IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Ubrolexin intramammary suspension for lactating dairy cows

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0221/001/MR
Name, strength and pharmaceutical form	Ubrolexin intramammary suspension for lactating dairy cows
Active substance(s)	Cefalexin (as monohydrate): Kanamycin (as monosulphate):
Marketing Authorisation Holder	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany
Legal basis of application	'Well established veterinary use' application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of procedure	02/07/2008
Target species	Cattle (lactating dairy cows)
Indication for use	Treatment of clinical mastitis in lactating dairy cows for bacteria susceptible to the combination of cefalexin and kanamycin such as *Staphylococcus aureus* (see section 5.1), *Streptococcus dysgalactiae, Streptococcus uberis* and *Escherichia coli*.
ATCvet code	QJ51RD01
Concerned Member States	AT, BE, CY, CZ, DE, EE, EL, ES, FR, HU, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK

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 website.

I. SCIENTIFIC OVERVIEW

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 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

Each 10 g (12 ml) intramammary syringe contains:
Cefalexin (as monohydrate) 200 mg
Kanamycin (as monosulphate) 100,000 I.U.
Paraffin, yellow soft
Paraffin, liquid
Immediate packaging: syringe containing 12 ml intramammary suspension consisting of a barrel with plunger and sealed sterile tip, all made of low density polyethylene. 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 at a licensed manufacturing site.
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 Cefalexin (as cefalexin monohydrate) and Kanamycin (as monosulphate) both are established active substances described in the European pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with the specifications have been provided.

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

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.

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.

F.Stability

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

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing Pharmacological Studies

Ubrolexin intramammary suspension is a combination of cefalexin and kanamycin in the ratio 1.5:1.

The applicant has conducted own studies, supplemented where necessary with bibliographical data, to characterise the pharmacological properties of the active substances when administered alone and in combination. The pharmacological properties are summarised as follows:

Pharmacodynamics

Cefalexin represents a first generation cephalosporin and belongs to the class of ß-lactam antibiotics. It provides a mainly time-dependent antibacterial activity against gram-positive pathogens by inhibiting the synthesis of the bacterial peptidoglycan cell wall.

Kanamycin belongs to the class of aminoglycosides and provides bactericidal activity against gram-negative pathogens and against *Staphylococcus aureus*. Kanamycin provides mainly a concentration-dependent antibacterial activity through inhibition of bacterial protein synthesis and reduction of translation fidelity at ribosomal level.

The combination of cefalexin and kanamycin showed a bactericidal mode of action against *Staphylococcus aureus, Streptococcus dysgalactiae, Streptococcus uberis, Streptococcus agalactiae* and *Escherichia coli.*The effect of cefalexin and kanamycin in combination is mainly time-dependent.

Minimum inhibitory concentration, checkerboard analysis, kill kinetic and post antibiotic effect data demonstrate an advantage of the combination by broadening the activity spectrum and by showing synergistic antibacterial activity: the effect of cefalexin is enhanced by kanamycin and vice versa.

Further, the combination produces a larger suppression of bacterial growth (post antibiotic effect) against all target mastitis pathogens compared with the individual compounds.

Staphylococcus aureus has the potential to evade the immune system and establish deep-seated infection in the mammary gland. Thus, as is the case for other intramammary products, bacteriological cure rates in the field are expected to be low. *In vitro* studies have demonstrated that isolates (2002-2004) of *Staphylococcus aureus* are susceptible to the combination of active substances.

In vitro studies demonstrate that isolates (collected in 2004) of *Streptococcus agalactiae* and coagulase-negative staphylococci are susceptible to the combination of active substances.

Pharmacokinetics

After intramammary infusion on two consecutive days at 24 hour intervals the absorption and distribution of both active ingredients in the blood stream were fast but limited.
Kanamycin plasma concentrations reached a C_{max} of 0.504 and 1.024 µg/ml after the first and second dose respectively at T_{max} of six and four hours respectively. Plasma cefalexin levels reached 0.85 to 0.89 µg/ml two hours after administration.

The available metabolism data indicate that both parent substances, cefalexin and kanamycin, are the major compounds with antimicrobial activity.

Following intramammary administration of the product, cefalexin and kanamycin were mainly excreted via milk during milking.The highest concentrations of kanamycin A in milk were detected 12 hours after the first dose, with concentrations ranging between 6360 to 34500 µg/kg. Kanamycin A concentrations peaked again after the second dose administration with residues detected in the range of 3790 to

22800 µg/kg. The highest concentrations of cefalexin in milk were detected at 36 hours, with concentrations ranging between 510 µg/kg and 4601µg/kg.

Toxicological Studies

The applicant has provided data to allow characterisation of the toxicological profile of the active substances. The data provided and the interpretation of those data are in line with the toxicological profiles detailed in the relevant EMEA Maximum Residue Limit Summary Reports published on the EMEA website.
The excipients present in this formulation are commonly used in veterinary pharmaceuticals and are generally considered to be safe.

User Safety

The applicant has provided a satisfactory user safety assessment. Based on this assessment, it was noted that cephalosporins have a documented, low potential to elicit hypersensitivity reactions in man. Therefore, the standard user safety statements for penicillins and cephalosporinshave been included in section 4.5 of the SPC.

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.

1.Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
2.Take all recommended precautions. Handle this product with great care to avoid exposure by accidental contact with the skin. It is recommended to wear gloves when handling or administering the product. Wash exposed skin after use.
3.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.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

When used in accordance with label recommendations, the product does not pose a hazard to the environment.

III.B Residues Documentation

The applicant has conducted confirmatory residue depletion studies for the purposes of determining appropriate withdrawal periods for meat and milk. Both studies were conducted in accordance with relevant guidance and GLP requirements.

The analytical method was fully validated.

MRLs

Cefalexin and Kanamycin (marker residue Kanamycin A) are listed in Annex I of Council Regulation 2377/90, as amended.

MRLs for cattle are listed below:

	Cefalexin	Kanamycin A
Muscle	200 µg/kg	100 µg/kg
Liver	200 µg/kg	600 µg/kg
Kidney	1000 µg/kg	2500 µg/kg
Fat / skin	200 µg/kg	100 µg/kg
Milk	100 µg/kg	150 µg/kg

Withdrawal Periods

Based on the data provided, withdrawal periods of 10 days for meat and 5 days for milk are justified.

IV. CLINICAL ASSESSMENT

IV.APre-Clinical Studies Pharmacology

See Part III.A

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study in accordance with GLP requirements. The product (final formulation) was administered at a dose rate of a single syringe per quarter on two occasions at a 24-hour interval.

No treatment related adverse effects were seen in the study conducted. In addition, in the field studies conducted with the final formulation, no adverse effects to treatment were observed.

Laboratory Trials

The applicant has conducted various in vitro studies which show that the combination of cefalexin and kanamycin showed a bactericidal mode of action against Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberisStreptococcus agalactiae and E. coli.

MIC, checkerboard analysis, kill kinetic and post antibiotic effect data indicate an advantage of the combination by broadening the activity spectrum and by showing synergistic antibacterial activity: the effect of cefalexin is enhanced by kanamycin and vice versa. Further, the combination produces a larger suppression of bacterial growth (post antibiotic effect) against all target mastitis pathogens compared with the individual compounds.

Field Trials

The applicant conducted two clinical efficacy studies to investigate the clinical efficacy of Ubrolexin Intramammary Suspension. Both studies used control animals

that were treated with an authorised reference product. Both studies were conducted in accordance with GCP.

One study was conducted at 8 sites in the UK and 11 sites in Germany. The second study was conducted at 10 sites in the UK and 12 sites in France.

For both studies, analysis of the data shows that the bacteriological and clinical cure rates were comparable between both treatment groups (test product and reference product). Statistical analysis confirmed that Ubrolexin (when administered at a dose of one syringe per infected quarter, with a second treatment administered after 24 hours) was non-inferior to the reference products.

Based on the *in vitro* and field data provided, the claimed indication for use and the posology have been adequately justified.

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.

VI. 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 HPRA website.

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.

Changes:
None.