Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cevaprost 250 µg/ml Solution for Injection

Date Created: November 2020

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Cevaprost 250 µg/ml Solution for Injection
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance	Cloprostenol
ATC Vetcode	QG02AD90
Target species	Cattle
Indication for use	- Silent heat - Ovarian luteal cysts - Termination of pregnancy - Induction of parturition - Removal of mummified foetus - Chronic endometritis (pyometra) - Synchronisation of oestrus (within 2 to 5 days) in groups of cyclic females treated simultaneously

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.
Date of conclusion of the procedure	21st September 2020

I. SCIENTIFIC OVERVIEW

This was a generic application for Cevaprost 250 µg/ml Solution for Injection submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Estrumate 250 µg/ml Solution for Injection, marketed in the UK since April 1981.

The product is indicated for use in cattle, for the treatment of silent heat, ovarian luteal cysts, termination of pregnancy, induction of parturition, removal of mummified foetuses, chronic endometritis (pyometra), and synchronisation of oestrus (within 2 to 5 days) in groups of cyclic females treated simultaneously. The product is administered via single or repeated 2 ml dose, by intramuscular injection. Refer to the Summary of Product Characteristics (SPC) for contraindications.

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, 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 [1] 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.

[1] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 0.250 mg/ml cloprostenol and the excipients benzyl alcohol (E1519), sodium citrate, citric acid anhydrous, sodium chloride and water for injections.

The container/closure system consists of 10 ml and 20 ml Type I colourless glass vials sealed with bromo-butyl rubber stoppers closed by aluminium flip-off caps. The product is marketed in boxes with one 10 or 20ml vial or boxes with 10 x 20ml vials. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of a 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 mixing and aliquoting of the ingredients with appropriate checks and controls.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substance is cloprostenol, 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. An Acceptable Certificate of Suitability was provided.

All excipients are monographed in the European Pharmacopoeia, and packaging is suitably controlled.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 are those for: appearance, extractable volume, pH at 20°C, assay and identification of active substance and benzyl alcohol 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. Stability data on the product shelf-life and in-use were also satisfactory. Protection from light was proposed.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.
Do not store above 25°C.
Keep vial in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Due to a biowaiver being accepted for this application as an *in vitro* equivalence study was provided, no data other than a user safety report and environmental risk assessment were required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

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:

- Direct contact with skin or mucous membranes of the user should be avoided. Prostaglandins of the F2α type may 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.**
- Pregnant women, women of childbearing age, asthmatics and persons with other respiratory tract diseases should exercise caution when handling cloprostenol.
- Those persons should avoid contact or wear disposable gloves during administration of the product.
- Accidental spillage on the skin should be washed immediately with soap and water.
- The possible incidence of bronchospasm with the product is unknown.
- Should shortness of breath result from accidental inhalation or injection, seek urgent medical advice and show the doctor this warning.
- Wash hands after use.

Environmental Safety

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

A Phase I assessment has been performed, ending at question 17, based on the PEC_{soil} values being well below the trigger value for a Phase II assessment. The disposal advice is satisfactory to ensure that there is an acceptable risk to the environment when the product is used as recommended.

Residue Depletion Studies

The active substance is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. Since a bioequivalence waiver between the proposed and reference product was agreed, the absence of residue studies can be accepted. A confirmatory residues study was performed at the injection site in animals given a single 2 ml injection containing 500 µg of cloprostenol.

This study showed that there were no detectable residues over the LLOQ within the 12 hours of administration. Therefore, a zero day withdrawal period for meat and offal has been proposed. However due to the legal basis of the application this should be the same as authorised for the reference product (1 day meat and

offal, zero hours milk), to ensure consumer safety. A zero hour withdrawal period for milk was acceptable given that bioequivalence has been demonstrated with the reference product.

Withdrawal Periods

Cattle
Meat : 1 day
Milk : zero hours

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The requirements as outlined in section 7.1.b) of the Guideline (EMA/CVMP/016/2000-Rev.3) have been met. The product is intended for intramuscular administration, the product is of the same type of solution as the reference product, the product contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary product. Therefore, the omission of additional pharmacological, toxicological and clinical data is acceptable.

Tolerance in the Target Species

Due to the nature of the application, no data were required for this section.

IV.II. Clinical Documentation

Due to the nature of the application, no 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 is favourable.

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.

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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.

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