Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
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MUTUAL RECOGNITION PROCEDURE
DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Synulox LC Plus Intramammary Suspension for Lactating Cattle (DE)

Clavamox LC Intramammary Suspension for Lactating Cattle (UK)

Synulox LC (BE/LU)

Date: 09th October 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0315/001/DC
Name, strength and pharmaceutical form	Synulox LC Plus Intramammary Suspension for Lactating Cattle
Applicant	Zoetis Deutschland GmbH Schellingstr. 1 10785 Berlin Germany
Active substance(s)	Amoxicillin trihydrate Potassium clavulanate Prednisolone
ATC Vetcode	QJ51RV01
Target species	Cattle
Indication for use	For use in clinical cases of mastitis including cases associated with infections with the following pathogens: Staphylococci (including β-lactamase producing strains) Streptococci (including *S.agalactiae*, *S.dysgalactiae* and *S.uberis*) *Escherichia coli* (including β-lactamase producing strains)

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	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	25th September 2013
Date of completion of current Mutual Recognition Procedure	7 June 2017
Concerned Member States for original procedure	First use: UK (former RMS) Repeat use: BE, LU

I. SCIENTIFIC OVERVIEW

Clavamox LC has been developed as a generic of the reference product Synulox LC, which was first authorised in the UK in 1986. The product is a generic with the same formulation and manufacturing process as the reference product therefore bioequivalence can be assumed.

Clavamox LC is indicated for the treatment of clinical mastitis in dairy cattle. The product is packaged in 3g syringes, with one syringe infused per affected udder quarter immediately after milking. Clavamox LC is contraindicated in cattle known to be hypersensitive to β-lactam antibiotics.

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. A. Composition

The product contains the active substances amoxicillin (as amoxicillin trihydrate), clavulanic acid (as potassium clavulanate) and prednisolone. The excipients are calcium sodium aluminosilicate, emulsifying wax, white soft paraffin and light liquid paraffin.

The container/closure system consists of low density polyethylene intramammary syringes containing 3g of product and packaged in cardboard cartons containing 3, 12, 24 or 300 intramammary syringes. 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 product is manufactured by firstly sterilising the raw materials and then melting the wax in a paraffin base under aseptic conditions. Prednisolone is then added to the base before the addition of potassium clavulanate, amoxicillin trihydrate and calcium sodium aluminosilicate. The suspension is then mixed and filled into sterile plastic syringes. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are amoxicillin trihydrate, potassium clavulanate and prednisolone, established active substances described in the European Pharmacopoeia. Certificates of suitability have been provided for each of the active substance manufacturers. The active substances are 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.
The excipients liquid light paraffin, white soft paraffin and emulsifying wax are all described in a pharmacopoeia and are all well-known excipients used in veterinary medicines; the manufacture complies with the relevant monograph. Calcium sodium aluminosilicate is not the subject of a pharmacopoeia and a specification has been provided to describe the manufacture. Certificates of analysis have been provided for each excipient.

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

Scientific data 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.

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 include those for identification and assay of each active substance, appearance, moisture, sterility and identification of impurities.

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.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 24 months has been established for amoxicillin trihydrate. A retest period of 3 months is stated for the irradiated blend of amoxicillin trihydrate and potassium clavulanate, whilst a retest period of 24 months is determined for prednisolone.

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. Data were provided for 3 batches stored at 25°C/60%RH for 12 or 18 months. A shelf life of 18 months has been established for the finished product.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale is 18 months.
- Do not store above 25°C.
- Store in a dry place.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and as bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and as bioequivalence with the reference product can be assumed because of the nature of the product, results of toxicological studies are not required.

User Safety

The applicant has provided a user risk assessment in compliance with the relevant guideline which shows that the formulation and manufacturing process for the test product and reference product are identical. 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:

- 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.
- Wash hands after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the exposure of the environment would not be extensive and therefore the product is not expected to pose a risk. 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

The formulation of the test product is identical to that if the reference product. In accordance with Article 13 (1) of Directive 2001/82/EC as amended, no bioavailability data are provided and the pharmacokinetic profile of the reference product applies to the test product. Residues studies are not required.

Withdrawal Periods

Based on the information above, the withdrawal periods of the reference product are applicable to the test product.
Meat and offal: 7 days
Milk: 84 hours
With cows milked twice daily, milk for human consumption may only be taken after the 7th milking after the last treatment. Where any other milking routine is followed, milk may be taken for human consumption only after the same period from the last treatment (e.g. with 3 times daily milking, milk may be taken for human consumption at the 11th milking).

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pre-clinical studies are not required.

IV.B Clinical Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of clinical studies 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 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.

•	09 October 2018	Change in RMS from UK to DE.
•	October 2018	Renewal – UK as RMS.
•	25 September 2018	Change in the contact details of the QPPV of an existing pharmacovigilance system as described in the DDPS.
•	28 March 2018	Submission of an updated Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer.
•	08 March 2018	Change in the specification limits of the finished product.
•	18 October 2017	Addition of an alternative sterilisation site for the active substance.
•	28 June 2017	Repeat Use application to add two new member states
•	13 July 2016	Addition of an alternative sterilisation site for the active substance. Addition of an alternative sterilisation site for the active substance. Introduction of a new site of manufacture for the active substance Submission of a new certificate of suitability for an active substance
•	17 May 2016	Submission of an updated Ph. Eur. certificate of suitability. Submission of an updated Ph. Eur. certificate of suitability.
•	02 June 2015	Addition of quantitative specification limits in finished product specification.
•	20 April 2015	Addition of a specification limit for the active substance.