SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ovarelin 50 µg/ml, solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition for 1 ml:

Active substance (s):
Gonadorelin (as diacetate tetrahydrate) .....50.0 µg

Excipient
Benzyl alcohol (E1519) .....15.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle: cows, heifers.

4.2 Indications for use, specifying the target species

Induction and synchronisation of oestrus and ovulation in combination with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 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.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The response of dairy cows to synchronisation protocols may be influenced by the physiological state at the time of treatment, which includes age of the cow, body condition and interval from calving.
Responses to treatment are not uniform either across herds or across cows within herds.
Where a period of progesterone treatment is included in the protocol, the percentage of cows displaying oestrus within a given period is usually greater than in untreated cows and the subsequent luteal phase is of normal duration.

4.5 Special precautions for use

Special precautions for use in animals
Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
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 cases 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 cases of skin contact, rinse immediately and thoroughly with water as GnRH analogues can be absorbed through the skin. In cases 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.

4.6 Adverse reactions (frequency and seriousness)

None.

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of a teratogenic or embryotoxic effects.
Observations in pregnant cows receiving the product in early pregnancy have not shown evidence of negative effects on bovine embryos.
Inadvertent administration to a pregnant animal is unlikely to result in adverse effects.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Intramuscular use.
100 µg of gonadorelin (as diacetate) per animal in a single injection.
i.e. 2 ml of the product per animal.

Judgement on the protocol to be used should be made by the veterinarian responsible for treatment, on the basis of the treatment objectives of the individual herd or cow. The following protocols have been evaluated and could be used:

Induction and synchronisation of oestrus and ovulation in combination with a prostaglandin F2α (PGF2α) or analogue:
- Day 0: First injection of gonadorelin (2 ml of the product)
- Day 7: Injection of prostaglandin (PGF2 α) or analogue
- Day 9: Second injection of gonadorelin (2 ml of the product) should be done.

The animal should be inseminated within 16-20 hours after the last injection of the product or at observed oestrus if sooner.

Induction and synchronisation of oestrus and ovulation in combination with a prostaglandin F2α (PGF2α) or analogue and a progesterone releasing intravaginal device:
The following FTAI protocols have been commonly reported in the literature:
- Insert progesterone releasing intravaginal device for 7 days.
- Inject gonadorelin (2 ml of the product) at the progesterone device insertion.
- Inject a prostaglandin (PGF2 α) or analogue 24 hours prior to device removal
- FTAI 56 hours after removal of the device, or
- Inject gonadorelin (2 ml of the product) 36 hours after progesterone releasing intravaginal device removal and FTAI 16 to 20 hours later.

Treatment of delayed ovulation (repeat-breeding):
GnRH is injected during oestrus.
To improve the pregnancy rates, the following timing of injection and insemination should be followed:
- injection should be performed between 4 and 10 hours after oestrus detection
- an interval of at least 2 hours between the injection of GnRH and artificial insemination is recommended.
- artificial insemination should be carried out in accordance with the usual field recommendations, i.e., 12 to 24 hours after oestrus detection.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

After single administration of up to 5 times recommended dose or one to three daily administrations of recommended dose, no measurable signs of either local or general clinical intolerance are observed.

4.11 Withdrawal periods

Meat and offal: zero days
Milk: zero hours

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Gonadotropin-releasing hormones
ATCvet code: QH01CA01

5.1 Pharmacodynamic properties

Gonadorelin (as diacetate) is a synthetic hormone physiologically and chemically identical to the Gonadotropin Releasing Hormone (GnRH) synthesized in mammalian species.
Gonadorelin stimulates the synthesis and release of the pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Its action is mediated by a specific plasma membrane receptor. Only 20% GnRH receptor occupancy is required to induce 80% of the maximum biological response. The binding of GnRH to its receptor activates protein kinase C (PKC) and also mitogen-activated protein kinase (MAPK) cascades which provide an important link for the transmission of signals from the cell surface to the nucleus allowing synthesis of the gonadotropin hormones.
In repeat breeding animals, one of the most prominent findings is the delayed and smaller preovulatory LH surge leading to delayed ovulation. Injection of GnRH during oestrus increases the spontaneous LH peak and prevents delay in ovulation in repeat breeding animals.

5.2 Pharmacokinetic particulars

Absorption
After intramuscular administration of 100 µg of gonadorelin (as diacetate) to the animal, absorption of GnRH is rapid. The maximum concentration (Cmax) of 120.0 ± 34.2 ng / litre is obtained after 15 min (Tmax). Concentrations of GnRH decreased rapidly in plasma.
The absolute bioavailability of gonadorelin (IM versus IV) was estimated to be around 89%.

Distribution
24 hours after intramuscular administration of 100µg of radiolabelled gonadorelin (as diacetate), the greatest amounts of radioactivity in tissues were measured in the main organs of excretion: liver, kidney and lungs.
8 or 24 hours after the administration, gonadorelin shows an extensive plasma protein binding of 73%.

Metabolism
Gonadorelin is a naturally occurring peptide which is rapidly broken down into inactive metabolites.

Elimination
After intramuscular administration of gonadorelin to the dairy cow, the principal excretion route is milk followed by urine and faeces. A high percentage of the administered dose is excreted as carbon dioxide in expired air.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E1519)
Potassium dihydrogen phosphate
Dipotassium phosphate
Sodium chloride
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

Material of the primary container

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

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Animal Health Ltd
Unit 3, Anglo Office Park
White Lion Road
Amersham
Buckinghamshire
HP7 9FB

8. MARKETING AUTHORISATION NUMBER

Vm 15052/4022

9. DATE OF THE FIRST AUTHORISATION

28 April 2006

10. DATE OF REVISION OF THE TEXT

April 2019

Approved: 18 April 2019