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

Orbenin LA 200 mg intramammary suspension for lactating cattle and sheep [DE]
Orbolan Lactating 200 mg intramammary suspension for cattle and sheep (UK)
Orbenin Lactation 200 mg intramammary suspension for cattle and sheep [NL]
Orbenin Lattazione 200 mg intramammary suspension for cattle and sheep [IT]

Date: 01 November 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0319/001/DC
Name, strength and pharmaceutical form	Orbenin LA 200 mg intramammary suspension for lactating cattle and sheep
Applicant	Zoetis Deutschland GmbH Schellingstr. 1 10785 Berlin GERMANY
Active substance(s)	Cloxacillin sodium
ATC Vetcode	QJ51CF02
Target species	Cattle and sheep
Indication for use	Lactating cows For the treatment of mastitis associated with staphylococcal and streptococcal species sensitive to cloxacillin. Ewes For the treatment of subclinical infections of the udder during the dry period, associated with staphylococcal species and Trueperella pyogenes sensitive to cloxacillin.

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	23 September 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	IT, NL, UK (former RMS)

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Orbolan Lactating 200 mg intramammary suspension for cattle and sheep, for which the reference product was Orbenin LA 200 mg intramammary suspension, which has been marketed in the UK since 1975. The product is indicated for use in lactating cows, for the treatment of mastitis associated with staphylococcal and streptococcal species sensitive to cloxacillin. The product is also for the treatment of ewes, for the treatment of subclinical infections of the udder during the dry period, associated with staphylococcal species and Trueperella pyogenes sensitive to cloxacillin.

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. 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.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains cloxacillin sodium and the excipients butylhydroxyanisole, castor oil, (hydrogenated), silica, (hydrophobic colloidal) and arachis oil (refined). The container system consists of low density polyethylene (LDPE) intramammary syringes comprising dual nozzle, barrel and cap.

Pack size:

12 intramammary syringes and cleaning towels per carton.

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.

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 manufacturing method consists of sterilisation and milling of the active substance, followed by mixing and preparation of the excipients. The active substance is added to the excipients, prior to mixing and aliquoting of the product. 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 cloxacillin sodium, 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, and is controlled by a current Certificate of Suitability.

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 are suitably monographed in the Ph. Eur.

C.4. Substances of Biological Origin

A suitable declaration was provided which complied with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products for lactose derived from calf rennet used within the product.

D. Control on intermediate products

Not applicable.

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 of the filled syringe, identification of the product components, water content, particle size, extractable mass and sterility.

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. Data were available from three batches of milled, sterile cloxacillin sodium, stored for 24 months and 25 °C/60 %RH. Non-sterile active substance may be stored for 48 months as compacted grade or 60 months as powder grade if suitably contained. Overall, a stability of 36 months was established when packaged appropriately.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Do not store above 25 °C.
Store in a dry place.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and pharmaceutical equivalence with a reference product was established, and a bio-waiver (formulation identical to reference product) was agreed, results of safety and residue studies tests were 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

Pharmacological Studies

In accordance with paragraph d) of section 7.1 of the Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2), a bioequivalence study was not presented as the following condition has been met: "*The formulations are identical (identical active substances and excipients as well as physicochemical properties [e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process*])". Therefore, a bioequivalence study is not required, and Orbolan Lactating 200 mg intramammary suspension for cattle and sheep can be considered to be bioequivalent to Orbenin LA 200 mg intramammary suspension. As a result no pharmacological, toxicological or studies of other effects are presented.

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, and are identical to the reference product:

- 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 reaction 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.

Environmental Safety

The product will only be used in a small number of animals in a flock or herd, the manure from which may be spread onto land. As a result it is considered that the environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

No residue depletion studies were conducted because the product is identical to the reference product.

Withdrawal Periods

Based on the data provided, the withdrawal periods for the product, where permitted are:

- Cattle - milk: 96 hours
- Not authorised for use in sheep producing milk for human consumption.
- Cattle and sheep - meat and offal: 7 days.

IV. CLINICAL ASSESSMENT (EFFICACY)

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

IV.I. Pre-Clinical Studies

Tolerance in the Target Species

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

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

As this is a generic application according to Article 13 (1), and pharmaceutical equivalence with a reference product has been established clinical data were not required. The efficacy claims for this product are equivalent to those of the reference product.

Field Trials

As this is a generic application according to Article 13 (1), and pharmaceutical equivalence with a reference product has been established, clinical data 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 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 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.

•	31 October 2018	Change in RMS from UK to DE.
•	25 September 2018	Change in the contact details of the QPPV of an existing pharmacovigilance system as described in the DDPS.
•	13 June 2017	Change of specifications of a former non Pharmacopoeial excipient starting material to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State
•	25 May 2016	Variation to include cleaning towels in the packaging.