Cystoreline®
gonadorelin diacetate (GnRH) for induction of ovulation

Improved conception rate at single use
Cystoreline® is a synthetic replicate of the native gonadorelin releasing peptide hormone (in a diacetate tetrahydrate form) that can promptly trigger the release of gonadotropin hormones (LH and FSH) from the gonadotrope cells in the anterior pituitary.

Gonadotropin hormones start to be released in a matter of a few minutes after GnRH treatment and maximum levels of LH are reached within 2h after its treatment. Ovulation of responsive dominant follicles will then happen within 30h after its use [1].

Cystoreline® uses in cattle are:
1. To treat the repeat breeding syndrome (RBS)
2. To treat follicular cysts
3. To treat large follicles in anovular conditions
4. In synchronisation programs
GnRH mode of action

GnRH is a small peptide produced and released by the GnRH neurones in the hypothalamus, and has been shown to have a central role on the reproductive function of cattle and many others species.

1. GnRH reaches the gonadotrope cells in the anterior pituitary through the hypothalamus-hypophise capillary portal system and triggers a rapid release of LH and FSH [2], which in turn will control follicular dynamics in the ovary and consequently the production of steroids by follicles and corpus luteum (CL).

2. These steroids (estrogens and progesterone) then act in a complex feed-back loop in association with other neuroendocrine compounds such as kisspeptin (3,4) to control the production and release of GnRH in the hypothalamus.

3. Progesterone and estradiol can also influence the amount of kisspeptin released in the hypothalamus, which in turn will affect the type of GnRH release in pulses or in a surge mode. They can also alter the amount of GnRH receptors in the cell surface of the gonadotropes changing its responsiveness to GnRH [5,6].

A review of physiology of cattle

Circulating levels of progesterone and estradiol can influence the pattern of GnRH-induced LH release. Under high progesterone environment, LH is released in small pulses to maintain follicle growth. Once CL regression happens, the pulsatility of LH rapidly increases. As a result, the granulose cells of the dominant follicle produce and release more estrogens into bloodstream that will cause the estrus behavior and also a LH-surge release followed by ovulation of the dominant follicle nearly 25h later.

But this sequence of physiological events around the time of ovulation is clearly disrupted in a subpopulation of cows [7], and several research groups have reported a wide variation in regards to interval from estrus to ovulation or LH-surge to ovulation [7-9].

Indeed 25% of cows ovulate too late after estrus detection (>35h later). So if Artificial Insemination (AI) is performed 12h after estrus detection, these animals may have reduced fertilization rates due to limited lifespan of sperm cells.

Interestingly late-ovulating cows have been found to have lower LH surge near ovulation time, therefore strategic use of GnRH at initial stages of behavioral estrus can be successfully used to avoid late ovulations.

Pattern of the LH surge release in cows having normal or delayed estrus to ovulation intervals. Adapted from Bloch et al., 2006.
The different types of GnRH analogs

Several types of native-like GnRH products and other GnRH analogs are available for use in cattle. The potency of the native GnRH can be altered through aminoacid modification [10], but although potency may vary among available GnRH products, the recommended label dose for each product is normally set in order to produce adequate LH release to induce ovulation [11, 12].

So even in cows with differing levels of circulating concentrations of progesterone, the 100mcg dose of gonadorelin is adequate and normally recommended to induce ovulation in cattle even in diestrus phase [13].

More potent doesn’t mean better!

Unlike many people think, GnRH analogs synthetically built aiming extremely high potency tend to cause downregulation of GnRH receptors. Sustained binding of highly potent GnRH analogs to its receptor will make these receptors unavailable for further GnRH binding and no gonadotropin will be released.

Regarding the activities of various molecules of GnRH in causing LH release, beyond a certain level, there is ovulation whatever the released quantity so having more potency won’t make any difference.

<table>
<thead>
<tr>
<th>Active</th>
<th>Concentration</th>
<th>Dose</th>
<th>Active/Dose</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>buserelin</td>
<td>0.004 mg/ml</td>
<td>2.5 ml</td>
<td>0.01 mg</td>
<td>25</td>
</tr>
<tr>
<td>gonadorelin diacetate (Cystoreline®)</td>
<td>0.05 mg/ml</td>
<td>2 ml</td>
<td>0.01 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>gonadorelin</td>
<td>0.1 mg/ml</td>
<td>2.5 ml</td>
<td>0.25 mg</td>
<td>1</td>
</tr>
</tbody>
</table>

Full dose is needed to achieve good efficacy!

Using products below their licensed dose may cause insufficient LH peak to cause ovulation. This is shown in the graph comparing injections of 0.1mg gonadorelin diacetate and gonadorelin.

Notice that recommended dose for gonadorelin is 2.5 ml
1. Improved effect under heat stress conditions!

A trial including 1289 dairy cows under heat stress conditions showed an improvement on conception rate when used near the time of Artificial Insemination and 12 days after ovulation.

2. Equivalent effect in Repeat breeding conception rates!

The effectiveness of Cystoreline® in terms of fertility has been demonstrated through the results of a study conducted in over 100 farms in Northern France between 2003 and 2005. The histogram below compares conception rates in repeat breeding Holstein dairy cows and it shows close to significance results towards Cystoreline® when the years are combined.

3. Single dose in all uses!

It is usually advocated to use a double dose of buserelin and gonadorelin to treat cystic follicles compared to inducing ovulation in repeat breeding cows. A double dose is not required with gonadorelin diacetate (Cystoreline®) and in fact it can cause adverse effect on conception rates!
Cystoreline® uses

- Follicular cysts
  - Cyst luteinisation
  - To produce a more ideal interval from AI to ovulation

- Repeat Breeding
  - To improve the quality of the oocyte by avoiding longer intervals from luteolysis to ovulation
  - To improve circulating progesterone post AI in cows having late ovulations

- In synchronisation protocols for timed insemination
  - FTAI (Fixed Timed Artificial Insemination) protocols

- Anovular conditions
  - Stimulating the ovarian activity in the presence of a dominant follicle

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References

Ask your Ceva representative for ReprodAction advice
Cystoreline® (Gonadorelin, Solution for injection for cattle). STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS: 1 ml contains Gonadorelin (as diacetate tetrahydrate) 50 μg. Benzyl alcohol 15 mg. INDICATION: 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 oestrous cycles (every 18-24 days), normal oestrus behaviour and no clinical abnormalities of the reproductive tract. CONTRAINDICATIONS: None. ADVERSE REACTIONS: None. If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon. TARGET SPECIES: Cattle: cows, heifers. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION: Intramuscular use. 100 μg of gonadorelin (as diacetate) per animal in one single injection. i.e. 2 ml of the product per animal. 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. WITHDRAWAL PERIOD: Meat and offal: zero days, Milk: zero hours. SPECIAL STORAGE PRECAUTIONS: Keep out of the reach and sight of children. Do not store above 25°C. Keep the vial in the outer carton in order to protect from light. Do not use after the expiry date stated on the vial. Shelf-life after first opening the container: 28 days. When the container is broached (opened) for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded should be worked out. This discard date should be written in the space provided on the label. SPECIAL WARNINGS: Special precautions to be taken by the person administering the medicinal product to the animals: Care should be taken when handling the product to avoid self-injection. Accidental spillage on the skin or eyes should be washed off with plenty of water. Users known to be hypersensitive to GnRH analogues, should not use this product. Pregnancy and lactation: Laboratory studies in rats and rabbits have not produced any evidence of 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. Incompatibilities: In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIAL, IF ANY: Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

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