CYSTORELIN® (GONADORELIN) AND SYNCHSURE™ (CLOPROSTENOL SODIUM) ARE Merial Products.

BETTER TOGETHER.

TOGETHER, CYSTORELIN AND SYNCHSURE SHOULD BE THE GO-TO COMBINATION FOR REPRODUCTIVE EFFICIENCY IN COWS AND HEIFERS.
TAKE THE GUESSWORK OUT OF YOUR BREEDING PROGRAM

CYSTORELIN and SYNCHSURE are labeled for use together to synchronize estrous cycles to allow for fixed-time artificial insemination (FTAI) in lactating dairy cows. Efficient reproduction is vital to the success of any operation, and it’s not something that should be left to chance. When used in combination, CYSTORELIN and SYNCHSURE provide shortened time to first service, increased estrus detection efficiency and improved first-service conception rate.

A MISSED HEAT CYCLE CAN COST AS MUCH AS $29¹
A MISSED PREGNANCY CAN COST AS MUCH AS $450²
EARLIER PREGNANCIES CAN INCREASE YOUR PROFITS BY $325³ PER COW³

EARLIER PREGNANCIES PROVIDE OPPORTUNITY FOR MORE LACTATIONS AND MORE MILK

AS DAYS OPEN INCREASE, PROFIT DECREASES⁴

CYSTORELIN IMPORTANT SAFETY INFORMATION: DO NOT USE IN HUMANS. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
SYNCHSURE IMPORTANT SAFETY INFORMATION: FOR ANIMAL USE ONLY, NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages women may be unaware of their pregnancies. SYNCHSURE (cloprostenol sodium) is readily absorbed through the skin and may cause abortion and/or bronchospasms: direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.
SAMPLE BREEDING SYNCHRONIZATION PROGRAMS

OVSYNCH PROGRAM

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystorelin (\text{GnRH})</td>
<td>Synchsure (\text{Prostaglandin})</td>
<td>Synchsure</td>
<td>Cystorelin</td>
<td>FTAI</td>
</tr>
</tbody>
</table>

Benefits:
- Increases the service rate in a herd of dairy cows. Instead of waiting for the cows to come into heat, all of the cows subjected to the protocol are inseminated.
- Allows cows to be bred on one day of the week to coordinate injections and artificial insemination, while also eliminating the need for heat detection.

PRE-SYNCH / OVSYNCH PROGRAM

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Day 35</th>
<th>Day 37</th>
<th>Day 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synch</td>
<td>Synchsure</td>
<td>Cystorelin</td>
<td>Synchsure</td>
<td>Cystorelin</td>
<td>FTAI</td>
</tr>
</tbody>
</table>

Benefits:
- Allows for tighter manipulation of breeding and adds greater control of breeding cycle for improved pregnancy rates.
- Increases the pregnancy rate of the ovsynch program by timing the ovsynch better to the estrus program.

DOUBLE OVSYNCH PROGRAM

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 24</th>
<th>Day 25</th>
<th>Day 26</th>
<th>Day 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystorelin</td>
<td>Synchsure</td>
<td>Cystorelin</td>
<td>Cystorelin</td>
<td>Synchsure</td>
<td>Synchsure</td>
<td>Cystorelin</td>
<td>FTAI</td>
</tr>
</tbody>
</table>

Benefits:
- Research shows use of a double ovsynch program results in the highest conception rate \(47\%\) at first service.\(^5\)
- Effectively pre-synchronizes cows to maximize progesterone during growth of the ovulatory follicle, which decreases the double ovulation rate and subsequent fraternal twinning.\(^6,7,8\)

CYSTORELIN AND SYNSCHURE ARE AVAILABLE BY PRESCRIPTION ONLY. TALK TO YOUR BI REPRESENTATIVE OR VETERINARIAN. VISIT SYNCTHEHERD.COM.

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For treatment of cystic ovaries in dairy cattle
For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
CYSTORELIN® is a sterile solution containing 43 mcg/mL of gonadorelin (GnRH) as 50 mcg/mL gonadorelin diacetate tetrahydrate suitable for intramuscular or intravenous administration according to the indication. Gonadorelin is a decapeptide composed of the sequence of amino acids—

Asp-Phe-Pro-His-Arg-Ser-Tyr-Glu-Leu-Arg-Pro-Gly-NH₂

Each mL of CYSTORELIN contains:
Gonadorelin diacetate tetrahydrate (equivalent to 43 mcg gonadorelin)...........................................50 mcg
Benzyl Alcohol ..............................................................................................................................0 mg
Sodium Chloride ........................................................................................................................................747 mg
Water for Injection ..........................................................................................................................q.s.

Each mL of CYSTORELIN contains 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow.

Dosage and Administration:

Pregnant Rats and Rabbits during Organogenesis:

The intravenous administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

INDICATIONS FOR USE:

Cystic Ovaries:

CYSTORELIN® is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-oedematous follicles with incomplete luteinization which result in nymphomaniac or ovarian estrus. Historically, cystic ovaries have been observed in an exogenous source of LH such as human chorionic gonadotropin. CYSTORELIN initiates release of endogenous LH to cause ovulation and luteinization.

Reproductive Synchrony:

CYSTORELIN® is indicated for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

INSTRUCTIONS FOR USE:

Cystic Ovaries:

The intramuscular dosing of CYSTORELIN® is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow.

Reproductive Synchrony:

The intramuscular dosage of CYSTORELIN® is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow, used in reproductive synchrony programs similar to the following:

1. Administer the first CYSTORELIN® injection (2 mL) at Time 0.
2. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first CYSTORELIN® injection.
3. Administer the second CYSTORELIN® injection (2 mL) 36 to 72 hours after the cloprostenol sodium injection.
4. Perform FTAI 0 to 24 hours after the second CYSTORELIN® injection, or inseminate cows on detected estrus using standard herd practices.

WARNINGS AND PRECAUTIONS:

Not for use in humans.
Keep out of reach of children.

WITHDRAWAL PERIODS:

No withdrawal period or milk discard time is required when used according to the labeling.

The Safety Data Sheet (SDS) contains more detailed occupational safety information. To obtain a SDS or for technical assistance, contact Merial at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary.

PHARMACOLOGY AND TOXICOLGY:

Endogenous gonadorelin is synthesized and/or released from the hypothalamus during various stages of the bovine estrus cycle following appropriate neurogenic stimuli. It passes via the hypophysial portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g., LH, FSH). Synthetic gonadorelin administered intravenously or intramuscularly also causes the release of endogenous LH or FSH from the anterior pituitary.

Gonadorelin diacetate tetrahydrate has been shown to be safe. The LD50 for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No adverse effects were noted among rats or dogs administered 120 mcg/kg/day or 72 mcg/kg/day intramuscularly for 15 days.

It had no adverse effects on heart rate, blood pressure, or EKG in unrestrained dogs at 60 mcg/kg. In anesthetized dogs it did not produce depression of myocardial or systemic hemodynamics or adversely affect coronary oxygen supply or myocardial oxygen requirements.

The intramuscular administration of 60 mcg/kg/day of gonadorelin diacetate tetrahydrate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

Further, CYSTORELIN® did not cause initiation at the site of intramuscular administration in dogs with a dose of 720 mcg/kg/day administered for seven (7) days.

TARGET ANIMAL SAFETY:

In addition to the animal safety information presented in the PHARMACOLOGY AND TOXICOLOGY section, the safety of CYSTORELIN® was established through the review and evaluation of the extensive published literature available for the use of gonadorelin-containing products.

The intramuscular administration of 1000 mcg gonadorelin diacetate tetrahydrate on five (5) consecutive days to normally cycling dairy cattle had no effect on hematology or clinical chemistry.

EFFECTIVENESS:

The intramuscular administration of 100 mcg gonadorelin diacetate tetrahydrate to allow for FTAI in lactating dairy cows was demonstrated through references to scientific literature. The use of CYSTORELIN® delivery 100 mcg gonadorelin diacetate tetrahydrate (66 mcg gonadorelin) for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows was also demonstrated through references to scientific literature.

HOW SUPPLIED:

CYSTORELIN® is available in a concentration of 50 mcg/mL, gonadorelin diacetate tetrahydrate (43 mcg/mL gonadorelin) pH adjusted with potassium phosphate (monobasic and dibasic), and Sodium Chloride, in 2 mL vials containing 100 mcg of gonadorelin diacetate tetrahydrate (as the diacetate salt) suitable for intramuscular administration.

STORAGE, HANDLING, and DISPOSAL:

Store at or below 77°F (25°C). Brief excursions to 86°F (30°C) are permitted. Use within 6 months of first puncture.

NADA 009-379. Approved by FDA
Manufactured by:
Merial Inc.
Duluth, GA 30096-4640 U.S.A.
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PROSTAGLANDIN F2ALIGUEE CAUSE RESPONSES THAT ARE DETECTABLE WITHIN 250 mcg cloprostenol/mL

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
SYNCHSURE® (cloprostenol sodium) is a synthetic prostaglandin analogue related to prostaglandin F₂α. SYNCHSURE® is indicated for intramuscular use at a low dose to induce luteolysis in beef and dairy cattle. The luteolytic action of SYNCHSURE® can be used to manipulate the estrous cycle to better fit certain management practices, to terminate pregnancies resulting from mismatings, and to treat certain conditions associated with prolonged luteal function.

USES OF SYNCHSURE:

Unobserved or Nondetected Estrus:
When a corpus luteum is present, SYNCHSURE® can be used to induce estrus. Estrus is expected to occur 2 to 5 days following injection. Treated cattle should be inseminated at the usual time following detected estrus or twice at 72 and 96 hours post injection if estrus detection is not possible or desirable.

Pyometra or Chronic Endometritis:
Endometritis is inflammation of the uterus and pyometra is characterized by the lack of cyclical estrus behavior and the presence of a persistent corpus luteum. SYNCHSURE® induces luteolysis which usually results in evacuation of the uterus and a return to normal cycling activity within 14 days after treatment.

Mummified fetus:
Induction of luteolysis with SYNCHSURE® usually results in the expulsion of the mummified fetus from the uterus. (Manual assistance may be necessary to remove the fetus from the vagina.) Normal cyclical activity usually follows.

Luteal Cysts:
Luteal cysts may cause abnormal cycling patterns in cows. Treatment with SYNCHSURE® can restore normal ovarian activity by causing regression of the luteal cyst.

Pregnancies from mismating:
SYNCHSURE® can be used to terminate unwanted pregnancies in cattle from 1 week after mating until about 5 months of gestation. The induced abortion is normally uncomplicated and the fetus and placenta are usually expelled 4 to 5 days after the injection. The efficacy of SYNCHSURE® in inducing abortion decreases after 5 months of gestation, while the risk of dystocia and additional complications increases.

Controlled Breeding:
SYNCHSURE® can be used to schedule estrus and ovulation for individual animals or a group of animals to control breeding times. SYNCHSURE® can be used in controlled breeding programs through either single or double injection protocols. Only animals with a mature corpus luteum should be treated with the single injection protocol to obtain a maximum response to the simple injection. Prior to treatment, cattle should be examined rectally and found to be anatomically normal and nonpregnant. Before a controlled breeding program is planned, the producer and his consulting veterinarian should review the operation’s breeding history, herd health and nutritional status and agree that a controlled breeding program is practical in that particular situation.

The use information provided here is not comprehensive. Talk to your veterinarian and consult the full prescribing information available at www.synchsure.com for further details on uses of SYNCHSURE®.

SAFETY AND TOXICITY:

At 50 and 100 times the recommended dose, mild side effects may be detected in some cattle including increased uneasiness, slight frothing, and milk lie-down. The risk information provided here is not comprehensive. To learn more, talk to your veterinarian about SYNCHSURE or call 1-888-637-4251. The full prescribing information can be found at www.synchsure.com.

CONTRAINDICATIONS:
SYNCHSURE® should not be given to pregnant animals whose calf is not to be abortion.

WARNINGS:

For animal use only. Do not use in humans. Keep out of reach of children. Women of childbearing age, asthmatics and persons with respiratory problems should exercise extreme caution with handling this product. In early stages, women may not be aware of their pregnancies. SYNCHSURE® is readily absorbed through the skin and may cause abortion and/or bronchospasm; direct contact with the skin should be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

PRECAUTIONS:

Careful aseptic techniques should be employed to decrease the possibility of post-injection bacterial infection. Antibiotic therapy should be employed at the first sign of infection. The Safety Data Sheet (SDS) contains more detailed occupational safety information. For technical assistance, to request an SDS, or to report a suspected adverse event, contact Merial Technical Support at 1-888-637-4251. For additional information about adverse event reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/Agricultural.

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