

The new-generation GnRH super-agonist

 **Dalmarelin**[®]

LECIRELIN



RESEARCH FOR REPRODUCTION



Lecirelin

A breakthrough in Pharmaceutical Design and Engineering

Dalmarelin contains Lecirelin, a new-generation GnRH super-agonist, which elicits a strong LH surge and a sustained FSH release from the anterior pituitary gland.



GnRH

GnRH (Gonadotropin-Releasing Hormone), a decapeptide produced by neurons in the basal hypothalamus, is the master hormone controlling reproductive physiology.

It stimulates the synthesis and secretion of FSH (Follicle-Stimulating Hormone) and of LH (Luteinizing Hormone) from the anterior pituitary gland. LH and FSH finally acts on the gonads to stimulate gametogenesis and steroidogenesis and to regulate the estrous cycle.

State-of-the-art research and technology have allowed to synthesize a drug which shows maximal potency, still preserving a physiological response

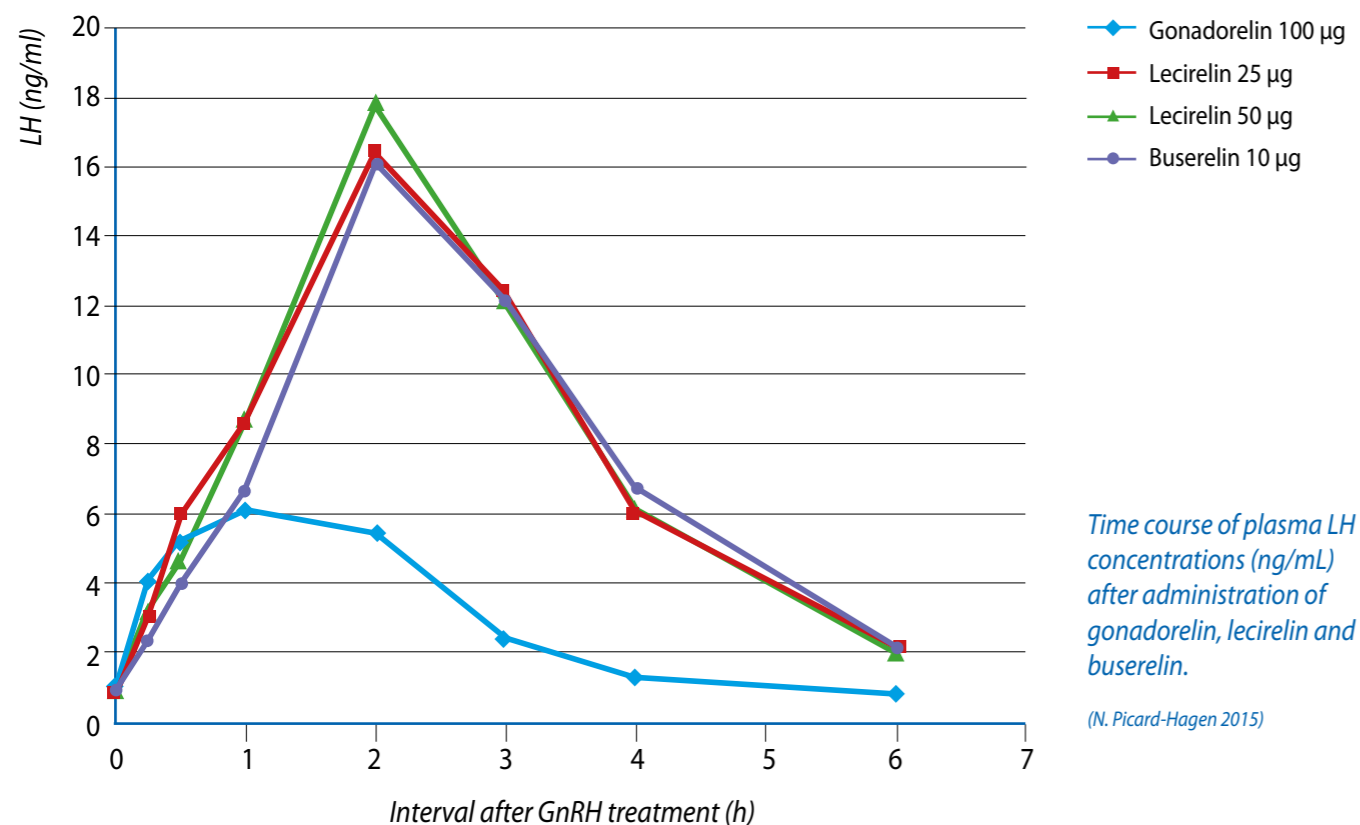
Lecirelin is a nonapeptide modeled after the natural GnRH decapeptide.

The design of this GnRH agonist has been directed toward stabilization of the molecule and increasing its affinity for the GnRH receptor.

Substitution of glycine at position 6 with **D-tert-leucin** has conferred greater stability against enzymatic degradation and increased receptor binding affinity. Replacement of glycine by **ethylamide** at position 10 has enhanced biological potency and conveyed further resistance to proteolysis.

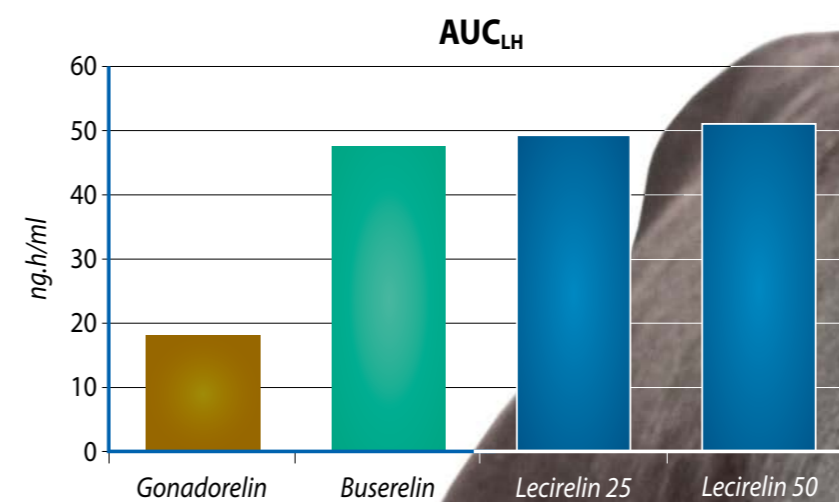
Potent action, high efficacy

For any of the clinical or management uses, the key biological response to evaluate efficacy of GnRH products is an adequate LH surge.



Time course of plasma LH concentrations (ng/mL) after administration of gonadorelin, lecirelin and buserelin.

(N. Picard-Hagen 2015)



Area under the LH concentration curve after administration of gonadorelin, lecirelin and buserelin.

(N. Picard-Hagen 2015)

Lecirelin induces a greater stimulatory effect on LH secretion than gonadorelin

LH response to three different GnRH analogs administered on day 6 or 7 of the estrous cycle was evaluated. These GnRH products were administered at the doses recommended for the induction of ovulation. In addition, for lecirelin, the biological response to a half dose was assessed. The mean C_{max} for LH was 2.5 lower after gonadorelin (6.92 ± 2.72 ng/ml) than after lecirelin at the doses of 25 and 50 µg or buserelin (16.9 ± 7.63 , 17.9 ± 5.86 , and 16.4 ± 5.70 ng.h/ml, respectively).

The LH response to GnRH administration is best assessed by calculating the area under the LH concentration curve (AUC_{LH}). The mean AUC_{LH} after a gonadorelin treatment (18.2 ± 8.20 ng. h/ml) was lower than the values obtained after lecirelin administration at the doses of 25 and 50 µg (49.7 ± 19.3 and 50.5 ± 16.3 ng.h/ml, respectively) or after buserelin treatment (47.7 ± 11.1 ng.h/ml).



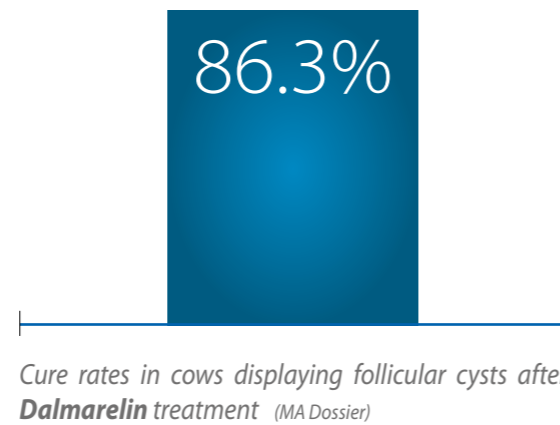
Treatment of follicular ovarian cyst

An inadequate GnRH release, incapable to trigger a pre-ovulatory LH surge, is an important component of the etiology of cystic ovary disease in cattle.

Dalmarelin induces a strong LH surge, leading to rapid luteinization and regression of follicular cysts and normalization of the estrous cycle.

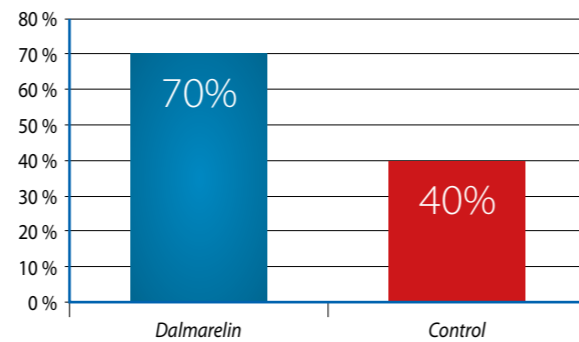
Clinical trials have shown that 86% of cows with follicular cysts are responsive to a single injection of Dalmarelin. Only a few cases require a second treatment.

HIGHEST CURE RATES AFTER JUST ONE TREATMENT



Induction of ovulation at the time of insemination

Dalmarelin administered at the time of insemination elicits a pre-ovulatory LH surge that synchronizes ovulation with insemination, induces ovulation in animals with absent or delayed ovulation and assures luteinization in cows with histories of cystic ovarian disease.



INDICATIONS AND POSOLOGY

Cow

4 ml Treatment of follicular ovarian cysts

2 ml Induction of ovulation at the time of insemination in cases of short, silent or prolonged heat

Ovulation induction in rabbit does

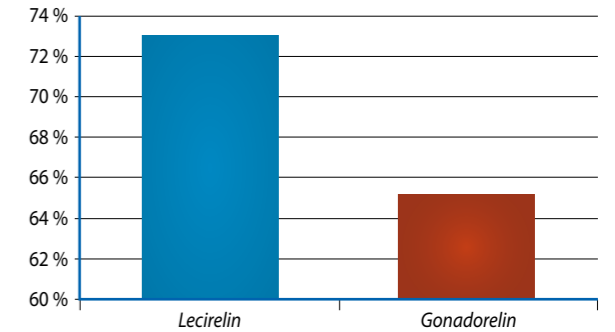
Ovulation in rabbit does during natural breeding is induced by mating.

Therefore, treatment with GnRH analogues at the time of AI is necessary due to the lack of the stimuli provided by the male.

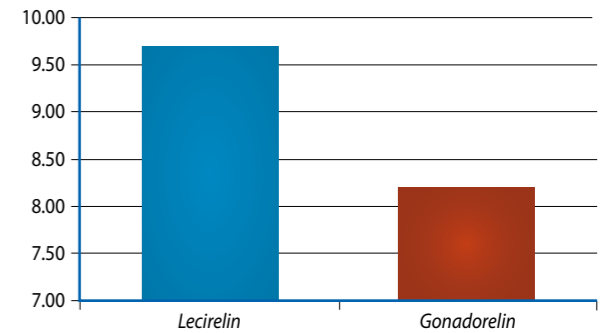
Dalmarelin is a high reliable method for inducing ovulation in rabbit does because it triggers a rapid and elevated LH peak, ensuring high ovulation rates and higher quality of oocytes and embryos.

Furthermore **Dalmarelin** does not induce antibody formation allowing for repeated treatments.

CONCEPTION RATE



LIVE BORN RABBITS PER LITTER



Conception rate and litter size in does during a 1-year experimental period were higher with lecirelin as compared with gonadorelin.

(D. Zapletal 2003)



INDICATIONS AND POSOLOGY

Rabbit

0.2 ml Induction of ovulation

0.3 ml Conception rate enhancement



The new-generation GnRH super-agonist



DALMARELIN is an injectable water solution containing Lecirelin, a long acting synthetic analogue of the hypothalamic polypeptide GnRH hormone. It induces release of LH and FSH gonadotropins on the part of the front lobe of the hypophysis. Lecirelin differs from the naturally occurring hormone in as much as it is a nonapeptide and not a decapeptide (substitution of glycine in 10th position with highly lipophilic ethyl amine group). This structural change increases affinity for specific hypophyseal receptors with resulting increases of LH and FSH levels and prolonging of effects for a period of up to 240 minutes, as opposed to the 90 minutes of the naturally occurring hormone. **DALMARELIN** is indicated for low fertility due to non-maturation or retarded maturation of follicle and ovulation due to insufficient FSH and LH hypophyseal secretion. Inoculation of gonadotropins determines exogenous effects of a physiologically non-controllable nature. Administration of **DALMARELIN**, by contrast, determines hypophyseal gonadotropin secretion controllable on the part of the organism through negative feedback. **COMPOSITION** Each ml contains: **Active ingredient:** Lecirelin 25 mcg. **Excipients** q.s. to 1 ml. **INDICATIONS Cows:** - Treatment and prevention of follicular ovarian cysts. - Induction of cycling in anoestrous cows or cows exhibiting irregular or prolonged cycles. - Short or silent heat, prolonged heat. - Repeat breeders. - Ovulation synchronization in heifers and cows in relation to prostaglandin induced heat. - Fertility enhancement. **Mares:** - Induction of ovulation. - Conception rate enhancement. **Rabbits:** - Induction of ovulation. - Conception rate enhancement. **CONTRAINDICATIONS** None. **DOSAGE AND INSTRUCTIONS FOR USE DALMARELIN** is indicated for i.m. route administration. Intravenous administration is possible, however. **Cows:** - *Treatment and prevention of follicular ovarian cysts* 2-4 ml. The highest dosage is normally indicated for persistence of cysts after a period of at least 2 weeks after first administration. For the prevention of cysts, administration of 2 ml at 14th-20th day post-partum is indicated. - *Induction of cycling in anoestrous cows or cows exhibiting irregular or prolonged cycles* 1-2 ml. In cases in which ovarian activity is not observed in the 10-12 day period following treatment, repeat treatment is indicated. - *Short or silent heat, prolonged heat* 1-2 ml. - *Repeat breeders* 1-2 ml, 2-8 h prior to insemination. - *Ovulation synchronization in heifers and cows in relation to prostaglandin induced heat* 1-2 ml, 72 h after administration of PGF_{2α}. - *Fertility enhancement* 1-2 ml immediately prior to insemination. **Mares:** - *Induction of ovulation and conception rate enhancement* 4 ml. Administration is carried out when, after gynaecological inspection, a follicle of a diameter of at least 40 mm is observed. Treatment may be repeated if, after a period of 24-36 h, ovulation is not verified. **Rabbits:** - *Induction of ovulation and conception rate enhancement* 0.2-0.3 ml. Treatment may be carried out already at 24 h post-partum. Mating or insemination must take place immediately after inoculation. **WARNINGS:** Should farm staff come into skin contact with this preparation (hands etc.), the person in question is advised immediately to carefully wash the skin in question with water and soap. **WITHDRAWAL TIMES** None. **STORAGE:** Store at room temperature (not above 25°C) and protect from light. **SHELF-LIFE:** 2 years. **PACKINGS:** Ask local distributor for available packaging options in your Country.

References

- Picard-Hagen N. et al., Effect of gonadorelin, lecorelin, and buserelin on LH surge, ovulation, and progesterone in cattle. *Theriogenology* 2015, volume 84, issue 2, pag. 177-183.
- Zapletal D et al., Effect of GnRH hormones application on performance of artificial inseminated rabbits (*Oryctolagus cuniculus*) during year. *Acta Universitatis Agriculturae et Silviculturae Mendeleianae Brunensis* 2003, volume 5, pag. 123-132.

