

Date of Approval: April 23, 2015

FREEDOM OF INFORMATION SUMMARY

SECTION 512(b)(1) SUPPLEMENT TO AN APPROVED ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-134

FERTAGYL

Gonadorelin

Sterile solution

Lactating dairy cows

This supplement provides for the addition of a new indication: For use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-134

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

FERTAGYL

D. Product Established Name

gonadorelin

E. Pharmacological Category

Peptide hormone

F. Dosage Form

Sterile solution

G. Amount of Active Ingredient

43 mcg gonadorelin/mL as gonadorelin acetate

H. How Supplied

20 mL vial

I. Dispensing Status

Rx

J. Dosage Regimen

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.

K. Route of Administration

Intramuscular injection

L. Species/Class

Lactating dairy cows

M. Indication

For use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows.

N. Reference Listed New Animal Drug

CYSTORELIN; gonadorelin diacetate tetrahydrate; NADA 098-379; Merial, Ltd.

O. Effect of Supplement

This supplement provides for the addition of a new indication, "For use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows."

II. BIOEQUIVALENCE

This supplemental ANADA did not require reevaluation of bioequivalence.

There are no pending citizen petitions that reference this generic product or the RLNAD cited in this application as of April 15, 2015.

III. EFFECTIVENESS

A. Dosage Characterization

1. Dose selection

This supplemental approval does not change the previously approved dosage of FERTAGYL for the treatment of cystic ovaries (86 mcg gonadorelin (2 mL) per cow, as gonadorelin acetate). This dose of FERTAGYL initiates release of endogenous luteinizing hormone (LH) to cause ovulation (Souza et al. 2009).

In addition, a dose of 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) is the dose used in most studies in the published literature for gonadorelin-prostaglandin reproductive synchrony/FTAI regimens in cattle (Fricke et al. 1998, Gumen et al. 2003, Jordan et al. 2002, Momcilovic et al. 1998, Pursley et al. 1995, Pursley et al. 1997, Stevenson et al. 1996, Stevenson et al. 1999). The data from these studies support the dose of 86 mcg gonadorelin (as gonadorelin acetate) as an appropriate dose for use in FTAI synchronization programs for lactating dairy cows.

The sponsor's multi-center field effectiveness study (Section II.B) formed the primary basis to establish the effectiveness of FERTAGYL for use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for FTAI in lactating dairy cows.

2. Timing of administration

Published literature was used to provide for additional flexibility to the timing of events reflected on the labeling for the use of FERTAGYL in estrous synchrony/FTAI regimens. Synchronization of estrous cycles with gonadorelin and a prostaglandin (e.g., cloprostenol sodium) is commonly referred to as a "GPG protocol" because it incorporates an initial gonadorelin (G1) injection, a prostaglandin (P) injection, and a final gonadorelin (G2) injection, followed by a single artificial insemination at a predetermined time (known as fixed time artificial insemination, FTAI). The scientific literature as well as the known biology of the bovine estrous cycle was used to define the GPG treatment schedule for FERTAGYL and ESTRUMATE. The timing between the last gonadorelin injection and FTAI was chosen based upon information available in the scientific literature.

Timing from G1 to P: The purpose of administering the initial gonadorelin injection (G1) is to initiate a new wave of follicular development (Pursley et al. 1995, Pursley et al. 1997, Schmitt et al. 1996, Thatcher et al. 1989, Twagiramungu et al. 1995). The conventional interval between G1 and P is seven days. Pregnancy rate to FTAI is similar when the interval between G1 and P is six or seven days (Martinez et al. 2002). The maximum duration between G1 and P is influenced by the typical duration of an ovarian follicular wave, which is seven to nine days (Fortune et al. 2001, Ginther et al. 2001). Durations beyond this timeframe may nullify the positive effect of inducing a new follicular wave and new dominant follicle. This supports a maximum interval of eight days between G1 and P to assure ovulation of the dominant follicle that emerged following G1. Taken together, these data support the directions for use statement "Administer 2 mL of ESTRUMATE (500 mcg cloprostenol sodium) by intramuscular injection 6 to 8 days after the first FERTAGYL injection."

Timing from P to G2: The purpose of treating cows with G2 is to induce a pre-ovulatory surge in LH in a predictable manner, such that ovulation in groups of animals occurs in a sufficiently narrow time-frame to allow for FTAI. The conventional interval between P and G2 is two to three days (e.g., 48 to 72 hours). A study by Pursley et al. (1997) demonstrated that in dairy cows the pregnancy rates were similar between cows given G1 and P and bred by artificial insemination (AI) based on detected estrus compared to cows given G1, P, G2 (30 to 36 hours after P), and bred by FTAI. Intervals shorter than 30 hours do not appear to maintain the same level of effectiveness (Rantala et al. 2009, Schmitt et al. 1996, Peters and Pursley 2003). An interval between P and G2 greater than 72 hours is not supported by the scientific literature and is unlikely to provide any benefit as the LH surge may have already occurred; dairy cows displayed an LH surge at an average of 71 hours after P (Louis et al. 1974). These data support the directions for use statement "Administer the second FERTAGYL injection (2 mL) 30 to 72 hours after the ESTRUMATE injection."

Timing from G2 to FTAI: The interval between G2 and FTAI varies for different estrous synchronization regimens. Pursley et al. (1998) demonstrated that pregnancy rate per AI did not differ among cows bred to FTAI 0, 8, 16, or 24 hours after G2, but was reduced in cows bred to FTAI 32 hours after G2.

However, a quadratic effect indicated that the numerically highest pregnancy rates per AI were obtained when insemination was between 8 and 24 h after G2 (Pursley et al., 1998). Brusveen et al. 2008 also found that pregnancy rates were lower when cows were bred 0 hours after G2 compared with cows bred 16 hours after G2. The field effectiveness studies reported below used an interval of 16 ± 8 hours between G2 and FTAI. Results from the field effectiveness studies combined with data from the published literature support use of FTAI 8 to 24 hours after G2.

Producers may opt to inseminate cows based on detected estrus after the prostaglandin (P) injection. Some cows may express estrus prior to G2 or prior to the predetermined time for FTAI. Several published studies demonstrated that the pregnancy rate in dairy cows to AI based on detected estrus after P was similar to pregnancy rates obtained after a GPG protocol with FTAI (Pursley et al. 1997, Santos et al. 2004). These results support use of AI based on detected estrus after P (with or without use of G2).

Taken together, these data support the directions for use statement "Perform FTAI 8 to 24 hours after the second FERTAGYL injection, or inseminate cows on detected estrus using standard herd practices."

Thus, the information generated in the sponsor's multi-center field effectiveness study (Section II.B) in combination with published literature supports the following labeling directions for use:

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.

3. Literature Cited

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Thatcher, W.W., Macmillan, K.L., Hansen, P.J., and Drost, M. (1989). Concepts for regulation of corpus luteum function by the conceptus and ovarian follicles improve fertility. *Theriogenology*, 31, 149-164

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B. Substantial Evidence

1. Multi-Center Field Effectiveness Study

a. Title:

“The effectiveness and safety of FERTAGYL (gonadorelin) injection for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed-time artificial insemination in lactating dairy cows compared to a saline control” (Study No. S13213; October 29, 2013 – February 22, 2014)

b. Investigators:

Table 1. Study Investigators and Locations

Site	Investigator	Study Location
1	Terry TerHune, DVM, PhD	Tulare, California
2a 2b	Joe Hogan, PhD*	Columbus, Ohio Wooster, Ohio
3	Billy Smith, DVM, MS	Cochranville, Pennsylvania
4	José Santos, DVM, PhD	Trenton, Florida
5	Alyn McClure, DVM	Stanfield, Arizona
6	Michael Capel, DVM	Phelps, New York

* Study was conducted by the same Investigator at two separate study sites.

c. Study Design:

(1) Objective:

To determine the effectiveness and safety of FERTAGYL (gonadorelin) for use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination in lactating dairy cows as compared to a saline control.

(2) Study Animals, Housing, and Management:

A total of 758 cows were enrolled. Cows were healthy, free of reproductive disorders, and had a body condition score between 2 and 4 (on a 5 point scale). All cows had calved at least once, were not detectably pregnant on Day 0, and were between 51 and 119 days in milk at first treatment.

The seven dairies used in this study were representative of the U.S. dairy industry. Breeds were predominantly Holstein with inclusion of some Jersey and crossbred cows. Approximately 27% of the cows on this study were in their first lactation and the remaining cows were multiparous. Cows were housed in freestall barns or dry lot pens. Management practices related to nutrition, housing, breeding, health, reproduction, lactation, and environment/climate varied among sites and were consistent with normal herd practices in the U.S.

The study began on October 29, 2013, when the first cow was treated, and finished on February 22, 2014, when the last cow completed the study. Heat stress conditions (defined as a temperature-humidity index > 72 (Mukherjee et al. 2012)) were present at two of the locations (Arizona and Florida) during the study. In addition, environmental conditions at three of the sites for the two months prior to the study were sufficient to cause significant heat stress for lactating dairy cows.

(3) Experimental Design:

This study was conducted in accordance with Good Clinical Practices (CVM Guidance No. 85 (VICH GL9)). The study was a randomized, masked, placebo-controlled study conducted under a common protocol. Animals were blocked by farm, and within each farm, cows were randomly assigned to one of two treatment groups, the test article treatment group (FERTAGYL) and a placebo control saline treatment group (control).

Cow was the experimental unit and study animals were commingled with the herd. Study personnel involved in treatment assignments and treatment administration were not masked during the study and were not involved in clinical assessments. Study personnel making clinical observations were masked to the treatment assignments.

(4) Drug Administration:

The two treatment groups used in this study were FERTAGYL, as part of a GPG regimen (initial FERTAGYL injection, an ESTRUMATE injection, a final FERTAGYL injection followed by FTAI) or a placebo saline control, as part of an SPS regimen (initial saline injection, an ESTRUMATE injection, a final saline injection followed by FTAI).

The test article was FERTAGYL, which contained 43 mcg/mL gonadorelin, present as the acetate salt. The control article was 0.9% sterile saline. The cloprostenol injection (ESTRUMATE) contained 250 mcg/mL of cloprostenol, present as the sodium salt. All injections were administered intramuscularly in the hindquarters, alternating sides for each treatment day.

Cows were treated according to the following schedule:

- Day 0 Cows injected with either 2 mL FERTAGYL or 2 mL saline (control), according to the treatment group assignment
- Day 7 All cows injected with 2 mL ESTRUMATE
- Day 9 Cows injected with either 2 mL FERTAGYL or 2 mL saline (control), according to the treatment group assignment, 47 to 60 hours after the ESTRUMATE injection
- Day 10 Cows bred by artificial insemination 16 ± 8 hours after the second FERTAGYL or saline injection

Each location selected the administration timings that were appropriate for their management practices to apply to all study animals within that site. All locations chose to administer the ESTRUMATE injection on Day 7 and to administer the second FERTAGYL or saline injection on Day 9.

(5) Measurements and Observations:

Cows were observed at least once daily for general health. In addition, the cows were observed for injection site reactions from Days 0 to 16. All cows were observed daily for estrus from Day 15 until the end of the study. Any cow showing signs of estrus after Day 15 and prior to the scheduled pregnancy check was considered to be a treatment failure. Pregnancy diagnosis was scheduled to occur on 45 ± 5 days (corresponding to 35 ± 5 days after FTAI) by trans-rectal ultrasound and/or rectal palpation.

d. Statistical Methods:

The primary variable of effectiveness was pregnancy rate to FTAI; animals determined as pregnant from FTAI were deemed a treatment success. The primary analysis for effectiveness was a comparison of the percent success in the FERTAGYL treatment group to the percent success in the control group using a generalized linear mixed model using a logit link and a binomial error distribution (SAS GLIMMIX). The statistical model included treatment group as a fixed effect and site and site by treatment interaction as random effects. A Kenward-Rogers adjustment was made to the

degrees of freedom for the denominator of the test for treatment effect and the difference between treatment groups was evaluated using a two-sided test at $\alpha = 0.05$.

e. Results:

A total of 758 cows were enrolled, of which 744 cows were included in the analysis. Five cows were excluded from the effectiveness analysis for data and/or dosing errors. Ten cows (eight and two cows in the control and FERTAGYL groups, respectively) were removed from the study for adverse health events; four of these were euthanized. Of these ten removed cows, nine were excluded from the effectiveness analysis and one was included based on pregnancy determination at removal. Removals were due to injury ($n = 5$), mastitis ($n = 2$), digestive disorders ($n = 2$), or weight loss ($n = 1$).

All of the reported adverse events during the study are summarized in Table 2. The adverse events represented common dairy cow conditions, such as mastitis, lameness, and gastrointestinal disorders. The control group had more adverse events than the treated group (53 and 37, respectively). None of the adverse events were attributed to the test article. In addition, no injection site reactions were observed at any site.

Table 2. Summary of number of Adverse Events reported by system organ class and treatment group

System Organ Class	Control	FERTAGYL	Total
Mammary gland	28	18	46
Skin and appendages	8	9	17
Musculoskeletal	9	6	15
Digestive tract	2	1	3
Systemic	2	1	3
Respiratory	1	1	2
Eye	1	1	2
Neurological	1	0	1
Lymphatic	1	0	1
TOTAL	53	37	90

Pregnancy rates for each treatment group at each site are shown in Table 3. The pregnancy rates in the FERTAGYL treatment groups were higher than the pregnancy rates in the control treatment group at six of the seven locations, including those sites experiencing heat stress, sites 4 and 5. In the remaining site, the two groups had similar pregnancy rates.

Overall, the pregnancy rate for the treated group was 33.4% and the pregnancy rate for the control group was 17.8%. The FERTAGYL treatment resulted in statistically significantly higher pregnancy rates compared to the control group ($P = 0.0051$).

Table 3. Pregnancy status at study completion for the treated and control groups

Site	Control	FERTAGYL	P -value
1	19.2% (14/73)	18.9% (14/74)	N/A
2a	16.7% (2/12)	58.3% (7/12)	N/A
2b	20.0% (2/10)	37.5% (3/8)	N/A
3	12.9% (4/31)	46.7% (14/30)	N/A
4	16.3% (13/80)	26.3% (21/80)	N/A
5	17.8% (19/107)	41.8% (46/110)	N/A
6	21.1% (12/57)	33.3% (20/60)	N/A
Overall	17.8% (66/370)	33.4% (125/374)	0.0051

f. Adverse Reactions:

There were no adverse effects on animal health attributable to the test article.

g. Conclusion:

FERTAGYL (2 mL; 86 mcg gonadorelin) used with ESTRUMATE (2 mL; 500 mcg cloprostenol) in a fixed time artificial insemination (FTAI) reproductive synchrony regimen in lactating dairy cows significantly (P = 0.0051) increased pregnancy rate compared to ESTRUMATE alone.

2. Literature Cited

Mukherjee, D., Bravo-Ureta, B.E., and De Vries, A. (2012). Dairy productivity and climatic conditions: econometric evidence from South-eastern United States. *The Australian Journal of Agricultural and Resource Economics*, 57, 123–140

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The Freedom of Information (FOI) Summaries for the original approvals for FERTAGYL (ANADA 200-134) and ESTRUMATE (NADA 113-645) contain information on the target animal safety of the two products. Target animal safety of FERTAGYL when used with ESTRUMATE was evaluated during the conduct of the field effectiveness study. The incidence of health abnormalities was not significantly greater in cows administered FERTAGYL than cows administered a placebo injection.

In addition, Intervet, Inc. provided pharmacovigilance data for FERTAGYL (from June 1, 2010, to May 31, 2013) and ESTRUMATE (August 1, 2008, to July 31, 2013) that addressed both the individual use of the products and their combined use in cattle for estrous synchronization programs. No cases of serious adverse reactions in animals were reported for FERTAGYL during the three year period. For ESTRUMATE a total of 22 cases of serious adverse reactions in cattle were reported during the five year period. Seven of the cases involved systemic hypersensitivity and the remaining fifteen involved injection site reactions such as edema, infection or necrosis, likely due to bacterial infection. The reported worldwide incidence of serious adverse reactions in animals to ESTRUMATE is low (<1/10,000).

Both drugs are rapidly and extensively metabolized in cattle and the levels of gonadorelin and cloprostenol in plasma return to pre-dosing levels within four and a half hours of administration. The drugs have their effects through different, highly specific receptors. The proposed dosing intervals between the administrations of FERTAGYL and ESTRUMATE are substantially longer than the half-lives of the drugs and thus no drug interactions leading to adverse effects are anticipated.

Estrous synchronization programs using gonadorelin products with cloprostenol have been extensively researched since the mid-1990s. Repeated exposure to gonadorelin and cloprostenol do not appear to cause any adverse effects on reproduction.

V. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

FERTAGYL (gonadorelin) and ESTRUMATE (cloprostenol injection) are not known to have antimicrobial properties; additionally, FERTAGYL and ESTRUMATE have not been shown to impact antimicrobial resistance among bacterial populations. Therefore, at this time, the Agency does not think that the use of FERTAGYL and ESTRUMATE to synchronize estrous cycles to allow for FTAI in lactating dairy cows will impact antimicrobial resistance among bacteria of public health concern in or on treated animals.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of FERTAGYL and ESTRUMATE are not known to have antimicrobial properties; additionally, literature available in the public domain does not indicate that residues and metabolites of FERTAGYL and ESTRUMATE impact bacterial populations. Therefore, at this time, residues and metabolites of FERTAGYL and ESTRUMATE in or on the edible tissues of treated lactating dairy cows are not predicted to have antimicrobial activity against the intestinal flora of human consumers and thus, there is no need to address their antimicrobial effects on human intestinal flora.

C. Toxicology

A toxicological acceptable daily intake (ADI), a final ADI and safe concentrations for total residues of FERTAGYL and ESTRUMATE were not needed for these approvals. The safety of FERTAGYL has been established in the original approval of ANADA 200-134 (61 FR 37682, dated July 19, 1996). The FOI Summary for the original approval of NADA 113-645 (47 FR 4678, dated February 2, 1982) contains a summary of all toxicology studies and information for cloprostenol.

D. Assignment of the Final ADI

It is not necessary to assign an ADI for gonadorelin residues.

E. Safe Concentrations for Total Residues

No safe concentrations for total residues of gonadorelin are needed.

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The original approval of ANADA 200-134 (61 FR 37682, dated July 19, 1996) contains a summary of residue chemistry studies for gonadorelin acetate in dairy cattle. The FOI Summary for the original approval of NADA 113-645 (47 FR 4678, dated February 2, 1982) contains a summary of residue chemistry studies for cloprostenol sodium in dairy cattle.

Based on the rapid depletion of gonadorelin and cloprostenol residues in cattle, there is sufficient time between the sequential uses of the two products to preclude any potential interaction between the two drugs. Therefore, there are no concerns for gonadorelin or cloprostenol residues in tissues or milk of treated dairy cows at zero day withdrawal period and zero hour milk discard time.

G. Analytical Method for Residues

Because there are no tolerances required for either gonadorelin acetate or cloprostenol sodium, no regulatory methods are required.

VI. USER SAFETY

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to FERTAGYL:

"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."

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ESTRUMATE:

"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."

VII. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that FERTAGYL, when used according to the label, is safe and effective for use with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows. Additionally, data demonstrate that residues in food products derived from species

treated with FERTAGYL will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because veterinary experience is required to properly diagnose ovarian follicular cysts and prescribe appropriate treatment, and because the use of this product for the synchronization of estrous cycles requires the use of ESTRUMATE, which also has Rx marketing status.

B. Exclusivity

This supplemental approval for FERTAGYL qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the new use of FERTAGYL with ESTRUMATE (cloprostenol injection) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows.

C. Supplemental Applications

This supplement approved under section 512(b)(1) of the FD&C Act did not require reevaluation of the safety or effectiveness data in the original application (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.