IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Ovarelin 50 ug/ml, solution for injection for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0598/001 (UK/V/0238/001)
Name, strength and pharmaceutical form	Ovarelin 50 ug/ml, solution for injection for cattle
Active substances(s)	Gonadorelin
Applicant	Ceva Santé Animale 10, avenue de La Ballastière 33500 Libourne France
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Date of Authorisation	27 September 2007 (UK) 07 December 2007 (IE)
Date product first authorised in the Reference Member State (MRP only)	28 April 2006 (UK)
Target species	Cattle
Indication for use	Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F_{2a} ($PGF_{2\alpha}$) or analogue with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols. Treatment of delayed ovulation (repeat breeding). A repeat breeder cow or heifer is generally defined as an animal that has been inseminated at least 2 or often 3 times without becoming pregnant, despite having regular normal œstrus cycles (every 18-24 days), normal œstrus behaviour and no clinical abnormalities of the reproductive tract.
ATCvet code	QH01CA01
Concerned Member States	Austria, Belgium, Germany, Hungary, Ireland (now RMS), Luxembourg, The Netherlands, Norway, Poland, Portugal. Concerned Member States added during Repeat Use procedure (first wave): Czech Republic, Estonia, Latvia, Lithuania, Slovenia, Slovakia. 2nd wave: Croatia, Denmark, Finland, Sweden. UK added via RMS change

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

This is a repeat-use (2nd wave) mutual recognition procedure for Ovarelin 50 µg/ml, Solution for Injection for Cattle.

The product was authorised initially in the UK as a National application in 2006, then via the mutual recognition procedure (MRP) with the UK as RMS and 10 CMSs (Austria, Belgium, Germany, Hungary, Ireland, Luxembourg, Netherlands, Norway, Poland and Portugal). This MRP procedure concluded in 2007. The product then underwent a repeat-use mutual recognition

procedure with six further CMSs (Czech Republic, Estonia, Latvia, Lithuania, Slovakia and Slovenia), the procedure concluding in 2012. The applicant now wishes the product to be authorised in Croatia, Denmark, Finland and Sweden.

The application is submitted as an Article 13a well-established veterinary use application of Directive 2001/82/EC, as amended by 2004/28/EC.

Ovarelin 50 µg/ml, Solution for Injection for Cattle contains 50 µg/ml gonadorelin as active substance. The product is indicated for the induction and synchronisation of oestrus and ovulation in combination with prostaglandin F2α, or analogue, with or without progesterone as part of a Fixed Time Artificial Insemination (FTAI) protocol. It is also indicated for the treatment of delayed ovulation (repeat breeding).

The recommended dose is 100 µg of gonadorelin (as diacetate) per animal in a single injection, i.e. 2 ml of the product per animal. The dossier was presented as an addendum to the assessment report prepared for the mutual recognition procedure.

This product is an injectable solution containing gonadorelin diacetate 50 µg/ml indicated for the treatment of repeat breeding syndrome in cattle. 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance gonadorelin (as diacetate tetrahydrate) and excipients benzyl alcohol, potassium dihydrogen phosphate, dipotassium phosphate, sodium chloride and water for injections.
The choice of the formulation and presence of preservative are justified.

Colourless glass vial type I (4 ml).
Colourless glass vial type II (10, 20 and 50 ml).
Chlorobutyl stopper.

Pack sizes
Box containing 1 glass vial of 4 ml
Box containing 1 glass vial of 10 ml
Box containing 1 glass vial of 20 ml
Box containing 1 glass vial of 50 ml
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 from a licenced manufacturing site.
Process validation data on the product have been presented in accordance with the relevant guidelines.

C. Control of Starting Materials

The active substance gonadorelin diacetate is an established active substance and supporting data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified. The active substance is manufactured in accordance with the principles of good manufacturing practice for starting materials.
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 other excipients are appropriately controlled by the application of the relevant monograph of the European Pharmacopoeia.

D. 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.

E. Control on intermediate products

There are no intermediate products.

F. 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 have been provided demonstrating compliance with the specification.

G. 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.

H. Genetically Modified Organisms

Not applicable

J. 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.
Storage conditions:
Do not store above 25°C.
Keep the container in the outer carton in order to protect from light.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
Pharmacological Studies
Pharmacodynamics

The applicant has provided bibliographical data describing the therapeutic effects, secondary pharmacological effects and mode of action. The pharmacodynamic activity of gonadorelin is well established and this is assessed in detail in part IV of this assessment report.

Pharmacokinetics

The applicant has provided bibliographical data from published literature of studies in laboratory animals. The applicant has also submitted 3 studies in the target species, two with the test formulation and one with radiolabelled compound. References are also made to 4 published papers describing with various ADME aspects of the pharmacokinetics of gonadorelin. These are reported in detail in Part IV of this assessment report.

Toxicological Studies

The applicant has provided bibliographical data for the following:
Single Dose Toxicity
The applicant has submitted references to published literature, which demonstrates that the acute toxicity of gonadorelin is acceptable.
Repeated Dose Toxicity
The applicant has submitted references from published literature which supports the conclusion that repeat use of gonadorelin is not expected to have toxic effects and the data are therefore acceptable.
Reproductive Toxicity, including Teratogenicity:
The applicant has submitted references from published literature, which supports the conclusion that there are no significant reproductive toxicity effects and therefore the data are acceptable.
Mutagenicity
The applicant has submitted references from published literature which report studies on a related substance and show the absence of mutagenic potential. It is considered that gonadorelin is not mutagenic.

Carcinogenicity (if necessary):
The applicant has not submitted any specific data because gonadorelin is not mutagenic, however a reference from published literature on a related substance which did not produce systemic toxicity has been submitted to support the justification for absence of carcinogenicity studies. This is considered satisfactory.

Other Studies

Immunotoxicity studies

The applicant has submitted references from published literature relating to immunotoxicity. The central nervous system is important for the maturation of the immune system in rats during the prenatal period. It was demonstrated *in vitro* in cell cultures, that the immune proliferative responses are restored after exogenous[1] administration of gonadorelin. Gonadorelin also shows the potential utility as an immunostimulatory agent in immunodeficient states. This was demonstrated in female rats with lymphopenia and depressed CD4 counts.

Dermal studies

The applicant has submitted references from published literature, which demonstrated that dermal absorption was very low, almost negligible.

Ocular studies

The applicant has submitted references from published literature which also demonstrated very low absorption.

Observations in Humans

The applicant has submitted 6 references from published literature. Gonadorelin is widely used in human medicine in the treatment of various reproductive and hormonal based disorders. Various adverse effects have been reported, which may be local reactions associated with the site of administration, or more general reaction although these are rare as are hypersensitization reactions. It has been reported that doses up to 3 mg twice a day have been administered without any reactions.

User Safety

The applicant has submitted a user risk assessment which is considered satisfactory. The main routes of exposure are from accidental dermal or ocular contact or by the parenteral route from accidental self-injection. The risk assessment includes consideration of worst case scenarios for these routes of exposure if a vial may be accidentally broken and the product may come into contact with skin or eyes and if the contents of a multiple dose syringe are accidentally self-injected. The vials contain 2 ml of product, therefore in the case of skin or eye contact, it is likely that the quantity will be very small. The recommended dose is a single injection of 2 ml, but a veterinary surgeon may use a multiple dose syringe to avoid excessive broaching of the vial – the maximum dose would be for 5 injections giving a total volume of 10 ml and this would result in a dose of 500 µg of gonadorelin. Gonadorelin is widely used in human medicine at doses ranging from 100-1800 µg/day and in the instance of accidental self-injection it is highly unlikely that the full syringe volume would be injected. In addition, there have been some rare instances of sensitisation in humans and therefore a warning for users that are hypersensitive to GnRH [2]analogues to not use the product is proposed. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

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.

Care should be taken to avoid skin and eye contact. In case of skin contact, rinse immediately and thoroughly with water as GnRH analogues can be absorbed through the skin. In case of accidental contact with eyes, rinse thoroughly with plenty of water. People with known hypersensitivity (allergy) to GnRH analogues should avoid contact with the veterinary medicinal product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is a hormone and it is known that some hormones which enter the environment can have adverse effects in non-target species particularly aquatic organisms. However, it is not considered that further assessment is required in this case as the active is highly unlikely to reach the aquatic environment in an active form and is not different from endogenous GnRH which is excreted by all female cattle of breeding age in normal circumstances. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

The applicant has not submitted residues depletion studies based on the pharmacokinetic data and has proposed zero withdrawal periods for meat and milk. Consumer safety is considered satisfactory to support this Marketing Authorisation.

MRLs
Gonadotrphin is listed in Annex II of Council Regulation 2377/90. All the excipients have Annex II status.

Withdrawal Periods
Based on the above, a withdrawal period of zero days for meat and offal and zero hours for milk are justified.

[1] Exogenous refers to an action or object coming from the outside of a system
[2] Gonadotrophin releasing hormone

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant has provided a description of the mode of action of gonadorelin based on published literature. The pharmacodynamic properties of the gonadorelin described in the SPC are considered sufficiently comprehensive and accurate.

Pharmacokinetics
The applicant has conducted three studies with gonadorelin – two with the test formulation and one with radiolabelled compound. References are also made to published papers dealing with various absorption, distribution, metabolism and excretion aspects of the pharmacokinetics of gonadorelin.

Studies conducted with the test formulation indicate that it is rapidly absorbed following intramuscular injection in cattle. Also, whilst the absolute bioavailability might not be as high as suggested, gonadorelin does appear to be well absorbed from the injection site.

A study apparently conducted with the existing product in cows indicated that concentration increased in relation with the administered dose. From this it was concluded that the pharmacokinetics of GnRH were linear
Studies with radio-labelled GnRH have indicated a widespread distribution in body tissues and extensive protein binding following intramuscular injection. Measured elimination in the dairy cow occurred mainly via the milk and also in the urine and faeces. In addition, it is apparent from the published literature that much of the administered dose is excreted as carbon dioxide in expired air.

The information provided on the metabolism of GnRH is taken from the published literature and whilst some is based on work in other species, there is also relevant information from bovine tissues. It appears that this hormone is quite rapidly metabolised following administration by peptidases and that most of the residues excreted are inactive metabolites rather than parent compound.

Tolerance in the Target Species of Animals

The applicant has referred to studies relevant to target species tolerance. These consist of two specific studies dealing with local and general tolerance respectively and a third relates to animal safety information gained during the clinical trial.

The studies in which possible local and general effects of Ovarelin were studied under closely controlled conditions demonstrated that cattle tolerated the proposed formulation very well even at elevated dose levels and when administered at the recommended dose rate daily for three days. These findings were confirmed in the clinical trial conducted in a number of cows under normal field conditions in several European countries. In this study, there were no generalised adverse effects connected with treatment and local tolerance was the same with both active and placebo products.

The SPC accurately reflects that there are no adverse effects which might be expected.

Resistance

Gonadorelin is not known to possess any relevant activity on microorganisms or parasites. Consequently, the possibility of resistance does not arise.

IV.B Clinical Studies

Comprehensive data have been presented in the Clinical Documentation section of the dossier. Firstly, evidence from the published literature clearly demonstrates the value of GnRH in the treatment of repeat breeding syndrome (RBS) in cattle. Indeed, as stated by the Clinical Expert, the use of GnRH and its analogues is the only treatment that has been shown to be effective for this condition. Dose determination is based on the PK/PD analysis covered in the pre-clinical section and takes into account both studies with the test formulation and the findings of others working with GnRH or its analogues. The additional information and discussion provided in response to questions on this aspect have served to confirm that 100 µg GnRH per animal is the optimal dose for the gonadorelin based formulation.

Dose confirmation is based on the results of a clinical field trial conducted with a formulation containing 50 µg gonadorelin per ml in RBS cattle in typical dairy herds in four European countries. This trial was performed according to a multi-centric international, parallel, randomised and blinded experimental design conducted in accordance with GCP which compared pregnancy rates following treatment with either the test article or an excipient only placebo. The overall results indicated a small overall improvement in pregnancy rates in cattle treated with the test formulation. Optimum results required an interval of at least 4 hours from oestrus detection to injection of GnRH and that insemination should be carried out after, rather than at the same time, as injection. In those cases in which this was done, the results indicated a pregnancy rate of over 58% in animals treated with the gonadorelin formulation compared to about 43% in those receiving placebo. The results in this clinical trial form the basis for the timing of injection recommended in the proposed SPC

The applicant has also justified the proposed dosage regimen in relation to route of administration, dosage, time of injection and time of insemination. It was concluded that product gonadorelin based formulation administered at a dose rate of 100 µg at least 4 hours after the detection of oestrus and before artificial insemination increased the pregnancy rate in cattle with repeat breeding syndrome.

The benefit:risk analysis stated that gonadorelin is based on a naturally occurring peptide hormone which is converted quite rapidly in the body to inactive metabolites. Efficacy of GnRH is well documented in the published literature and the clinical trial in repeat breeder cattle confirmed the efficacy of the gonadorelin based formulation in improving pregnancy rates in such animals. It was concluded that the benefit:risk ratio is very favourable.

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.