IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Cepritect 250 mg Intramammary Suspension for Dry Cows

PRODUCT SUMMARY

EU Procedure number	IE/V/0559/001 (formerly UK/V/0635/001)
Name, strength and pharmaceutical form	Cepritect 250 mg Intramammary Suspension for Dry Cows
Active substances(s)	Cefalonium bp (as cefalonium dihydrate)
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industial Estate Monaghan Ireland
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 subclinical mastitis at drying-off and the prevention of new bacterial infections of the udder during the non-lactating period of cows caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, *Trueperella pyogenes*, *Escherichia coli* and *Klebsiella spp*. susceptible to cefalonium.
ATCvet code	QJ51DB90
Date of conclusion of the decentralised procedure	20 September 2017 (UK) 14 December 2022 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States	Austria, Bulgaria, Czech Republic, Estonia, France, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Poland, Portugal, Slovakia, 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 determined a generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC, as amended, because bioequivalence could not be demonstrated or inferred through bioavailability studies/waivers from bioequivalence study requirements. The reference product is Cepravin Dry Cow 250 mg Intramammary Suspension, authorised in the UK since January 1993. The proposed product is quantitatively and qualitatively the same as the reference product as regards the active substance, and qualitatively the same with regard to the excipients.
Cepritect 250mg Intramammary Suspension for Dry Cows is indicated for the treatment of subclinical mastitis at drying-off and the prevention of new bacterial infections of the udder during the non-lactating period of cows caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, *Trueperella pyogenes*, *Escherichia coli* and Klebsiella spp. susceptible to cefalonium.
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 contains 250 mg cefalonium and the excipients aluminium distearate and liquid paraffin.

The container/closure system consists of single dose, 3g, white LDPE syringes with a white LDPE dual push-fit cap. These are presented in cartons of 24 and 60 syringes or buckets of 120 syringes including 24, 60 or 120 individually wrapped teat cleaning towels containing isopropyl alcohol. 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.

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 the mixing and heating of the ingredients, microbial testing, followed by transfer of the product to syringes. The syringes are then sterilised via gamma irradiation prior to packing.

II.C. Control of Starting Materials

The active substance is cefalonium, 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.

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. Both excipients are monographed in the Ph. Eur. Use of the proposed packaging materials is suitably justified.

II.C.4. Substances of Biological Origin

The applicant has provided a declaration of compliance with the *Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products* (EMEA/410/01 rev. 3).

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

Not applicable.

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, cefalonium assay, cefalonium identification, water content, particle size, viscosity, uniformity of dosage units, seal/package integrity, deliverable mass and sterility.

II.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. A range of stability tests were performed on the finished product, showing that the product was stable, stored as defined in the SPC.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

This veterinary medicinal product does not require any special storage conditions.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Due to the nature of the application, pharmacological and toxicological data, (apart from toxicological data to support the user risk assessment), were not required. The pharmacodynamic, and pharmacokinetic properties of the active substance are detailed in Section IV.

User Safety
A user risk assessment was provided in compliance with the relevant guideline which shows that the product is considered to be safe to use when following the data cited on the SPC and product literature.
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:

- Wash hands after use.
- Penicillin and cephalosporins may cause sensitisation (allergy) following injection, inhalation, ingestion or skin contact. Sensitivity to penicillin 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 a skin rash you should seek medical advice and show the doctor this warning. Swellings of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.
- The cleaning towels provided with the intramammary product contain isopropyl alcohol. Wear protective gloves if skin irritation due to isopropyl alcohol is known or suspected. Avoid contact with eyes because isopropyl alcohol can cause eye irritation.

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

Phase I:
The Phase I decision tree was followed, and as PEC_{soil} calculations showed that values of the product in soil would not exceed 100 µg/ml, the analysis stopped at Question 17. The product is not expected to pose a risk to the environment when used as recommended.

III.B.2 Residues documentation
No residue depletion studies were conducted, because the proposed product is a generic-hybrid of the reference product.

Withdrawal Periods
The following withdrawal periods were approved:
Meat and offal: 21 days
Milk:
96 hours after calving if the dry period is longer than 54 days
58 days following treatment if the dry period is less than or equal to 54 days.

IV. CLINICAL ASSESSMENT

Bioequivalence could not be demonstrated or inferred through bioavailability studies/waivers from bioequivalence study requirements. Acceptable data with regard to proof of similarity between the proposed and reference product were provided under the requirements of the Guideline (EMA/CVMP/344/199-Rev 2).

IV.I. Pre-Clinical Studies
Pharmacology
The applicant has provided a review of published literature describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Pharmacodynamics
Cefalonium is an antibacterial drug of the first generation cephalosporin group.

It acts by inhibition of cell wall synthesis, (bactericidal mode of action). The antibacterial activity is not impaired in the presence of milk.
Three mechanisms of resistance to cephalosporin are known. These are: reduced permeability of the cell wall, enzymatic inactivation and absence of specific penicillin binding sites. In Gram-positive bacteria and particularly *staphylococci*, the main cephalosporin resistance mechanism is through alteration of penicillin binding proteins. In Gram-negative bacteria resistance may consist in the production of β-lactamases, especially extended-spectrum β-lactamases.
Cefalonium is active against the following: *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis, Trueperella pyogenes, Escherichia coli* and *Klebsiella* spp.
Pharmacokinetics
Cefalonium is extensively but slowly absorbed from the udder and excreted primarily in the urine. Between 7 and 13% of the active substance is eliminated in urine on each of the first three days post dosing whilst daily excretion in faeces is < 1% over the same period.
Mean blood concentration remains fairly constant during approximately 10 days after dosing which is consistent with slow but prolonged absorption of cefalonium from the udder.
The long term persistence of cefalonium in the dry udder was examined over a time span of 10 weeks after infusion. Effective levels of cefalonium in udder secreta remain up to 10 weeks after infusion.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application, which was for a generic 'hybrid' product.

Resistance

Adequate warnings and precautions appear on the SPC and product literature.

IV.II. Clinical Documentation

Due to the nature of the application, which was for a generic 'hybrid' product, no further data were required for this section.

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.