Proposed Package Insert (Clean)

VETERINARY MEDICINE

CYSTORELIN®

SCHEDULING STATUS:

South Africa S4

Namibia NS2

PROPRIETARY NAME (AND DOSAGE FORM):

CYSTORELIN® (injectable solution)

COMPOSITION:

Each mℓ contains 50 µg (micrograms) gonadorelin (as diacetate tetrahydrate) as the active ingredient.

The inactive ingredients are: dipotassium phosphate, potassium dihydrogen phosphate, sodium chloride, water for injection.

Preservative: Benzyl alcohol 15 *mg/ml (w/v)*

PHARMACOLOGICAL CLASSIFICATION:

C. 11.7 Reproductive system, ovulation controlling agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Gonadorelin is a synthetic decapeptide with a structure and mechanism of action identical to the natural GnRH (gonadotrophin releasing hormone) found in mammalian species. GnRH plays a key role in the reproductive system by stimulating the synthesis and release of the pituitary gonadotrophins, luteinising hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland, which results in the maturation and subsequent ovulation of the ovarian follicles. Follicular cysts arise from mature follicles which do not ovulate and are more or less luteinised, due to insufficient LH secretion by the pituitary. The presence of these follicles results in irregular and repeated oestrus. Optimal plasma levels of LH and FSH are induced after administration of the recommended exogenous gonadorelin dosage in the treatment of such cases. The FSH and LH released induce rupture of these follicular cysts, follicular maturation and subsequent ovulation.

Pharmacokinetics

Absorption

Following intramuscular (IM) administration in cows, gonadorelin is rapidly absorbed from the injection site, with a plasma half-life of approximately 20 minutes. Concentrations of gonadorelin decrease rapidly in the plasma after reaching a Cmax in the range of 120 ng/ℓ. The Tmax is 15 minutes. In comparison, the half-life of gonadorelin after intravenous (IV) administration is in the range of 4 minutes. The Cmax obtained is in the range of 322 ng/ℓ and the Tmax is 6 minutes.

The absolute bioavailability (IM versus IV) of gonadorelin in a study was shown to be about 89,3 %, indicating an effective absorption of gonadorelin.

Distribution

There is limited protein binding in the range of 5,18 % at Tmax (15 minutes) and extensive protein binding of 73 % at 8 to 24 hours post administration.

Distribution studies conducted in cows showed gonadorelin concentrations present in all the organs 8 hours post dosing, except for peri-renal fat, with the greatest concentration being present in the kidney, pancreas and pituitary gland.

24 hours post administration; the greatest concentrations of gonadorelin were measured in the main organs of excretion, liver kidney and lungs.

Metabolism

Gonadorelin is rapidly metabolised into smaller inactive peptides and amino acids.

Excretion

The major pathways of excretion are through the milk, urine and expired air.

INDICATIONS:

CYSTORELIN® is indicated for:

1) The treatment of follicular cysts in breeding cows and heifers, with or without signs of nymphomania, as part of the Repeat Breeding Syndrome (RBS). A repeat breeder cow or heifer is generally defined as an animal that has been inseminated at least 2 or 3 times without becoming pregnant, despite having regular normal oestrous cycles (every 18-24 days).
2) Regularisation of the oestrus cycle

a. Prevention of delayed ovulation by injecting **CYSTORELIN®** on the day of artificial insemination.

CONTRA-INDICATIONS:

Do not use in pregnant cows or heifers.

WITHDRAWAL PERIOD:

Withdrawal period for meat and offal: 0 days

Withdrawal period for milk: 0 hours

DOSAGE AND DIRECTIONS FOR USE:

CYSTORELIN® must be administered intramuscularly or intravenously at a dosage of 2 mℓ (100 µg gonadorelin) per cow as follows:

- To improve the pregnancy rates:

  Inject between 4 to 10 hours after oestrous detection

  An interval of at least 2 hours between injection of **CYSTORELIN®** and artificial insemination is recommended (artificial insemination should be carried out in accordance with the usual field recommendations, i.e., 12 to 24 hours post oestrous detection).

- Treatment of cystic ovaries:

  About one week after treatment, the presence of a corpus luteum can be felt on the surface of the ovary through rectal palpation. If this is not the case or if new follicular cysts are apparent, then it is necessary to repeat the treatment. Insemination of the cow in the first oestrous after treatment is usually successful, usually this is about 20 days post-injection of **CYSTORELIN®**.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

None known.

KNOWN SIGNS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Refer to "**Side-effects and Special Precautions**". In case of overdosage, symptomatic treatment should be initiated.

IDENTIFICATION:

Clear, colourless solution, practically free from visible particles. Sterile and free from visible particles.

PRESENTATION:

CYSTORELIN® is available in four multi-dose presentations:

- 4 ml Type I colourless glass vial sealed with a red-brown chlorobutyl stopper and crimped with an aluminium capsule in an outer carton.
- 10 ml Type II colourless glass vial sealed with a red-brown chlorobutyl stopper and crimped with an aluminium capsule in an outer carton.
- 20 ml Type II colourless glass vial sealed with a red-brown chlorobutyl stopper and crimped with an aluminium capsule in an outer carton.
- 50 ml Type II colourless glass vial sealed with a red-brown chlorobutyl stopper and crimped with an aluminium capsule in an outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep out of reach of children and uninformed persons.

Shelf-life of opened bottle: Use within 28 days after initial withdrawal/use of the solution.

Protect from light.

REGISTRATION NUMBER:

10/11.7/10

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ceva Animal Health (Pty) Ltd

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DATE OF NOTIFICATION OF APPROVAL OF THIS SCIENTIFIC PACKAGE INSERT

21 May 2018