reference product, with regard to qualitative and quantitative composition. This was in accordance with 7.1.c of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products.

For chickens, the recommended dosage is 15 mg amoxicillin trihydrate per kg bodyweight (equivalent to 15 mg product/kg/bwt) per day. The total period of treatment should be for 3 consecutive days or in severe cases for 5 consecutive days. For ducks, the recommended dosage is 20 mg amoxicillin trihydrate/kg bodyweight (equivalent to 20 mg product/kg/bwt) per day for 3 consecutive days. For turkeys, the recommended dosage is 15-20 mg amoxicillin trihydrate/kg bodyweight (equivalent to 15-20 mg product/kg/bwt) per day for 3 consecutive days or in severe cases for 5 consecutive days.

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. QUALITY ASPECTS

II.A. Composition

The product contains 1000 mg/g amoxicillin trihydrate and no excipients. The container/closure system consists of 250 g, 500 g, 1 kg of product presented in a fold-up carton with inner layer (paper/PE/Alu/PE), and 2.5 kg, 5 kg of product in a kard-o-seal-bag (PE/paper/PE/Alu/PE). 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 licensed manufacturing sites. The manufacturing method consists of filling and sealing of the active substance into packs.

The product is manufactured 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. 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. Certificates of Suitability were provided from the manufacturing sites for the active substance and for the manufacturers of the packaging.

II.C.4. Substances of Biological Origin

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

A signed declaration and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 include those for appearance of active substance and subsequently formed solution, dissolution time in water, pH, identity of active substance, analysis of impurities, microbiological quality and filling quantity.

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. Re-test periods or full stability studies were provided.

Stability studies on the finished product were provided in accordance with VICH[3] requirements. Data were provided for long-term and accelerated conditions according to EMA[4] guidance. Storage analyses were conducted at 25°C ± 2°C/60% RH ± 5% RH and 40°C ± 2°C/74% RH ± 5% RH for 6, 24 or 36 months, in various commercial packaging presentations.

In-use stability studies were conducted in accordance with EMA guidelines, under a variety of conditions. Results showed that the product remained stable according to required specifications. A study was presented based on the assumption of treating 300 turkeys (bodyweight 10 kg), for up to 5 days, for a total time period of 12 weeks. Samples were tested after 7 days, 14 days, 28 days, 8 weeks and 12 weeks,

[3] VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.
[4] EMA – European Medicines Agency.

with samples stored at 25°C/60% RH. The results show that the finished product remained in line with requirements.

G. Other Information

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

Shelf life after first opening the immediate packaging: 14 days.

Shelf life after dilution or reconstitution according to directions: 12 hours.

Keep the container tightly closed in order to protect from light and moisture.

Store in a dry place.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and an exemption from providing bioequivalence studies was permitted, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Documentation

User Safety

A user risk assessment was provided, but was not required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion and 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 ENl43.
- Wear impervious gloves during preparation and administration of medicated water.
- Wash any exposed skin after handling the product or medicated water

Environmental Safety

Phase I:

The initial predicted environmental concentration (PEC) of amoxicillin in soil was greater than 100 µg/kg and a Phase II ERA was therefore required. The $PEC_{soil\text{-}initial}$ was recalculated, as amoxicillin is known to degrade rapidly in manure into the more stable degradation product amoxicillin penicilloic acid (APA). To confirm these findings, a degradation study was provided. It was found that amoxicillin trihydrate is unstable in chicken manure, and is largely degraded under aerobic conditions. Phase II data were therefore performed using APA, and were based on the synthesised substance APA sodium salt (APA-Na).

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 of APA

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	79.9 g/l	Soluble in water
Dissociation constants in water pKa	OECD 112	pK_{A1}=8 pK_{A2}=10.1	Two constants - no dissociation at environmentally relevant pH

Study type	Guideline	Result	Remarks
UV-Visible Absorption Spectrum	OECD 101	pH<2: 230 nm, 272.4 nm pH7: 228.3 nm, 271.5 nm pH>10: 245 nm, 280.7 nm	Acceptable result
Melting Point/Melting Range	OECD 102	No melting before decomposition (at approx. 270°C)	Acceptable result
Vapour Pressure	OECD 104	3.6 x 10^{-16} Pa	Calculation considered sufficient
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	log P_{OW} =-2.2 (main component). log P_{OW}=-0.51-0.46 (minor components/impurities)	low log P_{OW}; no bioaccumulation potential

The Log K_{OW} (n-octanol/water partition coefficient) was shown to be less than 4. There was therefore no requirement for further assessment with regard to bioaccumulation.

Environmental fate

Study type	Guideline	Result	Remarks
Soil sorption	OECD 106	K_{OC} 66.7	APA is mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} 1.6 (mean days)	APA is a non-persistent molecule in soil

Environmental effects

Study type	Guideline	Endpoint	Result	Remarks
Algae, Growth Inhibition Test (*Anabaena flos-aquae*)	OECD 201	EC_{50}	172 mg/l APA-Na	None
Daphnia sp. Immobilisation Daphnia magna	OECD 202	EC_{50}	No effect at 1000 mg/l APA-Na	None

Study type	Guideline	Endpoint	Result	Remarks
Fish, acute toxicity/*Species*	OECD 203	LC_{50}	96 hour lethal concentration > 1000 mg APA-Na/l. (94.3 APA base)	None
Soil Micro-organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	Nitrate production < 25% of control at 28 days	None
Terrestrial Plants, Growth Test (nitrogen transformation. Nitrate production < 25% of control at 28 days) *Avena sativa* (oat) *Allium cepa* (onion) *Brassica alba* (mustard) *Lactuca sativa* (lettuce) *Solanum lycopersicum* (tomato) *Phaseolus aureus* (mung bean)	OECD 208	EC50	Lowest EC_{50} >1152 mg/kg APA-Na/kg dwt (*Lactuca sativa*)	None
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC	≥2000 mg APA Na/kg	None

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.

Target animal	PEC		
	soil-initial (µg/kg)	Groundwater-refined (µg/l)	Surfacewater-initial (µg/l)
Broiler chickens	643.08	0.00 (using $PEC_{soil\text{-}initial}$ at 839.65)	41.39

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

Test organism	End point	AF	PNEC (ug/kg or l)	PEC	RQ
Cyanobacteria	EC_{50}	100	1720	41.39	0.07
Daphnia spp.	EC_{50}	1000	1000	41.39	0.12
Fish	LC_{50} > 1000 mg APA-Na/l	1000	1000	41.39	0.12
Soil Micro-organisms:	< 25% difference in N transformation (28 d)	N/A	N/A	N/A	N/A
Terrestrial Plant	EC_{50} = >1152 mg APA-Na/kg	100	11520	643.08	0.06
Earthworm reproduction	NOEC = ≥ 2000 mg APA Na/kg	10	200 000	643.08	0.00

As all RQ values were less than 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

Residue depletion studies were not required because an exemption from providing bioequivalence studies was granted. The applicant provided a confirmation residue and pharmacokinetic study in turkeys, (considered a minor species under MUMS guidelines), in order to reduce the withdrawal period for this species, as compared to the reference product. The data were used to support the extrapolation of the meat withdrawal period derived for chickens. The data were acceptable.

MRLs

Data from Table 1 in the Annex of Commission Regulation (EU) No. 37/2010.

MRLs are listed below. Marker substance/active substance - amoxicillin:

Target tissue (all food-producing species)	MRLs (µg/kg)
All edible tissues	50

A separate study noted that the MRL for turkeys, for kidney, liver, skin/fat and muscle was also 50 µg/kg. Other provisions: For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which eggs are produced for human consumption.

A separate study noted that the MRL for turkeys, for kidney, liver, skin/fat and muscle was also 50 µg/kg.

Withdrawal Periods

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

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

Not authorised for use in birds producing eggs for human consumption and within 3 weeks of onset of laying.

IV. CLINICAL ASSESSMENT (EFFICACY)

This was a generic application according to Article 13 (1), and bioequivalence studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species

This was a generic application according to Article 13 (1). The proposed product was deemed to be identical to the reference product, and tolerance studies were therefore not required for this application.

Resistance

Adequate warnings and precautions appear on the product literature:

There are three main mechanisms of resistance to beta-lactams: beta-lactamase production, production of penicillin binding proteins (PBP), and decreased penetration of the outer membrane. One of the most important is the inactivation of penicillin by beta-lactamase enzymes produced by certain bacteria. These enzymes are capable of cleaving the beta-lactam ring of penicillins, making them inactive. The beta-lactamase could be encoded in chromosomal or plasmidic genes.

Cross-resistance is observed between amoxicillin and other penicillins, particularly with aminopenicillins.

IV.II. Clinical Documentation

This was a generic application according to Article 13 (1), and bioequivalence studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

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 Heads of Veterinary Medicinal 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.

20171005 RMS change from UK to DE. Former EU procedure number UK/V/0567/001/DC