REPRODUCTION MANAGEMENT RESOURCES: STRATEGIES FOR SUCCESS

CONFIDENCE · CARE · COMMITMENT

DAIRY CARE365®

MERCK Animal Health

FERTAGYL® (GONADORELIN) MAKES FERTILITY SIMPLE.

The flexibility you need. The quality you demand. Now approved to get the job done, effective April 23.

FERTAGYL OFFERS:

- On-label use with Estrumate® (cloprostenol sodium) to synchronize estrous cycles to allow for fixed-time artificial insemination in lactating dairy cows.
- Treatment of ovarian follicular cysts in dairy cattle.
- Easy administration by 2mL intramuscular or intravenous injection.
- Available in 10-dose/20mL bottle. A 50-dose/100 mL bottle coming soon.

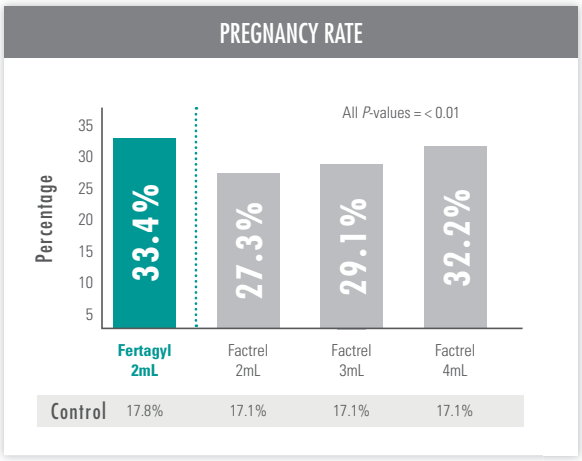
	FERTAGYL MERCK ANIMAL HEALTH	CYSTORELIN MERIAL	FACTREL ZOETIS	OVACYST BAYER	GONABREED PARNELL
ACTIVE INGREDIENT	Gonadorelin diacetate tetrahydrate	Gonadorelin diacetate tetrahydrate	Gonadorelin hydrochloride	Gonadorelin diacetate tetrahydrate	Gonadorelin acetate
FDA-APPROVED SYNCHRONIZATION CLAIM	**Yes**	No	Yes	No	Yes
EFFECT ON OVULATION[1]	**73.6%**	76.7%	55.3%	85.0%	n/a
PREGNANCY RATE	**33.4% (2mL)[2]**	n/a	27.3% - 2mL[3] 29.1% - 3mL[3] 32.2% - 4mL[3]	n/a	33.4% (1mL)[4]
CONTROL	17.8%[2]	n/a	17.1%[3]	n/a	13.63%[4]
P-VALUE	0.0051[2]	n/a	0.0123 - 2mL[3] 0.0051 - 3mL[3] 0.0011 - 4mL[3]	n/a	< 0.0001[4]
TREATMENT OF OVARIAN CYSTS CLAIM	Yes	Yes	Yes	Yes	Yes
DOSE SIZE	2mL	2mL	2 - 4mL	2mL	1mL
ROUTE OF ADMINISTRATION	IM or IV	IM or IV	IM	IM or IV	IM or IV
BOTTLE SIZE	10 and **50 dose**[5]	5 and 15 dose	10 dose	6 and 18 dose	20 and 100 dose

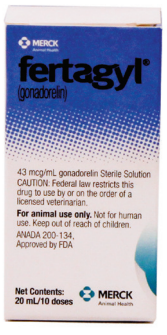
[1] Souza, A.H., et al., 2009, Comparison of gonadorelin products in lactating dairy cows, *Theriogenology.* 72:271-279.
[2] Food and Drug Administration, Office of New Animal Drug Evaluation, Freedom of Information Summary, 2015. www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm442410.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
[3] Chenault, J.R., et al., 2014, Evaluation of gonadotropin-releasing hormone hydrogen chloride at 3 doses with prostaglandin F_{2a} for fixed-time AI in dairy cows, *J. Dairy Sci.* 97:2816-2821.
[4] Freedom of Information Summary, 2013. ANADA 200-541, GONABREED (gonadorelin acetate) injectable solution. www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM338852.pdf
[5] **50-dose bottle coming soon**

For complete information on use, ask your veterinarian and refer to product package insert.

FERTILITY FROM FDA SYNCHRONIZATION CLAIM STUDIES.

Fertagyl and Estrumate outperformed the control as did Factrel and Lutalyse in separate research trials submitted to the FDA to secure synchronization claim approvals. Fertagyl, used in combination with Estrumate in a fixed-time AI program, resulted in pregnancy rates of 33.4 percent vs. 17.8 percent (control), and Factrel/Lutalyse at 27.3, 29.1 and 32.2 percent for 2, 3 and 4 mL vs. control (17.1 percent). See chart.





Food and Drug Administration, Office of New Animal Drug Evaluation, Freedom of Information Summary, 2015. www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm442410.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Chenault, J.R., et al., 2014, Evaluation of gonadotropin-releasing hormone hydrogen chloride at 3 doses with prostaglandin F_{2a} for fixed-time AI in dairy cows, *J. Dairy Sci.* 97:2816-2821

ESTRUMATE® (CLOPROSTENOL SODIUM) BRINGS THE HEAT.

Estrumate allows you to use AI (artificial insemination) more conveniently, to control breeding and calving intervals and to schedule the entry of heifers into the milking herd.

ESTRUMATE PROVIDES:

- Increased convenience of heat detection and controlled breeding.
- Improvement of luteolysis and reproductive performance.
- Convenient, low-volume 2mL intramuscular injection.
- Reliable, fast onset of estrus.[1]
- Available in both 10-dose/20mL and 50-dose/100 mL bottles.

Estrumate®
(cloprostenol sodium)

REDUCE REARING COSTS AND MAKE HEIFERS PROFITABLE QUICKER WITH ESTRUMATE.

Don't overlook your breeding-age heifers in your dairy reproductive management protocols. Heifer rearing costs are the second largest expense on most dairies. With Estrumate, you can expedite breeding and save on feed costs. Your first-calf heifers can join the milking string and start generating income sooner – easily justifying the $2 Estrumate investment.[2]

WITHOUT PROSTAGLANDIN:

- On average, it takes 12 days to first breeding.[2]
- Heifers showing estrus is approximately five percent per day (approximately 13 percent in the first three days).[2]

WITH PROSTAGLANDIN:

- Days to first breeding will be reduced to approximately eight days.[2]
- Prostaglandin will bring heifers into estrus sooner with the largest portion in the first three days (approximately 48 percent).[2]

This is a four days-on-feed savings which at $2 per day feed cost equals an $8 savings generated from just one $2 Estrumate injection. This profit margin will continue to grow if using Estrumate every 11 days. Also, this will expedite your heifers out of the unproductive phase and into the profitable milking phase.

At 50 and 100 times the recommended dose, mild side effects may be detected in some cattle; these include increased uneasiness, slight frothing and milk let-down. For complete safety information, refer to product package insert.

[1] Estrumate (prescribing information), Summit, NJ: Schering-Plough Animal Health; 2006.

[2] Stevenson, J.L., et. al., 2008, Effect of breeding protocols and reproductive tract score on reproductive performance of dairy heifers and economic outcome of breeding programs, *J. Dairy Sci.* 91:3424-3438.

FOR MORE INFORMATION ABOUT MERCK ANIMAL HEALTH'S PRODUCTS AND SERVICES, ASK YOUR VETERINARIAN AND VISIT **DairyCare365.com.**

ANADA 200-134, Approved by FDA

FERTAGYL®

(GONADORELIN)

43 mcg/mL gonadorelin Sterile Solution

FOR THE TREATMENT OF CYSTIC OVARIES IN DAIRY CATTLE

FOR USE WITH ESTRUMATE (CLOPROSTENOL INJECTION) TO SYNCHRONIZE ESTROUS CYCLES TO ALLOW FOR FIXED TIME ARTIFICIAL INSEMINATION (FTAI) IN LACTATING DAIRY COWS

CAUTION
FEDERAL LAW RESTRICTS THIS DRUG TO USE BY OR ON THE ORDER OF A LICENSED VETERINARIAN.

DESCRIPTION

Fertagyl is a sterile solution containing 43 mcg gonadorelin (GnRH; as gonadorelin acetate) per milliliter suitable for intramuscular or intravenous administration according to the indication.

Gonadorelin is a decapeptide composed of the sequence of amino acids –

5 -oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 with a molecular weight of 1182.32 and empirical formula $C_{55}H_{75}N_{17}O_{13}$.

Gonadorelin is the hypothalamic releasing factor responsible for the release of gonadotropins (e.g., LH, FSH) from the anterior pituitary.

Synthetic gonadorelin is physiologically and chemically identical to the endogenous bovine hypothalamic releasing factor.

PHARMACOLOGY AND TOXICOLOGY

Endogenous gonadorelin is synthesized by and/or released from the hypothalamus during various stages of the bovine estrous cycle following appropriate neurogenic stimuli. It passes via the hypophyseal portal vessels, to the anterior pituitary to effect the release of gonadotropins (e.g. LH, FSH).

Synthetic gonadorelin administered intramuscularly or intravenously also causes the release of endogenous LH and FSH from the anterior pituitary.

Gonadorelin acetate has been shown to be safe. The LD_{50} for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mcg/kg, respectively. No untoward effects were noted among rats or dogs administered 120 mcg/kg/day intramuscularly or 72 mcg/kg/day intravenously for 15 days.

It had no adverse effects on heart rate, blood pressure or EKG, when administered to unanesthetized 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 intravenous administration of 60 mcg/kg/day gonadorelin acetate to pregnant rats and rabbits during organogenesis did not cause embryotoxic or teratogenic effects.

The intramuscular administration of 1000 mcg gonadorelin acetate to normally cycling dairy cattle had no effect on hematology or blood chemistry.

Further, gonadorelin acetate did not cause irritation at the site of intramuscular administration in dogs. The dosage administered was 72 mcg/kg/day for 7 days.

INDICATION AND DOSAGE
Cystic Ovaries
Fertagyl (gonadorelin) is indicated for the treatment of ovarian follicular cysts in dairy cattle. Ovarian cysts are non-ovulated follicles with incomplete luteinization which result in nymphomania or irregular estrus.

Historically, cystic ovaries have responded to an exogenous source of luteinizing hormone (LH) such as human chorionic gonadotropin.

Fertagyl initiates release of endogenous LH to cause ovulation and luteinization.

The recommended intramuscular or intravenous dosage of Fertagyl is 86 mcg gonadorelin (2 mL) per cow.

Reproductive Synchrony
Fertagyl (gonadorelin) is indicated for use with Estrumate (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows.

The recommended intramuscular dosage of Fertagyl is 86 mcg gonadorelin (2 mL) per cow, used in reproductive synchrony programs similar to the following:

- Administer the first Fertagyl injection (2 mL) on Day 0.
- Administer 2 mL of Estrumate (500 mcg cloprostenol, as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first Fertagyl injection.
- Administer the second Fertagyl injection (2 mL) 30 to 72 hours after the Estrumate injection.
- Perform FTAI 8 to 24 hours after the second Fertagyl injection, or inseminate cows on detected estrus using standard herd practices.

TARGET ANIMAL SAFETY
In addition to the target animal safety information presented in the section addressing pharmacology and toxicology, target animal safety of, and injection site reactions to, Fertagyl (gonadorelin) when used with Estrumate (cloprostenol injection) were evaluated during the conduct of the effectiveness field studies. The incidence of health abnormalities was not significantly greater in cows administered Fertagyl than cows administered a placebo injection.

EFFECTIVENESS
The effectiveness of Fertagyl (gonadorelin) for use with Estrumate (cloprostenol injection) to synchronize estrous cycles to allow for FTAI in lactating dairy cows was demonstrated in a field study at six different locations in the U.S. A total of 758 healthy, non-pregnant, primiparous or multiparous lactating dairy cows within 50-120 days postpartum were enrolled in the study. A total of 377 cows were administered Fertagyl (2 mL; 86 mcg gonadorelin as the acetate salt) and 381 cows were administered an equivalent volume of saline as an intramuscular injection twice in the following regimen:
Day 0: 2 mL Fertagyl or saline
Day 7: 2 mL Estrumate (cloprostenol injection)
Day 9: 2 mL Fertagyl or saline

Fixed time AI was performed on Day 10, 16 ± 8 hours after the Day 9 injection. Cows were evaluated for pregnancy on 45 ± 5 days by trans-rectal ultrasound or rectal palpation. Pregnancy rate to FTAI was significantly higher (P=0.0051) in cows treated with Fertagyl (33.4%) than the pregnancy rate to FTAI to cows treated with saline (17.8%).

Each mL of Fertagyl contains:

Gonadorelin (as gonadorelin acetate)	43 mcg
Benzyl Alcohol	9 mg
Sodium Chloride	7.47 mg
Water for Injection, USP	q.s.

pH adjusted with sodium phosphate (monobasic and dibasic).

STORAGE CONDITIONS: Keep refrigerated: 2° - 8°C (36° - 46°F).

PRECAUTIONS
FOR ANIMAL USE ONLY. NOT FOR HUMAN USE. KEEP OUT OF THE REACH OF CHILDREN.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects in users to obtain a MSDS or for assistance call 1-800-211-3573.

HOW SUPPLIED
Fertagyl is a sterile solution containing 43 mcg gonadorelin (GnRH; as gonadorelin acetate) per milliliter suitable for intramuscular or intravenous administration according to the indication. Fertagyl is supplied in multidose vials containing 20 mL of sterile solution.

Manufactured for:
Intervet Inc (d/b/a Merck Animal Health)
Madison, NJ 07940
By:
INTERVET INTERNATIONAL GmbH
Unterschleissheim - Germany

MERCK Animal Health

Estrumate®

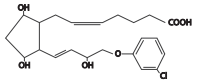
143266 R2

(cloprostenol sodium)

Prostaglandin Analogue for Cattle

Equivalent to 250 mcg cloprostenol/mL

Estrumate® (cloprostenol sodium) is a synthetic prostaglandin analogue structurally related to prostaglandin F2 α (PGF2 α). Each mL of the colorless aqueous solution contains 263 mcg of cloprostenol sodium (equivalent to 250 mcg of cloprostenol) in a sodium citrate, anhydrous citric acid and sodium chloride buffer containing 0.1% w/v chlorocresol BP as a bactericide. pH is adjusted, as necessary, with sodium hydroxide or citric acid.



ACTION:
Estrumate causes functional and morphological regression of the *corpus luteum* (luteolysis) in cattle. In normal, nonpregnant cycling animals, this effect on the life span of the *corpus luteum* usually results in estrus 2 to 5 days after treatment. In animals with prolonged luteal function (pyometra, mummified fetus, and luteal cysts), the induced luteolysis usually results in resolution of the condition and return to cyclicity. Pregnant animals may abort depending on the stage of gestation.

INDICATIONS:
For intramuscular use to induce luteolysis in beef and dairy cattle. The luteolytic action of Estrumate can be utilized 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.

RECOMMENDED USES:

Unobserved or nondetected estrus
Cows which are not detected in estrus, although ovarian cyclicity continues, can be treated with Estrumate if a mature *corpus luteum* is present. Estrus is expected to occur 2 to 5 days following injection, at which time animals may be inseminated. Treated cattle should be inseminated at the usual time following detection of estrus. If estrous detection is not desirable or possible, treated animals may be inseminated twice at about 72 and 96 hours postinjection.

Pyometra or Chronic Endometritis
Damage to the reproductive tract at calving or postpartum retention of the placenta often leads to infection and inflammation of the uterus (endometritis). Under certain circumstances, this may progress into chronic endometritis with the uterus becoming distended with purulent matter. This condition, commonly referred to as pyometra, is characterized by a lack of cyclical estrous behavior and the presence of a persistent *corpus luteum*. Induction of luteolysis with Estrumate usually results in evacuation of the uterus and a return to normal cyclical activity within 14 days after treatment. After 14 days posttreatment, recovery rate of treated animals will not be different than that of untreated cattle.

Mummified Fetus
Death of the conceptus during gestation may be followed by its degeneration and dehydration. Induction of luteolysis with Estrumate usually results in 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
A cow may be noncyclic due to the presence of a luteal cyst (a single, anovulatory follicle with a thickened wall which is accompanied by no external signs and by no changes in palpable consistency of the uterus). Treatment with Estrumate can restore normal ovarian activity by causing regression of the luteal cyst.

Pregnancies from Mismating
Unwanted pregnancies can be safely and efficiently terminated 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 about 4 to 5 days after the injection with the reproductive tract returning to normal soon after the abortion. The ability of Estrumate to induce abortion decreases beyond the fifth month of gestation while the risk of dystocia and its consequences increases. Estrumate has not been sufficiently tested under feedlot conditions; therefore, recommendations cannot be made for its use in heifers placed in feedlots.

Controlled Breeding
The luteolytic action of Estrumate can be utilized to schedule estrus and ovulation for an individual cycling animal or a group of animals. This allows control of the time at which cycling cows or heifers can be bred. Estrumate can be incorporated into a controlled breeding program by the following methods:

1. Single Estrumate injection: Only animals with a mature *corpus luteum* should be treated to obtain maximum response to the single injection. However, not all cycling cattle should be treated since a mature *corpus luteum* is present for only 11 to 12 days of the 21-day cycle.
   Prior to treatment, cattle should be examined rectally and found to be anatomically normal, be nonpregnant, and have a mature *corpus luteum*. If these criteria are met, estrus is expected to occur 2 to 5 days following injection, at which time animals may be inseminated. Treated cattle should be inseminated at the usual time following detection of estrus. If estrous detection is not desirable or possible, treated animals may be inseminated either once at about 72 hours or twice at about 72 and 96 hours post injection.
   With a single injection program, it may be desirable to assess the cyclicity status of the herd before Estrumate treatment. This can be accomplished by heat detecting and breeding at the usual time following detection of estrus for a 6-day period, all prior to injection. If by the sixth day the cyclicity status appears normal (approximately 25%-30% detected in estrus), all cattle not already inseminated should be palpated for normality, nonpregnancy, and cyclicity, then injected with Estrumate. Breeding should then be continued at the usual time following signs of estrus on the seventh and eighth days. On the ninth and tenth days, breeding may continue at the usual time following detection of estrus, or all cattle not already inseminated may be bred either once on the ninth day (at about 72 hours post injection) or on both the ninth and tenth days (at about 72 and 96 hours post injection).
2. Double Estrumate injections: prior to treatment, cattle should be examined rectally and found to be anatomically normal, nonpregnant, and cycling (the presence of a mature *corpus luteum* is not necessary when the first injection of a double injection regimen is given). A second injection should be given 11 days after the first injection. In normal, cycling cattle, estrus is expected 2 to 5 days following the second injection. Treated cattle should be inseminated at the usual time following detection of estrus. If estrous detection is not desirable or possible, treated animals may be inseminated either once at about 72 hours or twice at about 72 and 96 hours following the second Estrumate injection.
   Many animals will come into estrus following the first injection; these animals can be inseminated at the usual time following detected estrus. Animals not inseminated should receive a second injection 11 days after the first injection. Animals receiving both injections may be inseminated at the usual time following detection of estrus or may be inseminated either once at about 72 hours or twice at about 72 and 96 hours post second injection.
   Any controlled breeding program recommended should be completed by either:
   - observing animals (especially during the third week after injection) and inseminating or hand mating any animals returning to estrus,
     or
   - turning in clean-up bull(s) 5 to 7 days after the last injection of Estrumate to cover any animals returning to estrus.

REQUIREMENTS FOR CONTROLLED BREEDING PROGRAMS:
A variety of programs can be designed to best meet the needs of individual management systems. A controlled breeding program should be selected which is appropriate for the existing circumstances and management practices.
Before a controlled breeding program is planned, the producer's objectives must be examined and he must be made aware of the projected results and limitations. 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 the producer's specific situation. For any successful controlled breeding program:

- cows and heifers must be normal, nonpregnant, and cycling (rectal palpation should be performed);
- cattle must be in a fit and thrifty breeding condition and on an adequate or increasing plane of nutrition;
- proper program planning and record keeping are essential;
- if artificial insemination is used, it must be performed by competent inseminators using high-quality semen.

It is important to understand that Estrumate is effective only in animals with a mature *corpus luteum* (ovulation must have occurred at least 5 days prior to treatment). This must be considered when breeding is intended following a single Estrumate injection.

SAFETY AND TOXICITY:
At 50 and 100 times the recommended dose, mild side effects may be detected in some cattle. These include increased uneasiness, slight frothing, and milk let-down.

CONTRAINDICATIONS:
Estrumate should not be administered to a pregnant animal whose calf is not to be aborted.

PRECAUTIONS:
There is no effect on fertility following the single or double dosage regimen when breeding occurs at induced estrus or at 72 and 96 hours post treatment. Conception rates may be lower than expected in those fixed time breeding programs which omit the second insemination (ie, the insemination at or near 96 hours). This is especially true if a fixed time insemination is used following a single Estrumate injection. As with all parenteral products, 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.

DOSAGE AND ADMINISTRATION:
Two mL of Estrumate (500 mcg of cloprostenol) should be administered by *INTRAMUSCULAR INJECTION* for all indications in both beef and dairy cattle.
Do not puncture stopper more than 12 times.

WARNINGS
For veterinary use only.
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. Estrumate is readily absorbed through the skin and may cause abortion and/or bronchiospasms; direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

STORAGE CONDITIONS:
1. Protect from light.
2. Store in container.
3. Store at controlled room temperature 59°-86° F. (15°-30° c).
4. Use within 28 da ys of first use.

HOW SUPPLIED:
20mL and 100mL multidose vials

143266 R2

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

Made in Germany.

Schering-Plough Animal Health

MERCK Animal Health
The Science of Healthier Animals.™