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

Rhemox Forte, 1000mg/g Powder for use in Drinking Water for chickens, ducks, turkeys (AT, BE, DE, EL, HU, IT, NL, PL, PT, RO, UK)
Amox Vet., 1000mg/g Powder for use in Drinking Water for chickens, ducks, turkeys (DK)
Rhemox Forte, 871,24 mg/g Powder for use in Drinking Water for chickens, ducks, turkeys (FR)
Robucina, 1000mg/g Powder for use in Drinking Water for chickens, ducks, turkeys (ES)

Date Created: August 2016

PuAR correct as of 07/06/2018 when RMS was transferred to ES.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0555/001/DC
Name, strength and pharmaceutical form	Rhemox Forte, 1000mg/g Powder for use in Drinking Water for chickens, ducks, turkeys
Applicant	LIVISTO Int'l, S.L. Av. Universitat Autònoma, 29 08290 Cerdanyola del Vallès (Barcelona) Spain
Active substance	Amoxicillin trihydrate
ATC Vetcode	QJ01CA04
Target species	Chickens, ducks, turkeys
Indication for use	Treatment of infections in chickens, ducks and turkeys 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 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	Austria, Belgium, Denmark, France, Germany, Greece, Hungary, Italy, The Netherlands, Poland, Portugal, Romania, Spain.

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. Bioequivalence was claimed with the reference product via a biowaiver in accordance with sections 7.1 c) and 7.1 d) from the bioequivalence guideline EMA/CVMP/016-Rev-2. The reference product was Amoxinsol 100% w/w Powder for Oral Solution, marketed in the UK since August 1996. The proposed product is indicated for the treatment of infections in the target species caused by bacteria susceptible to amoxicillin. The recommended dose rate for chicken is 15 mg amoxicillin trihydrate/kg bodyweight. In turkeys, the recommended dose rate is 15-20 mg amoxicillin trihydrate/kg bodyweight. In ducks the recommended dosage is 20 mg/kg bodyweight. Treatment is administered for 3 consecutive days, or in severe cases, 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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

Acceptable solubility studies showed that the proposed product was equivalent to the reference product.

II.A. Composition

The product contains 1000 mg/g amoxicillin trihydrate and no excipients. The container/closure system consists of 100g, 200g, 0.5 kg, 1 kg, 5 kg PET/ALU/PE sachets. 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 a licensed manufacturing site. The manufacturing method consists of the measuring of amoxicillin trihydrate into packaging, and sealing the product. 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. 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. The packaging materials are made to specification.

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 sites have been provided demonstrating compliance with the specification.

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. Appropriate retest periods are established.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Batches were stored under VICH[3] conditions of 25°C/60% RH and 40°C/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale:
2 years
100g, 200g, 500g:
Shelf life after first opening the immediate packaging:
3 months
1kg, 5kg:
Shelf life after first opening the immediate packaging:
6 months

Shelf life after dilution or reconstitution according to directions:
24 hours

Store in a dry place.
This veterinary medicinal product does not require any special temperature storage conditions.

Keep the bag tightly closed after first opening in order to protect from moisture and light. Any medicated water which is not consumed within 24 hours should be discarded.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

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

Warnings and precautions as listed on the product literature are the same as those of the reference product and 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 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: 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 impervious gloves during preparation and administration of medicated water.
- Wash any exposed skin after handling the product or medicated water.
- Wash hands after use.

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.

Environmental Safety

The Environmental Risk Assessment (ERA) was in accordance with VICH and CVMP guidelines. During the Phase I risk assessment, initial predicted environmental concentrations (PECs) in soil were greater than 100 µg/kg) and, as a result, a Phase II ERA was required. However, as it was demonstrated that amoxicillin was not stable in hen manure, the Phase II assessment was carried out on penicilloic acid of amoxicillin (APA), the primary degradation product of amoxicillin.

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, unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	84 g/l at 20°C	Soluble
Dissociation constants in water pKa	OECD 112	7.8	
Melting Point/Melting Range	OECD 102	~285°C	No melting point before decomposition
Vapour Pressure	OECD 104	Not determinable	
n-Octanol/Water Partition Coefficient	OECD 107	Log K_{ow} -2.00	K_{ow} < 4, not bioaccumulative

Environmental fate

Study type	Guideline	Result	Remarks
Soil sorption behaviour	OECD 106	adsorption K_{OC} 74.2	APA is mobile in soil.
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} 1 day	APA is a non-persistent molecule in soil

Environmental effects

Study type	**Guideline**	**Endpoint**	**Result**
Algae, Growth Inhibition *Anabena flos-aquae*	OECD 201	EC_{50}	172.5 mg APA-Na/l (163 mg APA base/l)l
Daphnia spp. Immobilisation *Daphnia magna*	OECD 202	EC_{50}	>800 mg APA-Na/l (754.6 mg APA base/l)
Fish, acute toxicity *Danio rerio*	OECD 203	LC_{50}	> 100 mg APA-Na/l (94.3 mg APA base/l)
Soil Microorganisms: Nitrogen Transformation Test	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}	>1000 mg APA-Na/kg dwt for all species (>943.3 mg APA base/kg dwt)
Earthworm/ subacute/reproduction *Eisenia fetida*	OECD 220/222	NOEC	≥ 241.7 mg APA-Na/kg soil dwt (≥ 228 mg APA base/kg dwt)

Exposure assessment

PEC values 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 (APA)		
Soil (µg/kg)	**Groundwater (µg/l)**	**Surfacewater (µg/l)**
665	116.5 µg/L	38.8 µg/L

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 0 µg/l 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 or l)**	**PEC (µg/kg or l)**	**RQ**
Cyanobacteria,	EC_{50} = 124.2 mg APA-Na/l	100	1242	38.8	0.031
Daphnia sp.	EC_{50} = >800 mg APA-Na/l	1000	800	38.8	0.049
Fish	LC_{50} = > 100 mg APA-Na/l	1000	100	38.8	0.39
Soil Microorganisms:	< 25% difference in N transformation (28 d)	NA			
Terrestrial Plants	EC_{50} = > 1000 mg APA-Na/kg	100	10,000	665	0.067
Earthworm	NOEC ≥ 241.7 mg APA Na/kg	10	24,170	665	0.028

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 demonstrated.

MRLs

MRLs are listed below. The active substance and residue marker are amoxicillin:

	MRLs for all food species (ug.kg)
Muscle	50
Liver	50
Kidney	50
Fat	50
Milk	4

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.

Withdrawal Periods

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

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.

Do not use within 3 weeks of onset of laying.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.I. Pre-Clinical Studies

Pre-clinical studies were not required as bioequivalence was demonstrated with the reference product via acceptable solubility studies.

Resistance

The bibliographic information provided is reflected in the SPC. It is stated that there are three key mechanisms of resistance to beta-lactamases. These are beta-lactamase reduction, modification of penicillin binding proteins, and decreased penetration of the outer cell membrane. A significant resistance mechanism is the inactivation of the active substance by beta-lactamase enzymes produced by certain bacteria. The beta-lactamase can be encoded in plasmidic or chromosomal genes. Cross-resistance has been noted between amoxicillin and other penicillins, in particular, with aminopenicillins. The use of amino-penicillins may lead to the selection of multi-resistant phenotypes, for example those producing extended spectrum beta-lactamases (ESBLs).

IV.II. Clinical Documentation

Clinical studies were not required as bioequivalence was demonstrated with the reference product via suitable dissolution studies.

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.

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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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