ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Stabox 1000 mg/g Powder for Use in Drinking Water for Chickens, Ducks, Turkeys

PuAR correct as of 10/09/2018 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0402/001/DC
Name, strength and pharmaceutical form	Stabox 1000 mg/g Powder for Use in Drinking Water for Chickens, Ducks, Turkeys
Applicant	Virbac 1ère avenue - 2065m – LID Carros 06516 France
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 Heads of Medicines Agencies (veterinary) (HMA(v)) 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	31st July 2013
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, Italy, Netherlands, Poland, Portugal, Spain.

I. SCIENTIFIC OVERVIEW

Stabox 1000 mg/g Powder for Oral Solution has been developed as generic product. Bioequivalence is claimed with the reference product Amoxinsol 100% w/w powder for Oral Solution. The product contains 100% w/w amoxicillin trihydrate and is indicated for the treatment of pasteurellosis and colibacillosis in chickens, pasteurellosis in turkeys and infections caused by *Streptococcus bovis*, *Pasteurella anatipestifer* and *Escherichia coli* in ducks. The product is contraindicated for use in ruminants, horses, lagomorphs and rodents such as rabbits, hamsters, gerbils and guinea pigs.

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; the slight 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 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

II. QUALITY ASPECTS

A. Composition

The product contains the active substance amoxicillin trihydrate and no excipients.

The container/closure system consists of 100g, 500g, 1000g or 5000g of product packaged into aluminium bags (PET-ALU-LDPE). The 5000g bags will include a zip lock. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The amoxicillin trihydrate filled into the containers to the appropriate weight and the containers are closed by heat sealing. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia. Certificates of Suitability have been supplied for the two active substance manufacturers. 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. 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. The tests on the finished product include those for identification and

assay of the active substance, appearance, pH, tests for impurities and microbial purity.

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.

G. 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. The retest period for the active substance is 4 years as stated on the Certificates of Suitability from both active substance manufacturers.

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. Six months stability data for the product stored at 25°C/60%RH and 40°C/75%RH. In-use stability studies were also performed with 3 months data supplied. A shelf life of 36 months has been established for the product as packaged for sale and a 3 month shelf life after first opening the immediate packaging has been determined.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale is 36 months.
- Shelf life after first opening the immediate packaging is 3 months.
- Shelf life after dilution or reconstitution according to directions is 24 hours.
- After opening do not store above 25°C.
- Keep the bag tightly closed after first opening in order to protect from moisture and light.
- Any medicated water which has not been consumed within 24 hours, should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which identified the main routes of exposure as dermal, ocular or inhalation of the dust as well as ingestion via hand-to-mouth exposure. The active substance, amoxicillin trihydrate, has a safe and well established use in veterinary medicine. Warnings and precautions as listed on the SPC and product literature are adequate to ensure safety to users of the product:

- Persons handling this product should avoid inhalation of any dust and contact with skin.
- Wear either disposable half-mask respirator conforming to European Standard EN 149 or a non-disposal respirator to European Standard EN 140 with filter EN 143 when mixing or applying this product.
- Impermeable gloves should be worn when mixing or applying this product. Hands and exposed skin should be washed thoroughly after use.
- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or 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.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that the product could enter the environment via spreading of manure. The majority of the active substance amoxicillin trihydrate is degraded in less than 24 hours. The PEC_{soil}[2] was calculated for both amoxicillin and the degradation product. For amoxicillin this was below the trigger value of 100 µg/kg but >100 µg/kg for the degradation product. Therefore the Phase II assessment focused on the degradation product.

Studies showed that the degradation product is not likely to accumulate in soil and is unstable in aqueous compounds. The PEC and PNEC[3] were calculated for soil, ground and surface water and the effects on various organisms considered. The RQ[4] <1 in all cases and it was concluded the product does not provide a risk to the environment when used as directed in the SPC.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of residue studies are not required.

MRLs

Amoxicillin is listed in Annex I of Council Regulation 2377/90.The marker substance is amoxicillin. MRLs are listed below:

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

Amoxicillin is not for use in animals from which eggs are produced for human consumption.

[2] PEC – Predicted environmental concentration
[3] PNEC – Predicted no effect concentration
[4] RQ – Risk Quotient (PEC/PNEC)

Withdrawal Periods

Based on the data provided above, the following withdrawal periods have been established:

Meat and offal:	Chicken	1 day
	Duck	9 days
	Turkey	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 ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of tolerance studies are not required.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application in accordance submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of laboratory trials are not 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 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 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)