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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(Germany)

MUTUAL RECOGNITION PROCEDURE
DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cepravin Dry Cow 250 mg

Date: 21 February 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V0184/001/
Name, strength and pharmaceutical form	Cepravin Dry Cow 250 mg, Intramammary suspension
Applicant	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleißheim Germany
Active substance(s)	Cefalonium (as cepfalonium dehydrate)
ATC Vetcode	QJ51DB90
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 caused by *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis, Arcanobacterium pyogenes, Eschericia coli* and *Klebsiella spp*. during the non-lactating period of cows.

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	24 September 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Bulgaria, Cyprus, Estonia, Germany (RMS), Latvia, Malta, The Netherlands, United Kingdom (previous RMS)

I. SCIENTIFIC OVERVIEW

This was a generic application in accordance with Article 13(1) of Directive 2001/82/EC. The reference product is Cepravin Dry Cow 250 mg Intramammary Suspsension which was first authorised in the UK in 1993. An exemption from the requirement to provide bioequivalence studies is claimed in accordance with exemption 4.c) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is quantitatively and qualitatively identical to the reference product.

The product is in intended for the treatment of subclinical mastitis at drying-off, and the prevention of new bacterial infections of the udder caused by *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis, Trueperella pyogenes, Eschericia coli* and *Klebsiella spp*. during the non-lactating period of cows. Each 3 g syringe contains 0.25 g of cefalonium (as cefalonium dehydrate). The content of one syringe should be infused into the teat canal of each quarter immediately after the last milking of the lactation. The product can be administered by short nozzle or long nozzle administration.

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 overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains cefalonium (as cefalonium dehydrate) 0.25 g and excipients aluminium distearate and liquid paraffin.

The container/closure system is a single dose 3 g white polyethylene syringe with a red polyethylene dual push-fit cap. The product comes in boxes of 20 intramammary syringes with cleaning towels or buckets of 144 intramamarry syringes with cleaning towels. The particulars of the containers and controls performed are provided and conform to the regulation.

The absence of preservative is justified.

[1] Summary of Product Characteristics.

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. Manufacturing formulae have been provided. Process validation data on several batches of the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is cefalonium (as cefalonium dehydrate) an established active substance described in the British Veterinary Pharmacopoeia. 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. The active substance in manufactured in accordance with an Active Substance Master File (ASMF). The excipient aluminium distearate in manufactured in accordance with the manufacturers own specifications, and liquid paraffin is manufactured in accordance with a European Pharmacopoeia monograph.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product. The applicant provided a declaration stating that Kepravine Dry Cow complies with Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

E. Control on intermediate products

Not applicable. There are no intermediate products.

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. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from several batches from the proposed production sites have been provided demonstrating compliance with the specification. Tests include those for appearance, identity, uniformity of extractible weight, particle size and sterility.

G. 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 re-test period of 2 years is supported for the non-milled, non-irradiated material.
Stability data on three commercial scale batches of the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product when stored under the approved conditions. Tests include those on appearance, related substances and sterility.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf life of the finished product as packaged for sale is 3 years. The following storage conditions are applicable:

- Do not store above 30 °C
- Do not freeze.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, the applicant is claiming exemption from the requirement to provide bioequivalence studies in accordance with exemption 4.c) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is quantitatively and qualitatively identical to the reference product. Therefore, the results of pharmacological and toxicological studies are not required. Warnings and precautions as listed on the product literature are similar to those of the reference product and are adequate to ensure safety of the product to users / the environment / consumers.

III.A Safety Testing

User Safety

The applicant has provided a user safety risk assessment in compliance with the relevant guideline which shows that the product is not expected to pose a risk for users

when used as recommended. Warnings and precautions as listed on the product literature are adequate to ensure safety to users and are in line with those of the reference product as follows:

- 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. Swelling of the face, lips or eyes or breathing difficulties are more serious symptoms and require urgent medical attention.

Ecotoxicity

The applicant has provided an environmental risk assessment in compliance with the relevant guideline which shows that the product is not expected to pose a risk for the environment when used as recommended on the SPC.

III.B Residues documentation

As this is a generic application according to Article 13, the applicant is claiming exemption from the requirement to provide bioequivalence studies in accordance with exemption 4.c) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is quantitatively and qualitatively identical to the reference product. Therefore, the results of residues studies are not required.

Withdrawal Periods

Meat and offal:
21 days

Milk:
Interval treatment-calving ≥ 54 days: withdrawal period = 96 hours aftercalving.

Interval treatment-calving < 54 days: withdrawal period = 54 days plus 96 hours after treatment, ensuring that at least 7 complete milkings are discarded.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, the applicant is claiming exemption from the requirement to provide bioequivalence studies in accordance with exemption 4.c) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is quantitatively and qualitatively identical to the reference product. Therefore, the results of pre-clinical and 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 risk benefit 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.

•	21 February 2018	Change in the RMS from UK to DE.
•	13 September 2017	Renewal – UK as RMS.
•	16 December 2016	Change in the safety database of an existing pharmacovigilance system as described in the DDPS.
•	28 September 2016	To tighten the shelf life limits for the active substance. Change in the specification parameters for the finished product. Addition of a test parameter for the finished product. Addition of a test limit for the finished product,
•	29 May 2015	Deletion of a manufacturing site of the active substance.
•	04 December 2014	Update to the DDPS.
•	4 June 2013	Variation to add an additional site for gamma irradiation of the active substance. This site is part of the same pharmaceutical group as the currently approved site.
•	15 July 2020	Amendment of the product information for Cepravin following a recent PSUR assessment with a wording already agreed by the authorities (updating section 4.5 (SPC) Special precautions for use in animals and to include the following information in order to harmonize the SPC with that of other products recently authorized or revised (corresponding changes were introduced to section 12 of the PAL) • "Use of the product should be based on susceptibility testing of bacteria isolated from milk samples from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria. Use of the

		product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to cefalonium and may decrease the effectiveness of treatment with other beta lactams. Dry cow therapy protocols should take local and national policies on antimicrobial use into consideration, and undergo regular veterinary review. • The feeding to calves of milk containing residues of cefalonium that could select for antimicrobial-resistant bacteria (e.g. production of beta-lactamases) should be avoided up to the end of the milk withdrawal period, except during the colostral phase. • The efficacy of the product is only established against the pathogens mentioned in Section 4.2 “Indications for use”. Consequently, serious acute mastitis (potentially fatal) due to other pathogen species, particularly Pseudomonas aeruginosa, can occur after drying off. Good hygienic practices should be thoroughly respected in order to reduce this risk.” In addition, a few editorial changes and text corrections were introduced, e.g. the product name Kepravine registered in the former RMS is no longer maintained as the registration has been withdrawn in UK.
•	21 July 2021	Addition of package size: bucket of 144 intramammary syringes.