Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Dalmarelin 25 Micrograms/ml Solution for Injection for Cattle and Rabbits

Date Created: June 2023

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Dalmarelin 25 Micrograms/ml Solution for Injection for Cattle and Rabbits , Solution for injection
Applicant	Fatro S.p.A., Via Emilia 285, I-40064 Ozzano Dell'Emilia BO, Italy
Active substance	Lecirelin acetate
ATC Vetcode	QHO1CA92
Target species	Cattle and Rabbits
Indication for use	Cattle • Treatment of follicular ovarian cysts. • Induction of ovulation in cycling cows in association with artificial insemination to optimise the time of ovulation. Rabbits • Induction of ovulation. • Conception rate enhancement.

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.
Date of conclusion of the procedure	14/4/2023

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 reactions observed are indicated in the SPC.[1] 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains lecirelin acetate and the excipients glacial acetic acid, disodium phosphate dodecahydrate, sodium chloride, benzyl alcohol and water for injections.

The container/closure system consists of Type I or II glass vials or a HDOE bag. The vials are closed with a chlorobutyl rubber stopper and a flip-off aluminium cap fitted with a tamper-evident polypropylene seal. 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 a novel pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

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

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of stirring, diluting, washing and sterilising.

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 lecirelin acetate, an established active substance. 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 comply with Ph. Eur.

The packaging materials also comply with 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 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 have been provided. Batch analytical data from the proposed production site<s> have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, pH, lecirelin identification and content, benzyl alcohol identification and content, bacterial endotoxins and sterility.

II.F. Stability

Stability data on 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.

Stability data on the finished product have 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

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.
Do not store above 25 °C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that lecirelin acetate is a synthetic analogue of gonadotropin releasing hormone (GnRH). It differs by substitution of D-tertiary leucine for glycine at position 6 and replacement of glycine by ethyl amide at position 10. Consequently, it is a nonapeptide. Due to structural differences between lecirelin and natural GnRH, the lecirelin molecule shows greater persistence at the site of the specific hypophyseal receptors. The physiological action of the gonadotropins results from stimulating the maturation of the follicle, inducing ovulation and the appearance of corpora lutea in the ovary.
The applicant has also provided bibliographical data which show that intramuscular administration of 50 µg of lecirelin to cows absorption is rapid. The maximum concentration (C_{max}) of 585.5 pg/ml is obtained after 15 - 30 min (T_{max}). Concentrations of lecirelin decreased rapidly with a plasma half-life of approximately 40 min.

Toxicological Studies

The applicant has provided bibliographical data.

Single Dose Toxicity

Rats received a single SC or IM doses at doses of 25, 62.5, 125, 187.5 and 250 µg/kg. No deaths or adverse clinical observations were reported.

Repeated Dose Toxicity

Repeated dose toxicity studies of 13 weeks to two years in duration, were conduction and administered via the SC route and at doses from 0.6 mg/kg bw/day to 32 mg/kg bw/day and performed in rodent, canine and primate

species. No adverse effects were observed in either sex other than those that could ne predicted to arise as a result of the pharmacological properties of a GnRH analogue. The LOAEL was determined to be 0.6 mg/kg bw/day based on a 1 year study in rats.

Reproductive Toxicity, including Teratogenicity:

Three studies were performed. Reproductive toxicity and teratogenicity studies in rats and rabbits for leuprolide acetate administered subcutaneously demonstrated adverse effects related to the pharmacological activity of a GnRH analogue, e.g., suppression of reproductive function and reproductive organ weight decrease. Effects were observed in both sexes. Adverse effects were dose-related, affected both sexes (low dose groups often not effected) and were reversible after treatment ended.

A foetal NOAEL of 0.00024 mg/kg was determined in rabbits receiving a subcutaneous dose of leuprolide acetate on gestation day six, based upon increased foetal mortality and decreased foetal bodyweight in higher dose groups.

No significant increase in foetal malformations at any dose was observed in any of the studies provided.

Leuprolide acetate is considered to be of sufficient similarity to lecirelin in terms of structure and pharmacology such that data on leuprolide acetate, in the absence of specific data on lecirelin, are considered acceptable.

Mutagenicity

The ability of the synthetic GnRH analogue to cause reversion mutations in bacteria was assessed in an *in vitro* prokaryotic study. Different doses were used, and plates were incubated with and without metabolic activation. No dose related increase was observed with any bacterial strain, either in the presence or absence of metabolic activation. Significant increases in the frequency of cells with chromosomal aberrations were not observed nor in the frequency of micronucleated erythrocytes.

Carcinogenicity

The carcinogenicity of leuprolide acetate was investigated in rats and mice and was administered via the SC route at 0.6, 6 and 60 mg/kg bw/day in mice and at 0.6, 1.5 and 4 mg/kg bw/day in rats for two years. This lack of increased tumour incidence in mice is in line with the findings of extended repeated administration in other mammals (dogs) and primates (monkeys).

Studies of Other Effects

The applicant has provided bibliographical data which show that lecirelin is unlikely to cause hypersensitivity.

Observations in Humans

Bibliographical information was provided, and synthetic GnRH and GnRH analogues are administered parentally in man, where they are prescribed for the treatment of a variety of conditions related to the hypothalamo-pituitary-gonadal axis. Observed side-effects for GnRH analogues include reversible, relatively minor effects which are related to their primary and secondary pharmacological action.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

Lecirelin has been shown to be foetotoxic in rats. The product should not be administered by pregnant women. Women of child-bearing potential should administer the product with caution. Administration should be performed with care in order to avoid accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
GnRH-analogues may be absorbed through intact skin. In case of dermal contact wash the exposed area immediately with soap and water.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The initial predicted environmental concentration (PEC) in soil is less than 100 µg/kg. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

Residue depletion studies using the final formulation have also been conducted in cattle. Samples of milk were taken from animals at several time points. The study did reveal that using the most sensitive analytical method available (a radioimmunoassay method with an assay limit of 6 pg/ml), no lecirelin residues above 6 pg/ml were detected from 1 hour up to 12 hours after treatment.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for meat in cattle and rabbits and zero hours for milk are justified.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical information describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Tolerance in the Target Species

The pivotal study provided supporting target species tolerance in cows evaluated the tolerance of the product following intramuscular administration of doses of 1 times, 1 times repeated once after 24 hours, 3 times the highest recommended dose compared to a control saline. There were no significant effects on milk production, general behaviour or appetite and rectal temperature and heart rate remained within normal physiological ranges. Minor local injection site swelling was recorded in some animals for several days. The study supports that, at the doses tested, IM administration did not induce significant or local systemic reactions in lactating cattle.

A study was supplied to demonstrate target species safety in rabbits. Rabbits were administered a single dose at doses of 0.33 times, 0.66 times, 1 times or 2 times or a saline control, by intramuscular injection. No significant treatment associated adverse events were reported.

It can be concluded that the product is well tolerated up to 3 times or 2 times the recommended dose in cattle or rabbits respectively.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided bibliographical data which show that 50 µg lecirelin was the most effective in cattle and that rabbits were responsive to doses of 5 µg or greater.

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 is favourable.

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.

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

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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