IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Luteoplan 0.25 mg/ml solution for injection for cattle and horses

PRODUCT SUMMARY

EU Procedure number	IE/V/0771/001/DC
Name, strength and pharmaceutical form	Luteoplan 0.25 mg/ml solution for injection for cattle and horses
Active substances(s)	Cloprostenol sodium
Applicant	Syn Vet-Pharma Ireland Limited Business Service Group 7A Durands Court 45 Parnell Street Waterford X91 P381 Ireland
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Date of completion of procedure	21/12/2022
Target species	Cattle (heifers and cows), horses (mares).
Indication for use	Cattle (heifers, cows) • Synchronisation or induction of oestrus; • Treatment of ovarian dysfunction (persistent corpus luteum, luteal cyst); • Treatment of uterine disorders related to a functioning or persistent corpus luteum (endometritis, pyometra); • Induction of abortion until day 150 of pregnancy; • Expulsion of mummified foetuses; • Induction of parturition Horses (mares): • Induction of luteolysis with a functional corpus luteum
ATCvet code	QG02AD90
Concerned Member States	BE, DE, ES, FR, HU, IT, NL, PL, PT, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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

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 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

A. Qualitative and Quantitative Particulars
The product contains cloprostenol (0.25 mg/ml) as the active substance and the excipients chlorocresol, citric acid, sodium hydroxide, ethanol anhydrous and water for injections.
The container/closure system is a 20 ml amber Type I glass vial with a grey elastomeric bromobutyl rubber stopper sealed with a plastic flip off button and an aluminium cap.
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 for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials
The active substance is cloprostenol (as cloprostenol sodium), an established 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 has been provided.
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.

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability
Stability data on the active substance cloprostenol has 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 finished product has 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)

This application was made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). The reference product cited by the applicant is Estrumate (VPA10996/227/001 – Intervet Ireland Ltd.) which was first authorised in the RMS on 01/10/1991 in accordance with a full application dossier. The reference product has been authorised for in excess of ten years and can therefore be accepted as a valid reference product in this generic application.
The applicant claims exemption from the requirement to conduct bioequivalence studies in accordance with paragraph 7.1(b) of Guideline (EMEA/CVMP/016/2000-Rev.3) which permits exemption in the following cases:
"*For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that*

the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance."
The results of studies conducted to compare the composition of the generic product with that of the reference product were presented and whilst differences in the excipient profiles were observed, comparability in terms of active substance and physicochemical properties was confirmed and the differences observed between the formulations was not expected to have a significant negative impact on availability of the active substance (and consequently, safety or efficacy).
Based on the argumentation/quality data presented, it was accepted that the test product can be considered bioequivalent to the reference product and *in vivo* bioequivalence studies are not required. The safety aspects of this product are considered to be comparable to those of the reference product. 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 and consumers.

III.A Safety Testing
Pharmacological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, results of pharmacological tests are not required.

Toxicological Studies
As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, results of toxicological tests are not required.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not present any greater risk to the user than that posed by the reference product. The proposed user safety statements are broadly in line with those of the reference product, however, a number of amendments to the user safety statements to reflect those agreed for similar products approved recently through European procedures were incorporated.
The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Prostaglandins of the F2α type, such as cloprostenol, can be absorbed through the skin and may cause bronchospasm or miscarriage.
- Care should be taken when handling the veterinary medicinal product to avoid self-injection or skin contact.
- Pregnant women, women of child-bearing age, asthmatics and people with bronchial or other respiratory problems should avoid any contact with the veterinary medicinal product.
- Wear disposable impervious gloves when administering the veterinary medicinal product.
- Accidental spillage on the skin should be washed off immediately with soap and water.
- If accidental contact with eyes occurs, rinse the affected eyes thoroughly with clean, fresh water.
- In case of accidental self-injection or spillage onto the skin, seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or label to the physician.
- Do not eat, drink or smoke while handling the veterinary medicinal product.
- Chlorocresol may cause irritation and allergic reactions. People with known hypersensitivity to chlorocresol should administer the veterinary medicinal product with caution.

Environmental Risk Assessment
Phase I
For horses the environmental risk assessment can stop in Phase I and no Phase II assessment is required because only a small number of animals are expected to be treated.
For cattle, the environmental risk assessment can stop in Phase I and no Phase II assessment is required because PEC_{soil} (predicted environmental concentrations in soil) calculations have been conducted and for both pasture and intensively reared cattle, the PEC_{soil} is less than the trigger value of 100 µg/kg.

Conclusion
Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

No residue depletion studies were conducted because bioequivalence with the reference product was considered to be supported and the formulation of the generic and reference products were considered to be sufficiently similar to permit extrapolation of withdrawal periods.

MRLs
The active substance cloprostenol is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 with "No MRL required" status.

Withdrawal Periods
Based on the data provided above, the following withdrawal periods are considered justified:
Cattle
Meat and offal: 1 day.
Milk: Zero hours.
Horses
Meat and offal: 4 days.
Milk: 24 hours.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. In addition, it is considered that the risk to the target species will be similar for both the generic and the reference products. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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.