IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Bioestrovet 0.250 mg/ml solution for injection for cattle

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0359/001/DC
Name, strength and pharmaceutical form	Bioestrovet 0.250 mg/ml solution for injection for cattle
Active substance	Cloprostenol Sodium
Applicant	Vetoquinol Ireland Limited Northbrook Road Ranelagh Dublin 6 Ireland
Legal basis of application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.
Date of completion of procedure	21/12/2016
Target species	Cattle
Indication for use	Cattle (heifers, cows): - Induction of luteolysis allowing resumption of oestrus and ovulation in cyclic females when used during dioestrus - Synchronisation of oestrus (within 2 to 5 days) in groups of cyclic females treated simultaneously - Treatment of suboestrus and uterine disorders related to a functioning or persistent corpus luteum (endometritis, pyometra) - Treatment of ovarian luteal cysts - Induction of abortion until day 150 of pregnancy - Expulsion of mummified foetuses - Induction of parturition
ATCvet code	QG02AD90
Concerned Member States	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, France, Croatia, Hungary, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia and United Kingdom

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the 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; any potential adverse reactions 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 250 micrograms/ml of cloprostenol, as cloprostenol sodium, and the excipients chlorocresol, anhydrous citric acid, sodium citrate dihydrate, sodium chloride and water for injections.
The container/closure system colourless, Type I glass vials containing 20 ml, 50 ml or 100 ml, closed with a bromobutyl Type I rubber stopper coated with a Teflon film, and sealed with a polypropylene flip off 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 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 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)

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This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.The reference product is Estrumate 250 micrograms/ml solution for injection – containing 0.25 mg/ml cloprostenol sodium.

While the reference product is authorised for use in both cattle and horses, the current application sought authorisation for use in cattle only.

III.A Safety Testing

Pharmacological Studies
It was claimed that the product has the same qualitative and quantitative composition in terms of active ingredient and has the same excipients in similar amount to the reference veterinary medicinal product, Estrumate. It was noted that the development of Bioestrovet was based on the formulation of Estrumate authorised in Ireland before April 2015 containing chlorocresol as preservative. In 2015, the Estrumate marketing authorisation was varied to change the formulation by replacing chlorocresol with benzyl alcohol.

Both products are solutions for injection and they are to be used in cattle, for the same indications, at the same dose and using the same administration method.

The claim that Bioestrovet can be considered identical to the reference product, as authorised up to 2015, was based on a comparison of the qualitative and quantitative composition of both products, including a comparison of physicochemical properties. Based on these data, the applicant argued that an exemption from the requirement to conduct an *in vivo* bioequivalence study was justified in accordance with current guidance, EMA/CVMP/016/00-Rev2 ("Guideline on the conduct of bioequivalence studies for veterinary medicinal products"), Chapter 7.1 (b):

For product 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 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.

Given that bioequivalence is assumed, it was argued that the test product should be accepted as a generic of the reference product and, consequently, that the applicant is not required to provide the results of safety and residue tests or of pre-clinical and clinical trials.

Based on the argumentation/quality data presented, it was accepted that the test product can be considered bioequivalent to the reference product.While it was noted that the formulation of the reference product changed in the recent past, it was considered that the change in preservative is unlikely to have a significant negative impact on availability of the active substance (and consequently, safety or efficacy). On this point, it was acknowledged that safety and efficacy of the reference product was established based on the previously authorised formulation (that is, containing chlorocresol as preservative). In addition, it is noted that numerous generics of Estrumate, authorised recently via European procedures, contain chlorocresol rather than benzyl alcohol, as preservative.

Toxicological Studies
As this is a generic application according to Article 13 (1), and as bioequivalence with a reference product is accepted, results of toxicological tests are not required.

The safety aspects of this product are accepted as being identical to those of the reference product.

Warnings and precautions as listed on the product literature are broadly in line with those of the reference product.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk to the user associated with this product is identical to that of the reference product. The proposed user safety statements are broadly in line with those of the reference product and are generally acceptable. However, a number of amendments to the user safety

statements to reflect the user safety statements agreed for similar products approved recently through European procedures were incorporated.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Prostaglandins of the $F_{2\alpha}$ type, such as cloprostenol, 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, especially by pregnant women, women of child-bearing age, asthmatics and people with bronchial or other respiratory problems.
- Wear disposable impervious gloves when administering the product.
- Accidental spillage on the skin should be washed off immediately with soap and 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 product.

Environmental Risk Assessment

Phase I
The environmental risk assessment (ERA) can stop in Phase I because use of the product will result in environmental exposures well below the PEC_{soil} concentrations of 100 micrograms/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

Residue Studies
No residue depletion studies were conducted.

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
Given that bioequivalence with the reference product is accepted, the withdrawal periods agreed for the reference product can be applied to the test product:

Meat and offal: 1 day
Milk: Zero hours

IV. CLINICAL ASSESSMENT

See IIIA.

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product is accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Further, given that the test product is considered identical to the reference product (as authorised in the RMS up to April 2015) in terms of active substance and excipient content, it is accepted that the risks to the target animal posed by the generic product will be identical to those posed by the reference product. The proposed text for SPC sections 4.6 and 4.10 reflects that of the authorised SPC 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.