IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

DIB 1.0 g Vaginal Delivery System for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0400/001/DC
Name, strength and pharmaceutical form	DIB 1.0g Vaginal delivery system
Active substance(s)	Progesterone
Applicant	Syn Vet-Pharma Ireland Limited Business Service Group, 7A Durands Court, 45 Parnell Street, Waterford, X91 P381, Ireland
Legal basis of application	Well established use application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of procedure	16/12/2020
Target species	Cattle
Indication for use	For the control of the oestrous cycle in cycling cows and heifers used in combination with prostaglandin F2α (PGF2α) or analogue, including synchronisation of oestrus, e.g. of donor and recipient animals for embryo transfer. For induction and synchronisation of oestrus in fixed time artificial insemination (FTAI) protocols: • In cycling cows and heifers: used in combination with PGF2α or analogue. • In cycling and non-cycling cows and heifers used in combination with Gonadotropin releasing hormone (GnRH) or analogue and PGF2α or analogue. • In non-cycling cows, used in combination with PGF2α or analogue and equine chorionic gonadotrophin (eCG).
ATCvet code	QG03DA04
Concerned Member States	BE, DE, ES, FI, FR, HU, IT, NL, PL, PT, UK(NI)

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; the slight 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 progesterone at 1.0 g/delivery system as the active substance and the excipients titanium dioxide (E171), zinc stearate and polydimethylsiloxane. The delivery system contains a core and tail component, both made from nylon.
The container/closure system consists of a tri-laminar bag consisting of a polyethylene terephthalate external sheet, an aluminium middle sheet and a polyethylene internal sheet. The bags are re-sealable using a zipper.
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 progesterone, an established active 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 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)

III.A Safety Testing
Pharmacological Studies
This marketing authorisation application was submitted in accordance with Article 13a (well-established use) of Directive 2001/82/EC, as amended.
The product contains the active substance progesterone. The product is indicated for the control of the oestrous cycle in cycling cows and heifers used in combination with prostaglandin F2α (PGF2α) or analogue, including synchronisation of oestrus, e.g. of donor and recipient animals for embryo transfer and for induction and synchronisation of oestrus in fixed time

artificial insemination (FTAI) protocols. The product is an intravaginal device which delivers 1.0 g of progesterone per the device per animal for 7 - 9 days (depending on indication).
The pharmacodynamic and pharmacokinetic properties of the active substance have been well characterised using published literature and has been reviewed previously by the CVMP in the context of an application to establish an MRL. The CVMP MRL Summary Report states that, progesterone is a naturally occurring steroid hormone. In veterinary medicine, progesterone is used in cows and mares for therapeutic (disorders of the reproductive system, including termination of an unwanted pregnancy) and zootechnical (oestrus synchronisation and preparation of donor and receptor animals in the case of embryo transfer) purposes.
Based on the literature provided, it is reported that a plasma concentration of 1-2 ng/ml of progesterone is needed to maintain plasma LH pulse frequency at a basal level that prevents follicles entering a pre-ovulatory phase of maturation. Following removal of the exogenous source of progesterone at the end of the treatment period, the rapid drop in concentrations of progesterone induces oestrus, thereby permitting synchronisation of oestrus within the herd. From published literature it has been demonstrated that when administered by intravaginal device, progesterone has a characteristic pharmacological profile. The overall plasma progesterone profile appears to be consistent with an initial rapid absorption phase with blood concentrations peaking within 1 – 2 days following application of such a device. A period of apparent steady-state concentrations then occurs around four days after application of the device. Following removal of a device, plasma concentrations fall rapidly to basal levels. The CVMP MRL Summary Report on progesterone states that the normal physiological range of progesterone in cows during oestrus is reported to be 0.2 to 8 ng/ml and during pregnancy less than 8 to 12 ng/ml.
In addition, a proprietary comparative pharmacokinetic study was conducted between the candidate product and a similar authorised product, in which a maximum mean concentration (C_{max}) of plasma progesterone in cows that had the candidate product applied was 10.51 ng/ml and progesterone plasma concentrations reduced to between 2.18 ng/ml and 5.47 ng/ml at 96 hours post application. From this study the following was accepted:

- peak plasma progesterone concentrations occurred at a similar time for both products,
- mean plasma progesterone concentrations were maintained above 2 ng/ml for 7 days for both products,
- plasma progesterone concentrations fell rapidly to basal levels following removal of both devices.

Toxicological Studies
This marketing authorisation application was submitted in accordance with Article 13a (well-established use) of Directive 2001/82/EC, as amended and as such, the applicant has made reference to published literature to characterise the toxicological properties of the active substance. The toxicological data is considered comprehensive and it can be accepted that the toxicity profile of progesterone has been adequately characterised.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline. The risk to the user has been assessed in the knowledge that similar products have been authorised in the Community in excess of 10 years for use in cattle. The risks to the user arising from dermal and ocular exposure are considered to have been satisfactorily addressed and appropriate risk mitigation measures have been proposed for inclusion in the product literature.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Progesterone is a potent steroid hormone and may cause adverse effects on the reproductive system in cases of high or prolonged exposure. Pregnant women should avoid using this product. The device should be inserted using the product specific applicator.
- Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product during insertion and removal.
- This product may cause eye irritation. Avoid accidental contact with the eyes. In case of accidental ocular exposure, flush the eyes thoroughly with water. Wash hands and exposed skin with soap and water after use.

Environmental Risk Assessment
The product is intended for single use in cattle to control breeding that may be reared outdoors on pasture. The environmental assessment concluded at Phase I, as the calculated $PEC_{soil\ initial}$ values for pasture and intensively reared cattle are all below the threshold of 100 µg/kg, assuming that 100 % of the herd is treated and 100 % of the product is excreted unchanged.

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

This marketing authorisation application was submitted in accordance with Article 13a (well-established use) of Directive 2001/82/EC, as amended and as such, the applicant has not included any propriety residue studies but has made reference to published literature, the CVMP MRL summary report on the active substance progesterone and the bioequivalence study.

MRLs

Progesterone is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as 'No MRL Required' when used only for intra-vaginal therapeutic or zootechnical use and in accordance with the provisions of Directive 96/22/EC.

Withdrawal Periods

Given the above and that the average mean concentration of plasma progesterone results in the proprietary bioequivalence study were below the normal physiological limit stated in the CVMP MRL summary report, a zero day withdrawal period for meat and offal and a zero day withdrawal period for milk are justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has evaluated target animal tolerance to the candidate product through a study conducted in the target species, with the candidate product and an authorised product containing the same active substance as a control. Each animal was administered the candidate product and the control bythe intravaginal route on two separate occasions with removal of the devices after 7 days. Detailed physical examinations were conducted and included a vaginoscopic exam. The only adverse reactions observed consisted of a slight vaginal discharge which resolved spontaneously within 7 days.
Bibliographical data have been provided which shows that the types of adverse effects observed following use of similar products, are consistent with those observed in the study conducted by the Applicant.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted a pharmacokinetic study and provided bibliographical data which show that following administration of the candidate product to the target animal species, mean plasma progesterone concentrations were attained (above 2 ng/ml) which were considered sufficient to control oestrus synchrony and ovulation.

Field Trials

In support of field efficacy, the applicant has provided a large volume of bibliographical data which evaluated similar formulations to the candidate product formulation. These data provided sufficient evidence to conclude that the proposed use of the candidate product, namely, the control of the oestrous cycle in cycling cows and heifers when used in combination with PGF2α or analogue, including synchronisation of oestrus and also for the induction and synchronisation of oestrus in fixed time artificial insemination protocols (in cycling cows and heifers, used in combination with PGF2α or analogue; In cycling and non-cycling cows and heifers, used in combination with Gonadotrophin releasing hormone or analogue and PGF2α or analogue; in non-cycling cows, used in combination with PGF2α or analogue and equine chorionic gonadotrophin) is well-established and based upon the data provided, it was accepted that the indications for this product have been adequately supported.

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.

VI. 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 HPRA website.
This section 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.

Changes:
None.