**IPAR**

**Publicly Available Assessment Report for a**
**Veterinary Medicinal Product**

Prolusyn 50 micrograms/ml solution for injection for cattle

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**PRODUCT SUMMARY**

| | |
|---|---|
| EU Procedure number | IE/V/0402/001/DC |
| Name, strength and pharmaceutical form | Prolusyn 50 micrograms/ml solution for injection for cattle |
| Active substance(s) | Gonadorelin (as gonadorelin acetate) |
| Applicant | Cyton Biosciences Ltd<br>68 Macrae Road<br>Eden Office<br>Ham Green<br>Bristol, BS20 0DD<br>United Kingdom |
| Legal basis of application | Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended. |
| Date of completion of procedure | 1st April 2020 |
| Target species | Cattle; cows and heifers |
| Indication for use | Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F2α (PGF2α) or analogue with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols.<br>Treatment of delayed ovulation. |
| ATCvet code | QH01CA01 |
| Concerned Member States | BE, FR, DE, IT, ES, UK |

**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.

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## 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 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 50 micrograms/ml of gonadorelin (as gonadorelin acetate) and the excipients sodium chloride, dipotassium phosphate, benzyl alcohol, potassium hydrogen phosphate and water for injections.
The container/closure system is amber glass type I vials closed with a grey bromobutyl stopper, 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.

*C. Control of Starting Materials*

The active substance is gonadorelin (as gonadorelin acetate), an established 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*

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

*D. Control on Intermediate Products (pharmaceuticals)*

Not applicable.

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*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.

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## III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application has been submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended, (a generic application). The reference product cited in this application is Ovarelin 50 micrograms/ml solution for injection containing gonadorelin diacetate tetrahydrate.
The safety aspects of this product are considered to be similar to that of the reference product. Warnings and precautions as listed on the product literature are in line with those approved for the reference product. **III.A Safety Testing**

***Pharmacological Studies***
The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application and therefore data on pharmacodynamics are not required.
The applicant claims exemption from the requirement to conduct bioequivalence studies in accordance with paragraph 7.1(b) of the Guideline for Conduct of Bioequivalence Studies (EMEA/CVMP/016/00-Rev.2).
Paragraph 7.1(b) of the guideline permits exemption from the requirement for bioequivalence studies 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.*"
Based on the argumentation and quality data provided by the applicant, the claimed exemption is accepted.
Studies have been conducted to determine the composition of this product compared with that of the reference product and it was accepted that the results confirm that the products are comparable in terms of composition and physicochemical properties. Consequently, systemic availability of the active substance following administration of 'Prolusyn 50 micrograms/ml' is assumed to be equivalent to that achieved following administration of the reference product 'Ovarelin 50 micrograms/ml', with the result that it was accepted that 'Prolusyn 50 micrograms/ml' and the reference product will have a similar safety and efficacy profile. Hence bioequivalence can be assumed and *in vivo* bioequivalence studies are not required. Given that bioequivalence with the authorised reference product can be accepted and that the test product is intended to be administered to the same target species, using the same routes of administration at the same dose rates as already approved for the reference product, the applicant is not required to provide the results of safety and residue tests or of pre-clinical and clinical trials.

***Toxicological Studies***
This application was submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC (as amended), i.e. a generic application. As bioequivalence with a reference product is accepted, results of toxicological tests are not required.
The safety aspects of this product are expected to be similar 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 that the product does not present any greater risk to the user than that presented by the reference product. The proposed user safety statements are broadly in line with those of the reference product and are acceptable.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

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- Gonadorelin is a Gonadotropin Releasing Hormone (GnRH) analogue which stimulates the release of sex hormones. The effects of accidental exposure to GnRH analogues in pregnant women or in women with normal reproductive cycles are unknown; therefore it is recommended that pregnant women should not administer the product, and that women of child-bearing age should administer the product with caution.
- Care should be taken when handling the product to avoid self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- Since GnRH analogues can be absorbed through the skin and benzyl alcohol may cause mild local irritation, care should be taken to avoid skin and eyes contact. In case of skin and/or eye contact, rinse immediately and thoroughly with plenty of water.
- GnRH analogues and benzyl alcohol may cause hypersensitivity (allergy). People with known hypersensitivity to GnRH analogues or benzyl alcohol should avoid contact with the veterinary medicinal product.

***Environmental Risk Assessment Phase I***

The environmental risk assessment can end at Phase I and no Phase II assessment is required.

**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 for this application. It was accepted that the similarity in formulation with the reference product was such that a difference between products with respect to residue depletion from both the primary target tissues and injection site is not to be expected. Therefore, the omission of studies investigating the depletion of residues was considered acceptable.

***MRLs***

Gonadotrophin releasing hormone is included in table 1 of the Annex to Commission Regulation (EU) No 37/2010.

| **Pharmacologically active substance** | **Marker residue** | **Animal species** | **MRL** | **Target tissues** |
|---|---|---|---|---|
| Gonadotrophin releasing hormone | Not applicable | All food producing species | No MRL required | Not applicable |

***Withdrawal periods***

Given that a difference between the test and reference products with respect to residue depletion is not to be expected it is accepted that the withdrawal periods currently authorised for the reference product can be applied to the test product. Accordingly the following withdrawal periods are considered appropriate:

| Withdrawal Period | Cattle |
|---|---|
| Meat and offal | Zero days |
| Milk | Zero hours |

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## IV. CLINICAL ASSESSMENT

As this is a generic application submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended, and exemption from the requirement to demonstrate bioequivalence with the reference product has been satisfactorily justified, safety and 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 test and the reference products.

## 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.

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