IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Qivitan LC 75 mg intramammary ointment for lactating cows

PRODUCT SUMMARY

EU Procedure Number	IE/V/0480/01 (formerly UK/V/0641/001)
Name, Strength, Pharmaceutical Form	Qivitan LC 75 mg intramammary ointment for lactating cows
Active Substances(s)	Cefquinome sulfate
Applicant	LIVISTO Int'l, S.L. Av. Universitat Autònoma, 29 08290 Cerdanyola des Vallès Barcelona E-08950 Spain
Legal Basis of Application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Target Species	Cattle
Indication For Use	For the treatment of clinical mastitis in the lactating cow caused by the following cefquinome-sensitive organisms: *Streptococcus uberis, Streptococcus dysgalactiae, Staphylococcus aureus* and *Escherichia coli*.
ATC Code	QJ51DE90
Date of conclusion of the decentralised procedure	28 March 2018 (UK) 01 June 2018 (IE)
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Austria, Belgium, Croatia, Cyprus, France, Germany, Greece, Hungary, Ireland (now RMS), Italy, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid' application, in accordance with Article 13 (3) of Directive 2001/82/EC, as amended. The product is locally acting, and therefore bioequivalence using plasma level of the active substance could not be demonstrated. A waiver from the requirement to conduct *in vivo* studies was permissible as outlined in the Guidance of conduct of efficacy studies for intramammary products for use in cattle (EMA/CVMP/EWP/14272/2011). The reference product is Cobacatan LC 75 mg Intramammary Ointment for Lactating Cows, marketed in the UK since March 1996.
The product is indicated for the treatment of clinical mastitis in the lactating cow caused by the cefquinome-sensitive organisms: *Streptococcus uberis*, *Streptococcus dysgalactiae, Staphylococcus aureus* and *Escherichia coli*.
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

II.A. Composition

The product, (8 g in a syringe), contains 75 mg cefquinome (as 88.92 mg cefquinome sulfate). The excipients are white soft paraffin and liquid paraffin.

The container/closure system consists of the following:

Prefilled 8 g single-dose intramammary syringe consisting of white opaque LDPE barrel with white opaque LDPE plunger and white opaque LDPE cap.
Cleaning towels (smooth, white crepe paper impregnated with isopropyl alcohol/benzalkonium chloride) individually wrapped.
Cardboard boxes of 3 syringes and 3 cleaning towels.
Cardboard boxes of 12 syringes and 12 cleaning towels.
Cardboard boxes of 24 syringes and 24 cleaning towels.
Cardboard boxes of 36 syringes and 36 cleaning towels.

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 a simple addition, mixing and sterilisation process. The product is then packaged for sale.

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 cefquinome, an established active for which the applicant provided specification. 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. An acceptable Certificate of Analysis was provided.

Packaging complies with the monograph for the rubber stoppers as cited in the European Pharmacopoeia, and with Directive 1935/2004 (EC) for the tin pack.
Excipients comply with monographs in the European Pharmacopoeia.

II.C.4. Substances of Biological Origin

No materials of animal origin are used during manufacture. A declaration of compliance with EMEA/410/01 has been provided.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Sterile micronised material is treated as intermediate product. Tests carried out on the immediate product are: appearance, identification of the active substance, colour and clarity of solution, pH, optical rotation, sulphated ash content, heavy metal content, water content, related substances, presence of endotoxins, sterility, assay of sulfate and particle size.

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, particle size, deliverable mass, viscosity, identification of active substance, assay of active substance and related substances and sterility.

II.F. Stability

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

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Do not store above 25°C.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the legal basis of the application, there was no requirement to submit pharmacological and toxicological data. A user risk assessment (URA) and environmental risk assessment (ERA) were included. The proposed product and the reference product are identical with regards to composition, pharmaceutical form and strength.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The risk profile of the proposed product was considered to be the same as that of the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- When infusing the product, protective gloves should be worn to avoid skin contact.
- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-sensitivity to cephalosporin 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 skin rash, you should seek medical advice and show the Doctor this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.
- The cleaning towels provided with this product contain isopropyl alcohol and benzalkonium chloride, which may cause skin irritation in some people. It is recommended to wear protective gloves when using the towels.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The applicant has provided a Phase I assessment consisting of a description of the product, information on the pattern of use, and a VICH Phase I decision tree.

The $PEC_{soil\ initial}$ values of 1.7 µg/kg (intensively reared dairy cattle), and 1.1 µg/kg (pasture reared dairy cattle) are below the trigger value (100 µg/kg). As such, the assessment can end at Phase I (Question 17 of the VICH decision tree) as exposure of the environment is not extensive. The SPC and product literature carry suitable warnings.

III.B.2 Residues documentation

Residue Studies

The formulation for this product is sufficiently similar to that of the reference product such that residue depletion data are not required and the withdrawal periods of the reference product apply.

Pharmacologically active substance(s)	**Marker residue**	**Animal species**	**MRLs (µg/kg)**	**Target tissues**
Cefquinome	Cefquinome	Bovine	50 µg/kg 50 µg/kg 100 µg/kg	Muscle Fat Liver

			200 µg/kg 20 µg/kg	Kidney Milk

Withdrawal Periods
Meat and offal: 4 days
Milk: 5 days (120 hours).

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology
Pharmacokinetics
No data required.

Pharmacokinetics
A biowaiver was established under Guideline EMA/CVMP/EWP/141272/2011, which states that:

'Efficacy and tolerance studies may be waived for generic products that are fully identical to the reference product.

Efficacy studies may also be waived if the following conditions are fulfilled: the proposed product has the same pharmaceutical form and contains qualitatively and quantitatively the same active substance(s) (same salts), the excipients of the generic are qualitatively and quantitatively very similar compared to the reference product, and the physicochemical properties (e.g. crystalline form, particle size distribution, viscosity, relative density, dissolution profile) of the generic product are similar to those of the reference product. Local tolerance data might be requested'.

Any differences between the formulations of the proposed and reference products were not expected to alter the disposition of the active substance. No further data were required.

Tolerance in the Target Species
No data were required due to the nature of the application.

Resistance
Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation
No data were required due to the nature of the application.

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.