Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Enzaprost 5 mg/ml Solution for Injection for Cattle and Pig [BE, BG, DK EE, FI, HR, IE, IT, LV, LT, PL, NL, NO, SE, SI, UK]
Enzaprost T 5 mg/ml Solution for injection for cattle and pig [AT, FR, DE, PT, ES]
Cevaprost 5 mg/ml Solution for injection for cattle and pig [EL]

PuAR correct as of 07/02/2019 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0184/001/E/007
Name, strength and pharmaceutical form	Enzaprost 5 mg/ml Solution for Injection for Cattle and Pigs
Applicant	Ceva Animal Health Ltd 90 The Broadway Chesham Buckinghamshire HP5 1EG
Active substance(s)	Dinoprost (as trometamol)
ATC Vetcode	QG02AD01
Target species	Cattle and Pigs
Indication for use	The product is indicated for its luteolytic effects in cattle and pigs. <u>Cattle:</u> - The luteolytic effect of the product can be exerted in the following therapeutic uses: - Oestrus synchronisation - Treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum, but do not express behavioural oestrus. - Induction of abortion until day 120 of pregnancy. - Induction of parturition. - As an aid in the treatment of chronic metritis or pyometra where there is a functional or persistent corpus luteum. Pigs: - Induction of parturition from day 111 of pregnancy. - Post partum use: reduction of the weaning to oestrus interval (WOI) and the weaning to fertile service interval (WFSI) in sows with puerperal problems such as metritis in herds with reproductive problems.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 of Directive 2001/82/EC, as amended.
Date of completion of the original mutual recognition procedure.	26 November 2003
Date product first authorised in the Reference Member State (MRP only)	08 January 2001
Concerned Member States for original procedure	First Use Austria, Belgium, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain. Repeat Use procedure 1st Wave Bulgaria, Estonia, Latvia, Lithuania, Poland, Slovenia. Repeat Use 2nd Wave Croatia, Denmark, Finland, Norway, Sweden

I. SCIENTIFIC OVERVIEW

This was a generic application submitted as a repeat use procedure in accordance with Article 13 (1) of Directive 2001/82/EC. The original MRP procedure was approved in November 2003. The product was first authorised in the UK via a national generic application in accordance with Article 5 (10) (a) (iii) of Directive 81/851/EEC in January 2001. The reference product for Enzaprost 5 mg/ml Solution for Injection is Lutalyse 5 mg/ml Solution for Injection which has been approved in the EU since 1981. As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product. However, the applicant did provide the results of pharmacokinetic studies to confirm bioequivalence in both target species in the original MRP procedure.

Enzaprost 5 mg/ml Solution for Injection is indicated for its lureolytic effects in cattle and pigs. In cattle in can be used for oestrus synchronisation, treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum, but do not express behavioural oestrus; induction of abortion until day 120 of pregnancy; induction of parturition; induction of parturition from day 111 of

pregnancy, and as an aid in the treatment of chronic metritis or pyometra where there is a functional or persistent corpus luteum. In pigs it can be used for induction of parturition from day 111 of pregnancy, and for postpartum use for reduction of the weaning to oestrus interval (WOI) and the weaning to fertile service interval (WFSI) in sows with puerperal problems such as metritis in herds with reproductive problems. The product should not be used in animals suffering from either acute or subacute disorders of the vascular system, gastrointestinal tract or respiratory system. It should also not be administered to pregnant animals unless it is desirable to induce parturition or interruption of pregnancy. The product should not be used in cases of known hypersensitivity to the active substance or to any of the excipients.

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 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. Composition

The product contains dinoprost 5 mg (as trometamol) and the excipients benzyl alcohol (E1519), sodium hydroxide (E524), and water for injections. The presence of preservative is justified.

The container/closure system is a colourless Type I glass vial with a chlorobutyl rubber stopper and aluminium overseal. The vials can contain 5 ml, 10 ml, 30 ml, or 50 ml and come in boxes of 10 vials of 5 ml, 5 vials of 10 ml, 1 vial of 30 ml and 1 vial of 50 ml. The particulars of the containers and controls performed are provided and conform to the regulation.

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 manufacture consists of the active substance and excipients being mixed together followed by sterilisation of the bulk and aseptic filling into sterile vials. Process validation data on the product have been presented in accordance with the relevant European guidelines.

[1] Summary of Product Characteristics.

C. Control of Starting Materials

The active substance is dinoprost (as dinoprost trometamol) an established substance described in the European 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 on 4 batches of the active substance demonstrating compliance with this specification have been provided.

The active substance is manufactured in accordance with an Active Substance Master File (ASMF).

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.

E. Control on intermediate products

There are no intermediate products involved.

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 the proposed production site have been provided demonstrating compliance with the specification.

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.

Stability data on 3 batches of the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first broaching the vial: 14 days

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

As this is a generic application according to Article 13 (1), on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of pharmacological and toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is safe for the user when used as recommended. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product and are similar to those of the reference product. User warnings specified on the SPC are:

- Prostaglandins of the PGF2α type can be absorbed through the skin and may cause bronchospasm or miscarriage.
- Care should be taken when handling the product to avoid self-injection or skin contact.
- Accidental spillage on the skin, or accidental eye contact should be washed off immediately with clean water.
- Impervious gloves should be worn to avoid skin contact.
- Accidental injection may be a particular hazard to women who are pregnant, intending to become pregnant, or whose pregnancy status is unknown and to asthmatics and persons with bronchial or other respiratory problems.
- Asthmatics and persons with bronchial or other respiratory problems should handle the product with care to avoid accidental self-injection and skin contact.
- Pregnant women, women of child-bearing age, asthmatics and persons with bronchial and other respiratory problems should not use the product or should wear disposable plastic gloves

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product will not pose a risk for the environment when used as recommended. No warnings regarding the environment are therefore required.

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13 (1), on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of residues studies are not required.

Withdrawal Periods

The withdrawal periods for this product are as follows:

Cattle: Meat and offal: 3 days
Milk: 0 hours

Pigs: Meat and offal: 2 days

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of pre-clinical and clinical studies are not required. However, the applicant did provide the results of pharmacokinetic studies to confirm bioequivalence in the target species in the original MRP procedure. Target species local tolerance studies were also provided in the original MRP procedure.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacokinetics

The results of pharmacokinetic studies in both target species were provided in support of the claim for bioequivalence. The pharmacokinetic profiles for Enzaprost 5 mg/ml Solution for Injection and the reference product were compared and were shown to be bioequivalent.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required; however, the applicant did provide the results of target species local tolerance studies in both target species in the original MRP procedure. These studies concluded that the product is well tolerated in both species under experimental conditions and that tolerance could be expected to be equivalent to that 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 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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)