Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Lutalyse 12.5 mg/ml solution for injection for cattle

Date Created: February 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Lutalyse 12.5 mg/ml solution for injection for cattle
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance	Dinoprost (as dinoprost tromethamine)
ATC Vetcode	QD02AD01
Target species	Cattle
Indication for use	Lutalyse is indicated for its luteolytic and/or oxytocic effects in cattle. The indications for use are: 1. To more effectively control the time of oestrus in cycling cows. 2. To treat cows which have a functional corpus luteum, but do not express behavioural oestrus (sub-oestrus or silent heat). 3. To induce abortion. 4. To induce parturition. 5. For treatment of chronic metritis and pyometra. 6. For controlled breeding in normally-cycling dairy cows: - oestrus synchronisation - ovulation synchronisation in combination with GnRH or GnRH analogues as part of fixed time artificial insemination protocols.

MODULE 2

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

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

This was an application for a full marketing authorisation for an extension to the authorisation for Lutalyse 5 mg/ml solution for injection, to add a new strength of the active substance.

The product is intended for use in cattle, in order to create luteolytic and/or oxytocic effects. The SPC[1] describes the specific indications. The individual dose administered is 2 ml, equivalent to 25 mg dinoprost.

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 [2] 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] SPC – Summary of Product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 12.5 mg/ml dinoprost (as tromethamine salt), and the excipients benzyl alcohol, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system consists of a Type I glass vial with a chlorobutyl rubber stopper and aluminium seal with a flip-off disc. The product is presented in a cardboard box containing one 10 ml, 20 ml or 100 ml vial. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence 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 addition of water to a processing tank, addition of an excipient followed by addition of the active substance, followed by pH adjustment and adjustment to volume, sterile filtration, finally filling into vials is performed. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is dinoprost, 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. All excipients are monographed in the Ph. Eur.

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 on 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, colour, identification of the active substance and associated impurities, sterility, volume of injection and microbial purity. These are the specifications defined for release. For shelf-life specification, some tests are not required.

II.F. Stability

Stability data on three batches of 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. Data were provided for the active substance stored under conditions as recommended by VICH[3] guidelines for 36 months at 25°C/60% RH.

For the finished product, three batches of product were tested under the following conditions, as stipulated by VICH guidelines: 25°C/60% RH, 30°C/60% RH and 40°C/75% RH. An in-use stability study was also conducted with product stored at 4 and 12 weeks at 30°C/65% RH and for 4 and 12 weeks at 30°C/ 65% RH. A supportive study and a photostability study were also provided. All studies supported the final shelf life data provided in the SPC.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this was a line extension of an existing Marketing Authorisation, certain data were not required. Pharmacokinetic data were provided in order to demonstrate bioequivalence with the pioneer product, (see Section IV). The applicant referred to toxicological and pharmacological data originally supplied for the authorisation of Lutalyse 5 mg/ml solution for injection. Both products have the same formulation, qualitatively. It was accepted that no further data need be submitted for the current application. Safety and efficacy parameters have been suitably established for the pioneer product. A user risk assessment and environmental risk assessment were provided for the Safety Section of the dossier.

[3] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main area of concern for any adverse reactions is for pregnant women, as the active substance may cause uterine contraction. Additional concerns with regard to eye and/or respiratory irritation are cited in the SPC. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

1. Prostaglandins of the F2α type may cause bronchospasm or miscarriage.
2. These substances can be absorbed through the skin, so care should be taken when handling the product to AVOID SELF-INJECTION or SKIN CONTACT.
3. Pregnant women, women of child-bearing age, asthmatics and those with bronchial or other respiratory problems should avoid contact with the product.
4. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
5. Avoid contact with the eyes. In case of accidental contact with eyes, rinse immediately with plenty of water.
6. Accidental spillage on the skin should be washed off immediately with soap and water.
7. Wash hands after use.

Environmental Safety

The data within the environmental risk assessment is no different to that originally created for the pioneer product, and stops at Phase I. The product, which is endogenous to mammals, will be provided to cattle at acceptable doses that will not have a major impact on the environment.

III.B.2 Residues documentation

As bioequivalence was established with the pioneer product, no further residues data were required. The SPC states:

Following administration, dinoprost tromethamine is rapidly dissociated to dinoprost (PGF2α). This compound has an extremely short blood half-life of only a few minutes. Near complete clearance occurs on one to two passages through the liver or lungs. No accumulation of dinoprost or residues have been observed in blood following repeated daily injections in cattle. Highest tissue concentrations of dinoprost are observed at the injection site which deplete to background concentrations by 24-48 hours post-injection. Residue concentrations in milk of cows peak at 2 hours post-injection and decrease rapidly thereafter.

Withdrawal Periods

Cattle (meat & offal): 1 day
Cattle (milk): Zero hours

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant conducted a pharmacokinetic comparison of the proposed product and the pioneer product to demonstrate bioequivalence.

This was a single-centre, GLP[4]-compliant, single dose, to period two sequence cross-over study, with a 48 hour washout period. The objective was to determine bioequivalence via plasma analysis, between the pioneer and proposed products. Twenty-four cattle (two groups, from an initial number of thirty-two), were given a progesterone implant in preparation for administration of the product, prior to treatment. The implant was removed on day -4, and injection of the pioneer or proposed product administered according to cross-over study protocol on day -5. Animals were expected to exhibit oestrus over the three days following removal of the implant. The cattle were therefore synchronised with regard to oestrus, providing a low baseline at the start of the study for PGF2α[5].

25 mg intramuscular injections were provided to cattle, according to the allocated sequence. Blood samples were collected at a variety of time points after each administration and suitably stored until analysis. Pharmacokinetic parameters were analysed as appropriate, with relevant $AUC^{6}_{0\text{-}t}$ estimates made from trapezoidal summation, and $AUC_{0\text{-}\infty}$ and $t^{7}_{½}$ estimated from the slope of the terminal log-linear phase. Using pre-defined limits for acceptance with a 90% confidence interval for both $AUC_{0\text{-}t}$ and C_{max}[8], bioequivalence between the pioneer product and proposed product was confirmed. No abnormal adverse reactions occurred.

Tolerance in the Target Species

The applicant has conducted an injection site tolerance study. Based on the type of application, and that bioequivalence was established between pioneer and proposed product, a systemic tolerance study was not required. The amount of active substance delivered in a single dose is the same for both pioneer and proposed products (25 mg dinoprost). The proposed product has a higher concentration of the active substance, thus the requirement to assess adverse reactions at the injection site.

[4] GLP – Good Laboratory Practice.
[5] PGF2α - Prostaglandin F2 alpha.
[6] AUC – Area under the curve.
[7] T – time.
[8] C_{max} – maximum plasma concentration of active substance.

The objective of this GLP-compliant study was to demonstrate the injection site tolerance of a proposed product when administered intramuscularly in cows. 25 mg dinoprost was injected twice, at an interval of 10 days. Eight non-lactating cattle with no injections given during the test period were injected to the left and right sides of the neck alternately, twice over a 10 day period. Physical examinations were performed as appropriate, with any adverse reactions at the injection site noted. Injection sites were also analysed at necropsy. No unexpected adverse reactions noted were attributable to the product. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.II. Clinical Documentation

Bioequivalence between the pioneer and proposed product was suitably demonstrated. There was therefore no requirement for data 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

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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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