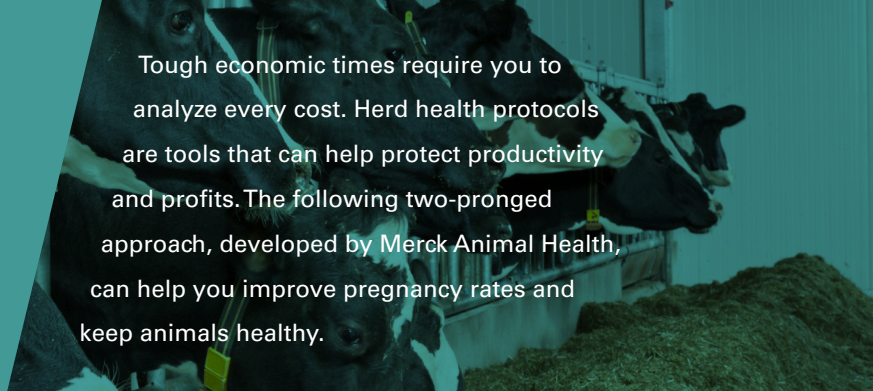


Two-pronged approach to keep cows productive



By Dr. Todd Bilby
Dairy Technical Services
Manager, Merck Animal Health



Tough economic times require you to analyze every cost. Herd health protocols are tools that can help protect productivity and profits. The following two-pronged approach, developed by Merck Animal Health, can help you improve pregnancy rates and keep animals healthy.

Nearly 15 years of peer-reviewed science has repeatedly shown the Vista[®] vaccine line provides protection against infection from bovine respiratory disease (BVD) deeper into pregnancy than other vaccines.¹ By providing this line of defense early, when animals are ready for breeding, they experience higher conception rates, fewer lost pregnancies and healthier calves.

Vista is the only BVD Type 1 and Type 2 vaccine that has been approved for the claim: "aids in the prevention of fetal infection, including persistently infected calves." A study concluded that vaccinating heifers pre-breeding with a minimum protective dose of Vista 5 SQ not only produced a measurable, protective immune response post-vaccination, but also reduced the risk of infection to the gestating fetus.²

The result: As shown in graph 1, calves born from dams vaccinated with Vista are protected from BVD when they hit the ground.

Timed breeding for better pregnancy rates

The ability to freshen cows on time and shorten calving intervals helps keep animals in the milking string and profitable. Shorter

calving intervals increase the number of peak lactations for a cow, resulting in higher lifetime production.

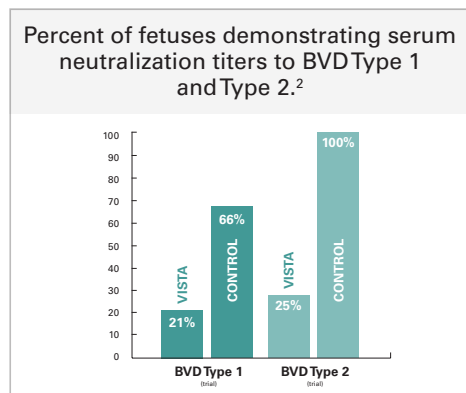
Fertagyl[®] (gonadorelin) and Estrumate[®] (cloprostenol sodium) help simplify fertility. Fertagyl, which triggers ovulation, is labeled for use with Estrumate to synchronize estrous cycles in lactating dairy cows.

At the 2018 American Dairy Science Association meeting, researchers presented results of a study designed to evaluate GnRH products to determine if they have comparable ovulation and pregnancy rates per service when used in a synchronization program. As shown on graphs 2 and 3, results found the ovulation and pregnancy rate of Fertagyl was comparable to Cystorelin[®] and much higher than Factrel[®].³

A healthy, productive herd

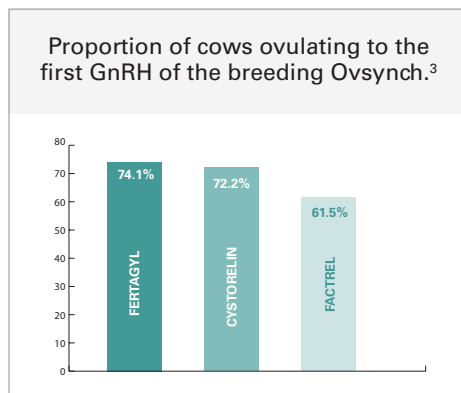
Getting and keeping cows pregnant are keys to the success of the dairy farm. Following this two-pronged protocol protects animals from reproductive challenges and shortens calving intervals to boost productivity.

GRAPH 1



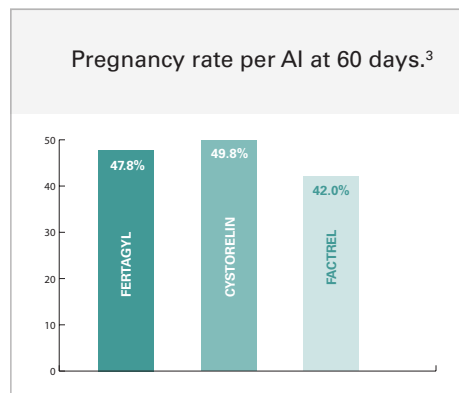
Vista 5 SQ provides a measurable, protective immune response post-vaccination for complete fetal protection.

GRAPH 2



Study compares the effectiveness of GnRH products in synchronizing lactating dairy cows.³

GRAPH 3



Study results show pregnancy rate per AI was similar between Fertagyl and Cystorelin, but both were greater than Factrel (42.0%).³

References:

- Xue W., Mattick D., Smith L., Maxwell J. Fetal protection against bovine viral diarrhea virus types 1 and 2 after the use of a modified-live virus vaccine. *Can J Vet Res.* 2009 Oct;73(4):292-7.
- Effect of Vista[®] 5 SQ Given Pre-Breeding for Protection from BVD Type 1 and Type 2 Fetal Infection. BV-VST-41405-BRSV-EFF 12/10.
- Luchterhand M., Gamarra C., Gennari R., Guenther, J., Carvalho P., Souza A., Barletta R. (2018, June). Fertility response to commercially available GnRH products in lactating cows synchronized with the Double Ovsynch protocol. 2018 American Dairy Science Association Annual Meeting, Knoxville, TN.

Cystorelin is a registered trademark of Merial. Factrel is a registered trademark of Zoetis. Fertagyl is a registered trademark of Intervet.

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IMPORTANT SAFETY INFORMATION ON ESTRUMATE: 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 information on use, withdrawal period, contraindication, adverse reactions, refer to product package insert.

IMPORTANT SAFETY INFORMATION ON FERTAGYL: Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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- α -oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂

with a molecular weight of 1182.32 and empirical formula C₅₂H₇₈N₇O₇.

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 hypophysial 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 LD₅₀ for mice and rats is greater than 60 mg/kg, and for dogs, greater than 600 mg/kg, respectively. No untoward effects were noted among rats or dogs administered 120 mg/kg/day intramuscularly or 72 mg/kg/day intravenously for 15 days.

It had no adverse effects on heart rate, blood pressure or ECG, when administered to unanesthetized dogs at 60 mg/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 mg/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 mg/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 (FAI) 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 (83.4%) 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).

USE WITHIN 28 DAYS OF FIRST USE

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 and 100 mL of sterile solution.

Manufactured for:
INTERVET INC (s/b/a Merck Animal Health)
Madison, NJ 07940
By: INTERVET INTERNATIONAL GmbH
Unterschleißheim - Germany



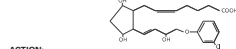
Estrumate®

(cloprostenol injection)

Prostaglandin Analogue for Cattle

Equivalent to 250 mcg cloprostenol/mL

Estrumate® (cloprostenol sodium) is a synthetic prostaglandin analogue structurally related to prostaglandin F_{2α} (PGF_{2α}). Each mL of the colorless aqueous solution contains 250 mcg of cloprostenol sodium (equivalent to 250 mcg of cloprostenol) in a sodium citrate, ethylenic citric acid and sodium chloride buffer containing 0.1% w/v chlorobutol 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 luteolysis 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 Fertagyl 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 normally, 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 postinjection).

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 with Estrumate (single 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 post 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
- burning 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, 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.

DOSEAGE 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.

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 bronchospasms; 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 days of first use.

HOW SUPPLIED:

20-mL multidose vials

CAUTION:

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

Made in Germany.

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