Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Solamocta 697 mg/g powder for use in drinking water for chickens, ducks and turkeys

Date Created: June 2016

PuAR correct as of 08/10/2018 when RMS was transferred to NL. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0540/001/DC
Name, strength and pharmaceutical form	Solamocta 697 mg/g powder for use in drinking water for chickens, ducks and turkeys
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands
Active substance(s)	Amoxicillin 697 mg (equivalent to amoxicillin trihydrate 800 mg)
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 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 completion of the original decentralised procedure	25 February 2016.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Portugal, Slovakia, Spain.

I. SCIENTIFIC OVERVIEW

This was an application for a generic hybrid product, submitted under Article 13 (3) of Directive 2001/82/EC as amended. The strength of the active substance is different to that of the reference product, which is Amoxinsol 100% w/w powder for oral solution, marketed in the UK since 1996. The applicant claimed exemption from requirement for bioequivalence studies in accordance with exemption 7.1.c) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

The indication is for the treatment of infections of chickens, turkeys and ducks caused by bacteria susceptible to amoxicillin. The product must not be used in horses, rabbits, guinea pigs, hamsters, gerbils or any other small herbivore. Do not use in animals with known hypersensitivity to penicillins or other β-lactam antibiotics or to any of the excipients. In chickens, the recommended dose is 13.1 mg amoxicillin (equivalent to 18.8 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days. In ducks, the recommended dose is 17.4 mg amoxicillin (equivalent to 25 mg veterinary medicinal product) per kg body weight for 3 consecutive days. In turkeys, the recommended dose is 13.1-17.4 mg amoxicillin (equivalent to 18.8 to 25 mg veterinary medicinal product) per kg body weight for 3 days, or in severe cases for 5 days.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on 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, equivalent to 800 mg/g amoxicillin trihydrate and the excipients sodium carbonate monohydrate, sodium citrate and silica colloidal anhydrous.

The container/closure system consists of 100 g, 250 g, 500 g and 1 kg sachet with outside to inside layers of polyethylene terephthalate, polyethylene, aluminum, polyethylene (PET/PE/ALU/PE), or 100 g, 250 g, 500 g and 1 kg sachet with outside to inside layers of polyethylene terephthalate, aluminium, polyamide, polyethylene (PET/ALU/PA/PE). The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of 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 guideline.

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 tests of a simple weighing and mixing process, followed by filling into packaging and quality control checking.

II.C. Control of Starting Materials

The active substance is amoxicillin, 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, along with an acceptable Certificate of Suitability. All excipients are monographed in the Ph. Eur. All packaging is in accordance with a certificate of Suitability (active substance), or is monographed in the Ph. Eur, (finished product).

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

II.C.4. Substances of Biological Origin

The product does not contain any material of animal origin. A signed and dated TSE declaration is provided stating compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMA/410/01 rev.3 of May 2011).

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, weight, loss on drying, microbial quality and identification of the active substance.

II.F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Data for the finished product included real-time and accelerated data, in accordance with VICH[3] guidelines.

G. Other Information

- In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.
- 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 dilution or reconstitution according to directions 12 hours.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic hybrid application according to Article 13 (3), and bioequivalence with a reference product was demonstrated, results of pharmacological and toxicological tests are not required.

[3] VICH – The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

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:

- People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
- Personal protective equipment consisting of impermeable gloves should be worn when handling the veterinary medicinal product.
- Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
- Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Environmental Safety

An Environmental Risk Assessment (ERA) was conducted in accordance with VICH and CVMP guidelines.

Phase I:

As the initial predicted environmental concentration (PEC) in soil exceeded 100 µg/kg, a Phase II ERA was 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 physico-chemical properties, environmental fate and environmental effects. All studies were carried out using the primary degradation product amoxicillin penicilloic acid (APA), because it was shown that the active substance, amoxicillin trihydrate rapidly degrades to APA. Results were adjusted by a theoretical correction factor of 1.14 to accommodate the molecular difference between the active substance and the degradation product. (APA 383.4 g/mole, APA ammonium salt 436.5 g/mole).

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	109.8 mg/l	Soluble
Vapour pressure	OECD 104	1.35 x 10^{-15} Pa	
Dissociation constant	OECD 112	pKa 1.3 – 9.6 pKa	
Octanol water partition coefficient	OECD 107	Log K_{ow}≤ -4at pH 2.7 and 9.0	Very low Log K_{ow}, indicates no bioaccumulation potential.

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	K_{OC} = 50	Acceptable result. Subsequently used to calculate groundwater and surface water PECs
Aerobic Transformation in Soil	OECD 307	DT_{50} = 21 and 17.5 hours	APA will not persist in soil.

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Cyanobacteria *Anabaenaflos-aquae*	OECD 201	EC_{50}	Growth and yield 72 hours EC50 = >114 mg/l (equivalent to 100 mg APA/l). Acceptable result.
Daphnia sp. immobilisation	OECD 202	EC_{50}	Immobilisation 48 hours EC50 = 114 mg/l (equivalent to 100 mg APA/l). Acceptable result.
Fish, acute toxicity/rainbow trout *Oncorynchus mykiss*	OECD 203	LC_{50}	LC_{50} >114 mg/l (equivalent to 100 mg APA/l). Acceptable result.
Soil Micro-organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	deviation from control 2.07% at 11.4 mg/kg. Acceptable result.
Terrestrial Plants: *Brassica napus*, (rapeseed), *Glycine max* (soy bean), *Helianthus annuus* (sunflower), *Cucumis sativus* (cucumber), *Allium cepa* (onion)	OECD 208	EC_{50}	EC50 >570 mg/kg (dwt) for all species, corresponding to >500 APA mg/kg soild (dwt). Acceptable result.
Earthworm *Eisenia foetida*	OECD 220/222	NOEC	NOEC = 182.4 mg/kg soil (dwt) for reproduction at 56 days. Corresponds to 160 mg APA/kg soil (dwt).Acceptable result.

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.

PEC		
Soil (initial, µg/kg)	**Groundwater (µg/l)**	**Surfacewater (µg/l)**
610	153	51

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 4.4.4. Results demonstrated that the 80th percentile annual average concentration of APA in leachate was less than 0.001 for all soils, confirming that appropriate use of the product will not pose a risk to drinking water.

Risk Characterisation

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 (µg/kg)	PEC	RQ
Algae, Growth Inhibition	EC_{50} = ≥100	100	1000	51	0.051
Daphnia sp. immobilisation	EC_{50} = ≥100	1000	100	51	0.51
Fish, acute toxicity	LC_{50} = ≥100	1000	100	51	0.051
Soil Micro organisms:	<25% difference in N transformation (28 d) (mg/kg)	NA	NA	NA	NA
Terrestrial Plants, Growth	EC_{50} = ≥500 (mg/kg)	100	50000	610	0.061
Earthworm	NOEC = ≥160 mg/kg	10	10000	610	0.01

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

The applicant claimed successfully claimed exemption from providing studies in this section as the proposed product was deemed essentially similar to the reference product.

Residue Studies

The applicant claimed successfully claimed exemption from providing studies in this section as the proposed product was deemed essentially similar to the reference product.

MRLs

The marker substance is amoxicillin.
MRLs are listed below:

Target tissue (all animal species)	MRLs (µg/kg)	Other provisions: 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.
Muscle	50	
Liver	50	
Kidney	50	
Fat / skin	50	
Milk	4	

Withdrawal Periods

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

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 lay.

IV CLINICAL DOCUMENTATION

As this is a generic hybrid application according to Article 1 (3), and bioequivalence with a reference product has been established, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. Dissolution studies showed that the proposed and reference products are essentially similar. Exemption from further studies 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) which states:

"If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved reference veterinary medicinal product presented as an aqueous oral solution at time of administration, bioequivalence studies may be waived if the excipients contained in it do not affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), solubility (e.g. co-solvents) or in vivo stability of the active substance. Any

differences in the amount of excipients should be justified by reference to other data, otherwise an in vivo bioequivalence study will be required…"

IV.I. Pre-Clinical Studies

Due to the nature of the application, no further studies were required.

IV.II. Clinical Documentation

Due to the nature of the application, 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(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)