Date of Approval: January 17, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

And

SECTION 512(b)(1) SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

ANADA 200-541

GONABREED

(gonadorelin acetate)

Injectable Solution

Dairy Cattle

For the treatment of ovarian follicular cysts in dairy cattle

and an additional indication for:

Lactating Dairy Cows and Beef Cows

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

Sponsored by:

Parnell Technologies Pty. Ltd.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-541

B. Sponsor

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Alexandria, New South Wales 2015
Australia

Drug Labeler Code: 068504

Contact: Robert Joseph
Parnell Technologies Pty. Ltd.
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C. Proprietary Name

GONABREED

D. Established Name

Gonadorelin acetate

E. Pharmacological Category

Peptide hormone

F. Dosage Form:

Injectable solution

G. Amount of Active Ingredient

100 mcg gonadorelin/mL as gonadorelin acetate

H. How Supplied

20 mL vial

I. Dispensing Status

Rx

J. Dosage Regimen

Cystic ovary indication: 100 mcg (1 mL) per cow.

Estrous synchrony indication: The recommended intramuscular dosage of GONABREED is 100 mcg (1 mL) per cow, used in reproductive synchrony regimens similar to the following:

1. Administer the first GONABREED injection (1 mL) at Time 0.
2. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first GONABREED injection.
3. Administer the second GONABREED injection (1 mL) 30 to 72 hours after the cloprostenol sodium injection.
4. Perform FTAI 0 to 24 hours after the second GONABREED injection, or inseminate cows on detected estrus using standard herd practices.

K. Route of Administration

Cystic ovary indication: Intravenous or intramuscular injection

Estrous synchrony indication: Intramuscular injection

L. Species/Class

Cystic ovary indication: Dairy cattle

Estrous synchrony indication: Lactating dairy cows and beef cows

M. Indications

For the treatment of ovarian follicular cysts 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.

N. Reference Listed New Animal Drug

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

II. BIOEQUIVALENCE:

A. Suitability Petition:

The sponsor submitted a suitability petition requesting permission to submit an abbreviated new animal drug application (ANADA) for a generic new animal drug that differed in strength from the reference listed new animal drug (RLNAD). The concentration of the RLNAD, CYSTORELIN is 50 mcg/mL of gonadorelin diacetate tetrahydrate. The sponsor proposed to increase the concentration of their generic product to 100 mcg/mL gonadorelin acetate. This petition was approved (2010-P-0028-0001) on March 30, 2010, under 512(n)(3)(C) of the Federal Food, Drug, and Cosmetic Act (the act).

B. Bioequivalence Waiver for Generic Approval:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an ANADA may be submitted for a generic version of a RLNAD. In most circumstances, new target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement to demonstrate *in vivo* bioequivalence (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

Based on the formulation characteristics of the generic product, Parnell Technologies Pty. Ltd. was granted a waiver from the requirement to demonstrate *in vivo* bioequivalence for their proposed generic product GONABREED (gonadorelin acetate) injectable solution. The generic product is administered as an injectable solution, contains the same active ingredient, is the same dosage form as the RLNAD, and contains no inactive ingredients that may significantly affect the absorption of the active ingredient. The RLNAD was approved on March 10, 1978.

The RLNAD, CYSTORELIN, contains 50 mcg/mL of gonadorelin diacetate tetrahydrate, which is equivalent to 43 mcg/mL of gonadorelin base. The labeled dose of CYSTORELIN for treatment of ovarian follicular cysts in dairy cattle is 2 mL per cow, which delivers 86 mcg of gonadorelin base to the treated animal. The GONABREED formulation in the waiver request contained 100 mcg/mL gonadorelin base (as gonadorelin acetate), and would be administered at a dose of 0.86 mL per cow.

C. Section 512(b)(1) Changes:

Parnell Technologies Pty. Ltd. as part of the current application also provided data to support a 512(b)(1) supplemental new animal drug approval for a different dose and an additional indication for GONABREED. The sponsor first met the requirements for demonstrating product bioequivalence for the purpose of copying the approved RLNAD indication for the treatment of ovarian follicular cysts in dairy cattle at the approved dose of 86 mcg of gonadorelin base. In the supplemental 512(b)(1) application, the sponsor sought approval of a different dose of 100 mcg gonadorelin (as gonadorelin acetate) for the treatment of ovarian follicular cysts and a new indication for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows, innovative changes that require supportive data in addition to meeting the bioequivalence requirements, as defined under section 512(b)(1) of the act. This data is summarized under the "Effectiveness" and "Target Animal Safety" sections of this summary.

III. EFFECTIVENESS:

A. Dosage Characterization:

1. Dose Selection

Through the evaluation of published literature and limited pharmacokinetic studies, it has been determined that an increase in dose from 86 mcg to 100 mcg gonadorelin base is effective for the treatment of follicular ovarian cysts in dairy cattle.

Additionally, most studies in the scientific literature use approximately 100 mcg of CYSTORELIN or other gonadorelin formulations for estrus synchronization (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. 1999, Stevenson et al. 1996). This is consistent with the dose of GONABREED approved for estrous synchronization and treatment of ovarian follicular cysts in Australia and New Zealand. GONABREED has been marketed in Australia and New Zealand since 2001. During 2001 – 2008, six studies were performed using the 1 mL dose (equivalent to 100 mcg gonadorelin base) to demonstrate effectiveness of the use of GONABREED with cloprostenol sodium for estrus synchronization to allow FTAI. The six studies represent a total of 8059 pastured lactating dairy cows in 101 herds. Overall pregnancy rates across the six studies averaged 31%.

These data support the dose of 100 mcg gonadorelin (as gonadorelin acetate) for the treatment of follicular ovarian cysts in dairy cattle and for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows.

2. Timing of Administration

Synchronization of estrous cycles with gonadorelin and a prostaglandin (e.g., cloprostenol sodium) are commonly referred to as GPG regimens because they incorporate an initial gonadorelin (G1) injection, a prostaglandin (P) injection, and a final gonadorelin (G2) injection, followed by artificial insemination at a predetermined time, or FTAI. For the use of GONABREED with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy and beef cows, the timing of administration of the gonadorelin acetate and cloprostenol sodium was considered. The timing between each of the injections as well as the timing between the last gonadorelin injection and FTAI was evaluated based upon information available in the scientific literature.

Timing from G1 to P: The conventional interval between the G1 and P is seven days. Pregnancy rate to FTAI is similar when the interval between the 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 the 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 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection six to eight days after the first GONABREED injection".

Timing from P to G2: 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) demonstrates 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). An interval greater than 72 hours is not supported by the scientific literature. The purpose of treating cows with G2 is to induce a pre-ovulatory surge in luteinizing hormone (LH) in a predictable manner, such that ovulation in groups of animals occurs in a sufficiently narrow time-frame to allow FTAI. Given that dairy cows displayed an LH surge at an average of 71 hours after P (Louis et al. 1974), an interval between P and G2 greater than 72 hours is unlikely to provide any benefit as the LH surge may already have occurred. These data support the directions for use statement "Administer the second GONABREED injection (1 mL) 30 to 72 hours after the cloprostenol sodium 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 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. The dose confirmation field studies reported below incorporated a wide range of intervals between G2 and FTAI. The study

conducted in beef cows performed FTAI immediately after the G2 (0 hour interval). The study conducted in lactating dairy cows performed FTAI 11 to 31 hours after the G2 injection. Results from the field studies combined with the data from Pursley et al. (1998) support use of FTAI 0-24 hours after G2.

In addition, producers may opt to inseminate cows based on detected estrus after P. Some cows may express estrus prior to the G2 or 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 full GPG regimen and FTAI were conducted (Pursley et al., 1997, Santos et al. 2004). These results support use of AI based on detected estrus after P, without use of G2.

Taken together, these data support the directions for use statement "Perform FTAI 0 to 24 hours after the second GONABREED injection, or inseminate cows on detected estrus using standard herd practices."

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B. Substantial Evidence:

1. Multi-center Field Study in Beef Cows

   a. Title: A Multi-center Clinical Study of the Effectiveness and Safety of Gonadorelin Injection for use with Cloprostenol Sodium to Synchronize Estrous Cycles to Allow for Fixed Time Artificial Insemination in Beef Cows (Study No. CP0902).

   b. Investigators: The study was conducted in 11 herds, representing major beef cattle management systems in the U.S.

Table 1. Clinical investigators and study locations for beef study.

Investigator Location	Investigator	Herd Locations
Summit Research Preston, ID	Breck Hunsaker, DVM	ID-01: Clifton, ID[1] Oxford, ID[1]
Professional Beef Services Canton, MO	Dan Goehl, DVM	IA-01: Keosauqua, IA MO-01: Wyaconda, MO
Professional Beef Services Canton, MO	Brad White, DVM	MO-02: Canton, MO MO-03: Palmyra, MO
Professional Beef Services Canton, MO	Mallory (Risley) Heaton	MO-07: Maywood, MO
Professional Beef Services Canton, MO	Brad Robert	MO-04: Knox City, MO MO-06: Ewing, MO
Stocker Health LLC West Point, MS	Matt Bell, DVM	MS-01: Lena, MS
Stocker Health LLC West Point, MS	Che Trejo, DVM	MS-02: Prairie, MS MS-03: Prairie, MS

c. Study Design:

1) Objective: To evaluate the clinical effectiveness of GONABREED (gonadorelin acetate) used with cloprostenol sodium for increasing pregnancy rates to FTAI compared to cloprostenol sodium alone in beef cows.

2) Experimental Design: This study was conducted in accordance with CVM's Good Clinical Practices (CVM Guidance No. 85 (VICH GL9)). The study was conducted in 11 independent sites, representing major beef cattle management systems in the US (ID, MO/IA, and MS). The study was a masked, placebo-controlled study that utilized a completely randomized design at each site. Cows at each site were randomly assigned to one of two treatment groups, either the test article (GONABREED; gonadorelin acetate) or a placebo control (water for injection). Cow was the experimental unit. All study personnel were masked to treatment assignment. The test and control articles were labeled at the manufacturing site as Product A (GONABREED) or Product B (water for injection). The study was 55 ± 5 d long, and was completed after pregnancy diagnosis.

3) Study Animals: In total, the study enrolled 791 cows from 11 privately-owned herds in three major cattle-producing regions in the United States. Breeds were typical of the U.S. beef industry. Cows were healthy, free of reproductive disorders, and had a body condition score between four to seven (on a 9-point scale). All cows had calved at least once, were not detectably pregnant on Day 0, and were between 40 and 150 days post-partum at the beginning of the study.

[1] The ID site enrolled animals from two herds under two different owners; however, the animals were run and managed as a single herd at one location and rotated between pastures at the two locations as needed.

4) Treatment Groups: The two treatment groups used in this study were the test article treatment group (GONABREED; gonadorelin acetate) and a placebo control treatment group (control).

5) Drug Administration: The test article was GONABREED (gonadorelin acetate), which contained 105 mcg/mL gonadorelin base, present as the acetate salt. The control article was sterile water for injection. The cloprostenol injection contained 250 mcg/mL of cloprostenol, present as the sodium salt. All injections were administered intramuscularly in the neck, alternating sides for each treatment day.

   Cows were treated according to the following schedule:

Day 0:	Cows injected with either 1 mL GONABREED or 1 mL water for injection (control)
Day 7:	All cows injected with 2 mL cloprostenol sodium
Day 9/10:	Cows injected with either 1 mL GONABREED or 1 mL water for injection (control)

   Day 9/10 injections took place approximately 60 hours after the Day 7 cloprostenol injection. Immediately after the Day 9/10 injection, all cows were bred by artificial insemination.

6) Measurements and Observations: Pregnancy was diagnosed by trans-rectal ultrasound at 55 ± 5 days (45 ± 5 days after FTAI). Animals were observed for injection site reactions or other adverse health events daily for Days 0 to 16, and weekly thereafter until pregnancy diagnosis.

7) 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 GONABREED treatment group to the percent success in the control group using a generalized linear mixed model. The statistical model included group as a fixed effect and site and site by group interaction as random effects, and assumed a binomial distribution with logit link. The difference between treatment groups was evaluated using a two-sided test at alpha =0.05. Estimated percent success (success of pregnancy to FTAI) and confidence intervals were back-transformed from the generalized linear mixed model (GLMM) least squares estimates.

d. Results:

1) Pooled Results

   The total number of cows initially enrolled, excluded from analysis, and included in the final database for analysis is shown in Table 2.

Table 2. Number of beef cows per treatment group.

	GONA-BREED Enrolled	GONA-BREED Excluded	GONA-BREED Analyzed	Control Enrolled	Control Excluded	Control Analyzed
ID-01	46	1	45	46	0	46
IA-01	42	0	42	38	1	37
MO-01	30	0	30	28	0	28
MO-02	34	0	34	30	0	30
MO-03	40	0	40	40	0	40
MO-04	44	0	44	41	0	41
MO-06	37	37	0	40	40	0
MO-07	35	1	34	35	3	32
MS-01	28	1	27	32	1	31
MS-02	31	0	31	23	0	23
MS-03	37	0	37	34	0	34
TOTAL	404	40	364	387	45	342

The study initially enrolled 791 cows, 404 cows in the GONABREED treatment group and 387 in the control treatment group. All 77 cows from one herd (MO-06) were excluded from the analysis of effectiveness because a bull entered the pasture on Day 9. An additional eight cows were excluded from the analysis of effectiveness; seven of these cows were excluded because of record-keeping errors or improper enrollment and one cow (control treatment group) because of the inability to correctly inseminate her on Day 10.

The effectiveness analysis contained 706 cows, 364 cows in the GONABREED treatment group and 342 in the control treatment group. The number of cows diagnosed pregnant to FTAI, as determined on Day 55 ± 5 (45 ± 5 after FTAI), was 86 in the GONABREED treatment group and 29 in the control treatment group. Table 3 summarizes the results of the statistical analysis, showing that the proportions of success in the two treatment groups were significantly different (P-value=0.0006). Based on the analysis, the pregnancy rate in the GONABREED treatment group was 21.7%, higher than the pregnancy rate of 7.4% in the control treatment group.

Table 3. Summary of the statistical analysis of the proportion of treatment successes in each group in beef study.

Treatment	Cows, #	Pregnancy rate to FTAI, %	95% Confidence Interval
GONABREED	364	21.74	(13.54, 33.01)
Control	342	7.38	(3.91, 13.48)

P-value: 0.0006

2) Individual Sites

Herds contained cows of Angus (IA-01, MS-01), Continental-Cross (MO-03, MO-04), or English-Cross (MO-06, MO-07, MS-02, MS-03) breeds, with some herds containing a combination of Angus and

English-Cross (ID-01) or Angus and Continental-Cross (MO-01, MO-02).

Cows were housed on pasture with or without shelter, ranging from flat rangeland (ID) to rolling and hilly grasslands with timber (MO/IA and MS). Stocking rates ranged from 0.2- 3 cows/acre (MO/IA and MS) to 1 cow/10-15 acres (ID). Rotational grazing was used at some sites, with three herds using intensive grazing practices (MO-01, MS-01, and MS-02). Pastures were generally fescue, often mixed with clover and other grasses such as Bermuda, orchard, vetch, or rye. Supplemental feeds included mineral supplements, hay or silage, and occasionally energy or protein supplements such as corn gluten, distillers grains, or soyhulls. Water was available from ponds and streams, with occasional troughs provided.

Prior to the study, herds typically used natural service, with three herds using AI (MO-01, MO-04, and MS-01), two herds using reproductive synchrony procedures (MO-01 and MS-01), and one herd using some embryo transfer procedures (MS-01). Calving seasons were generally once a year and ranged from mid-winter to late spring (December-May), with only one herd (MO-03) also having a fall calving season (September).

The study was conducted in the spring and summer at each site; critical study dates for each herd are shown in Table 4.

Table 4. Critical study dates in beef study.

Herd	Day 0	Day 7	Day 9/10	Pregnancy diagnosis
ID-01	05/25/10	06/01/10	06/04/10	07/20/10
IA-01	05/03/10	05/10/10	05/13/10	06/24/10 07/02/10
MO-01	04/21/10	04/28/10	05/01/10	06/12/10
MO-02	04/29/10	05/06/10	05/08/10	06/12/10
MO-03	05/11/10	05/18/10	05/21/10	07/06/10
MO-04	05/24/10	05/31/10	06/03/10	07/22/10
MO-06	05/28/10	06/04/10	06/07/10	07/26/10
MO-07	06/01/10	06/08/10	06/11/10	07/27/10
MS-01	05/01/10	05/08/10	05/10/10	06/22/10
MS-02	05/24/10	05/31/10	06/03/10	07/22/10
MS-03	05/25/10	06/01/10	06/04/10	07/23/10

Observations of any abnormal health events during the study are summarized in Table 5. Cows were generally healthy and few abnormal health observations were made during the study. The primary abnormalities included lameness, pinkeye, and neck lesions (abscesses, knots, or bruising). The lameness and pinkeye observations are common conditions in beef cattle and were not apparently related to treatment. At MO-04, eight of the ten observed incidences of neck lesions (abscesses, knots, or bruising) were not likely related to treatment; seven of these observations resulted from

a reaction to standard herd vaccinations and one was observed several weeks after treatment administration. One cow (control treatment group) was found moribund and euthanized on Day 57. No cause was determined, but it is unlikely that this was treatment related because this cow was in the control treatment group and 47 days had elapsed since the last treatment.

Table 5. Health observations in beef study.

	ID-01	IA-01	MO-01	MO-02	MO-03	MO-04	MO-06	MO-07	MS-01	MS-02	MS-03	TOTAL
GONABREED lameness	1	1	0	1	0	2	1	0	0	0	0	6
GONABREED pinkeye	0	0	3	0	0	2	0	0	0	0	0	5
GONABREED neck lesions	0	0	0	0	0	4	0	0	0	0	0	4
GONABREED death	0	0	0	0	0	0	0	0	0	0	0	0
Control lameness	0	0	0	2	0	0	0	0	2	0	1	5
Control pinkeye	0	0	3	0	0	2	0	0	0	0	0	5
Control neck lesions	0	0	1	0	0	6	0	0	0	0	0	7
Control death	0	0	0	0	0	1	0	0	0	0	0	1

Injection site reactions determined by palpation on treatment days are shown in Table 6. Injection site reactions to the Day 0 GONABREED or Control injection were evaluated on Day 7. Injection site reactions to the Day 7 cloprostenol injection were evaluated on Day 9. There were few reported injection site reactions, and little difference between the GONABREED and control treatments.

Table 6. Injection site reactions in beef study.

Herd	Reaction to Day 0 GONABREED	Reaction to Day 0 Control	Reaction to Day 7 cloprostenol
ID-01	1	0	0
IA-01	0	0	0
MO-01	1	0	0
MO-02	0	0	1
MO-03	0	0	1
MO-04	1	0	1
MO-06	0	0	1
MO-07	5	4	0
MS-01	0	0	0
MS-02	0	2	0
MS-03	0	0	0
TOTAL	8	6	4

Pregnancy rate to FTAI is shown in Table 7. Pregnancy rates were variable across the study sites. A number of factors can influence pregnancy rate, including herd management procedures, service sire, AI technician, and physiological condition (body condition score, days postpartum, nursing status). Regardless, the pregnancy rate in the

GONABREED treatment group was higher than the pregnancy rate in the control treatment group at each location.

Table 7. Pregnancy rate to FTAI in beef study.

Herd	GONA-BREED Total cows, #	GONA-BREED Pregnancy to FTAI, #	GONA-BREED Pregnancy to FTAI, %	Control Total cows, #	Control Pregnancy to FTAI, #	Control Pregnancy to FTAI, %
ID-01	45	14	31.1	46	9	19.6
IA-01	42	14	33.3	37	3	8.1
MO-01	30	9	30.0	28	3	10.7
MO-02	34	6	17.6	30	4	13.3
MO-03	40	3	7.5	40	1	2.5
MO-04	44	11	25.0	41	0	0.0
MO-06[2]	--	--	--	--	--	--
MO-07	34	14	41.2	32	4	12.5
MS-01	27	4	14.8	31	1	3.2
MS-02	31	1	3.2	23	0	0.0
MS-03	37	10	27.0	34	4	11.8
TOTAL	364	86		342	29	

e. Adverse Reactions: There were no adverse effects on animal health attributable to the test article.

f. Conclusion: GONABREED used with cloprostenol sodium in an FTAI reproductive synchrony regimen in beef cows significantly ($P < 0.05$) increased pregnancy rate to FTAI compared to cloprostenol sodium alone.

2. Multi-center Field Study in Dairy Cows

a. Title: A Multi-center Clinical Study of the Effectiveness and Safety of Gonadorelin Injection for use with Cloprostenol Sodium to Synchronize Estrous Cycles to Allow for Fixed Time Artificial Insemination in Lactating Dairy Cows (Study No. CP0901).

b. Investigators: The study was conducted in six herds, representing major lactating dairy cattle management systems in the U.S.

[2] Excluded from the analysis of effectiveness because a bull entered the pasture on Day 9

Table 8. Clinical investigators and study locations for dairy study.

Investigator Location	Investigator	Herd Locations[3]
Dairy Veterinary Services Chandler, AZ	Niles Jennett, DVM	AZ-01: Stanfield, AZ AZ-01-H: Stanfield, AZ
The Dairy Authority, LLC Greeley, CO	Greg Goodell, DVM	CO-01: Platteville, CO CO-02: Ault, CO CO-02-H: Ault, CO
North Valley Veterinary Clinic Gooding, ID	Mike Holland, DVM, Ph.D.	ID-01: Jerome, ID ID-02: Wendell, ID ID-01-H: Jerome, ID ID-02-H: Wendell, ID
Dairy Veterinary Management Services, LLC Fallston, MD	Jennifer Trout, DVM	PA-01: Cochranville, PA

c. Study Design:

1) Objective: To evaluate the clinical effectiveness of GONABREED (gonadorelin acetate) used with cloprostenol sodium for increasing pregnancy rates to FTAI compared to cloprostenol sodium alone in lactating dairy cows.

2) Experimental Design: This study was conducted in accordance with CVM's Good Clinical Practices (CVM Guidance No. 85 (VICH GL9)). The study was conducted in six independent herds representing major dairy cattle management systems in the US (AZ, CO, ID, and PA). Four of those herds conducted research in two different seasons with a different set of cows, yielding a total of ten independent trials. The study was a masked, placebo-controlled study that utilized a completely randomized design at each site. Cows at each site were randomly assigned to one of two treatment groups, either the test article (GONABREED; gonadorelin acetate) or a placebo control (water for injection). Cow was the experimental unit. All study personnel were masked to treatment assignment. The test and control articles were labeled at the manufacturing site as Product A (water for injection) or Product B (GONABREED). The study was 45 ± 5 d long, and was completed after pregnancy diagnosis.

3) Study Animals: In total, the study enrolled 1,862 cows from six privately-owned herds in four major cattle-producing regions in the United States. Four of those herds were used to conduct research in two different seasons with a different set of cows, yielding a total of ten trials. Breeds were typical of the U.S. dairy industry. Cows were healthy, free of reproductive disorders, and had a body condition score between 2.5 to 4 (on a 5-point scale). All cows had calved at least once, were not detectably pregnant on Day 0, and were between 40 and 150 days post-partum at the beginning of the study.

[3] Research was conducted at four sites (AZ-01, CO-02, ID-01, and ID-02) in two separate seasons, one of which was during months that cows would be exposed to high ambient temperatures.

4) Treatment Groups: The two treatment groups used in this study were the test article treatment group (GONABREED; gonadorelin acetate) and a placebo control treatment group (control).

5) Drug Administration: The test article was GONABREED (gonadorelin acetate), which contained 105 mcg/mL gonadorelin base, present as the acetate salt. The control article was sterile water for injection. The cloprostenol injection contained 250 mcg/mL of cloprostenol, present as the sodium salt. All injections were administered intramuscularly in the neck or leg, alternating sides for each treatment day.

   Cows were treated according to the following schedule:

Day 0:	Cows injected with either 1 mL GONABREED or 1 mL water for injection (control)
Day 7:	All cows injected with 2 mL cloprostenol sodium
Day 9:	Cows injected with either 1 mL GONABREED or 1 mL water for injection (control)
Day 9/10:	Cows bred by artificial insemination 11 to 31 hours after the Day 9 injection

6) Measurements and Observations: Pregnancy was diagnosed by trans-rectal ultrasound or palpation at 45 ± 5 days (35 ± 5 days after FTAI). Animals were observed for injection site reactions or other adverse health events daily for Days 0 to 16, and weekly thereafter until pregnancy diagnosis.

7) 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 GONABREED treatment group to the percent success in the control group using a generalized linear mixed model. The statistical model included treatment group as a fixed effect and site and site by treatment group interaction as random effects. The environmental condition (heat stress or non-heat stress) was included in the model as a covariate, and remained in the model regardless of the associated P-value. The model assumed a binomial distribution with logit link. The difference between treatment groups was evaluated using a two-sided test at alpha=0.05. Estimated percent success (success of pregnancy to FTAI) and confidence intervals were back-transformed from the generalized linear mixed model (GLMM) least squares estimates.

d. Results:

1) Pooled Results

   The total number of cows initially enrolled, excluded from analysis, and included in the final database for analysis is shown in Table 9.

Table 9. Number of dairy cows per treatment group.

	GONA-BREED Enrolled	GONA-BREED Excluded	GONA-BREED Analyzed	Control Enrolled	Control Excluded	Control Analyzed
AZ-01	150	2	148	150	3	147
AZ-01-H	34	3	31	32	0	32
CO-01	127	27	100	127	26	101
CO-02	130	12	118	130	21	109
CO-02-H	29	2	27	32	1	31
ID-01	116	3	113	115	4	111
ID-01-H	35	0	35	35	1	34
ID-02	124	2	122	126	8	118
ID-02-H	35	0	35	35	1	34
PA-01	150	74	76	150	65	85
TOTAL	930	125	805	932	130	802

The study enrolled 1,862 cows, 930 cows in the GONABREED treatment group and 932 in the control treatment group. Two hundred and fifty five cows were excluded from the analysis of effectiveness; reasons included improper enrollment (141 cows), breeding prior to study day 28 (47 cows), sale due to low milk production or health problems (32 cows), inability to locate cow on critical study day (10 cows), administration of other reproductive drugs during the study (9 cows), death (8 cows), inconsistency in the data (5 cows), an interfering health problem (2 cows), and incorrect administration of treatment (1 cow).

The effectiveness analysis contained 1,607 cows, 805 cows in the GONABREED treatment group and 802 in the control treatment group. The number of cows diagnosed pregnant to FTAI, as determined on Day 45 ± 5 (35 ± 5 after FTAI), was 283 in the GONABREED treatment group and 117 in the control treatment group. The effect of season was not statistically significant (P = 0.4239). Table 10 summarizes the results of the statistical analysis, showing that the proportions of success in the two treatment groups were significantly different (P-value< 0.0001). Based on the analysis, the pregnancy rate in the GONABREED treatment group was 33.4%, higher than the pregnancy rate of 13.6% in the control treatment group.

Table 10. Summary of the statistical analysis of the proportion of treatment successes in each group in dairy study.

Treatment	Cows, #	Pregnancy rate to FTAI, %	95% Confidence Interval
GONABREED	805	33.40	(27.11, 40.34)
Control	802	13.63	(10.13, 18.09)

P-value: 0.0001

2) Individual Sites

Herds contained cows of Holstein (AZ-01, CO-01, CO-02, ID-01, PA-01), or Jersey (ID-02) breeds, with some herds containing a few other dairy breeds such as Guernsey, Shorthorn, or crosses of dairy breeds. These breeds are typical of the U.S. dairy cow industry.

Cows were housed in freestall barns (AZ-01, CO-01, ID-01, PA-01) or dry lots (CO-02, ID-02). Herd sizes ranged from 1,572 to 6,120 cows, with a range of 120 to 400 cows per pen. Cows were milked two (ID-02 only) or three times per day in herringbone, parallel, or rotary style parlors. Average milk yield ranged from 69 to 86 lbs/cow/d for the Holstein herds (51 lbs/cow/d for the ID-02 Jersey herd), and rolling herd average ranged from 21,022 to 26,415 lbs/cow/year for the Holstein herds. Bovine somatotropin was administered in three herds (ID-01, ID-02, PA-01). All cows were fed total mixed rations. Feedstuffs were varied across the sites, but all rations generally contained corn silage, alfalfa hay or haylage or green chop, and corn. Additional feedstuffs included other silages (sorghum, oatlage), cottonseed, molasses, beet pulp, distillers grains, and mineral mixes. Water was available from in-pen waterers.

Prior to the study, herds exclusively used artificial insemination as part of their reproductive program. The voluntary wait period prior to breeding ranged from 50 to 80 days after calving. All herds used some form of hormonal breeding regimen. Two herds (AZ-01, ID-02), used PGF2α with breeding to detected heat. Other herds used a fixed time reproductive synchrony regimen (CO-01, CO-02, ID-01, PA-01), although one herd (CO-02) used this regimen only when cows were > 150 d postpartum. The fixed time procedure was commonly with a presynchronization protocol (CO-01, ID-01, PA-01). Cows were typically bred at a fixed time unless observed in estrus prior to the scheduled day of breeding.

Overall study dates for each herd are shown in Table 11. Because most herds enrolled cows in cohorts, the treatment dates for each cohort differed; therefore, only the initial and final treatment dates and the final pregnancy diagnosis date for all cohorts are presented. Four of the sites (AZ, CO-02, ID-01, and ID-02), conducted the study in two different seasons, one of which was during months that cows would be exposed to high ambient temperatures. The daily maximum and minimum temperatures indicated that the conditions during the study at these sites were representative of conditions that would cause heat stress in lactating dairy cows.

Table 11. Overall study dates in dairy study.

Herd	Initial Day 0	Final Day 9	Final pregnancy Diagnosis
AZ-01	03/10/11	04/09/11	05/14/11
AZ-01-H	08/11/11	08/20/11	09/23/11
CO-01	10/26/10	02/03/11	03/08/11
CO-02	10/25/10	12/29/10	01/31/11
CO-02-H	07/31/11	08/09/11	09/13/11
ID-01	03/19/11	04/04/11	05/12/11
ID-01-H	07/16/11	07/25/11	08/31/11
ID-02	04/09/11	05/09/11	06/14/11
ID-02-H	08/06/11	08/15/11	09/21/11
PA-01	01/31/11	05/15/11	06/16/11

Observations of any abnormal health events during the study are summarized in Table 12. Cows were generally healthy and few abnormal health observations were made during the study. The primary abnormalities included mastitis, lameness, and injury. These observations are common conditions in dairy cattle and were not apparently related to treatment. Two cows in the GONABREED treatment group had other conditions; one with neck swelling and one with abdominal pain and constipation. Eight cows died during the study. Four cows were euthanized due to injury, and the remaining deaths were due to hemorrhagic bowel syndrome, lymphosarcoma, pneumonia, and an unknown cause. Five of the cows were in the GONABREED treatment group (including three cows euthanized due to injury), and three of the cows were in the control treatment group. None of these deaths are likely attributable to the test article.

Table 12. Health observations in dairy study.

	AZ-01	AZ-01-H	CO-01	CO-02	CO-02-H	ID-01	ID-01-H	ID-02	ID-02-H	PA-01	TOTAL
GONABREED mastitis	2	0	1	4	3	6	1	8	1	2	28
GONABREED pneumonia	0	0	0	1	1	0	0	0	0	0	2
GONABREED Lameness/foot rot	0	0	0	1	0	0	0	0	0	2	3
GONABREED downer cow/injury	0	0	0	0	0	0	0	0	0	2	2
GONABREED death	0	3	1	0	1	0	0	0	0	0	5
GONABREED other	0	1	0	0	0	1	0	0	0	0	2
Control mastitis	4	1	2	3	1	4	1	8	0	2	26
Control pneumonia	0	0	0	1	0	0	0	0	0	0	1
Control lameness/foot rot	0	0	0	0	0	0	0	0	0	2	2
Control downer cow/injury	0	0	0	1	0	0	0	0	0	0	1
Control death	0	0	0	2	0	0	0	0	0	1	3
Control other	0	0	0	0	0	0	0	0	0	0	0

Injection site reactions determined by palpation on treatment days are shown in Table 13. Injection site reactions to the Day 0 GONABREED or Control injection were evaluated on Day 7. Injection site reactions to the Day 7 cloprostenol injection were evaluated on Day 9. There were few reported injection site reactions, and little difference between the GONABREED and control treatments.

Table 13. Injection site reactions in dairy study.

Herd	Reaction to Day 0 GONABREED	Reaction to Day 0 Control	Reaction to Day 7 cloprostenol
AZ-01	0	0	0
AZ-01-H	1	0	0
CO-01	4	5	4
CO-02	8	9	14
CO-02-H	1	3	0
ID-01	8	12	26
ID-01-H	1	0	1
ID-02	9	11	11
ID-02-H	0	1	1
PA-01	0	0	1
TOTAL	32	40	58

Pregnancy rate to fixed time FTAI is shown in Table 14. Pregnancy rates were variable across the study sites. A number of factors can influence pregnancy rate, including herd management procedures, environmental conditions, service sire, AI technician, and physiological condition (body condition score, days postpartum, milk yield). Regardless, the pregnancy rate in the GONABREED treatment group was higher than the pregnancy rate in the control treatment group at each location.

Table 14. Pregnancy rate to FTAI in dairy study.

Herd	GONA-BREED Total cows, #	GONA-BREED Pregnancy to FTAI, #	GONA-BREED Pregnancy to FTAI, %	Control Total cows, #	Control Pregnancy to FTAI, #	Control Pregnancy to FTAI, %
AZ-01	148	48	32.4	147	22	15.0
AZ-01-H	31	4	12.9	32	3	9.4
CO-01	100	33	33.0	101	10	9.9
CO-02	118	48	40.7	109	16	14.7
CO-02-H	27	6	22.2	31	1	3.2
ID-01	113	36	31.9	111	15	13.5
ID-01-H	35	17	48.6	34	5	14.7
ID-02	122	50	41.0	118	23	19.5
ID-02-H	35	14	40.0	34	8	23.5
PA-01	76	27	35.5	85	14	16.5
TOTAL	805	283		802	117	

e. Adverse Reactions: There were no adverse effects on animal health attributable to the test article.

f. Conclusion: GONABREED used with cloprostenol sodium in an FTAI reproductive synchrony regimen in lactating dairy cows significantly ($P < 0.05$) increased pregnancy rate to FTAI compared to cloprostenol sodium alone.

IV. TARGET ANIMAL SAFETY:

Through the evaluation of published literature and limited pharmacokinetic studies, it has been determined that an increase in dose from 86 mcg gonadorelin base (100 mcg gonadorelin acetate) to 100 mcg gonadorelin base is safe for the treatment of follicular ovarian cysts in dairy cattle.

The two multi-center dose confirmation field studies in beef and dairy cows were used to evaluate the safety of 105 mcg gonadorelin base and the use of GONABREED with cloprostenol sodium in lactating dairy cows and beef cows under intended use conditions for the synchronization of estrous cycles to allow for FTAI (see Section III above). Few adverse events occurred during the study. There were no adverse effects on animal health attributable to the test article. GONABREED is approved for use with cloprostenol sodium for synchronization of estrus to allow for FTAI in Australia and New Zealand. Since its 2001 approval in Australia and New Zealand, approximately 1.7 million doses have been sold and only seven case reports have been filed. Three reports of these reports were of serious adverse drug experiences involved the deaths of four animals possibly related to use of the drug. One of the deaths was attributed to infection by *Clostridium chauvoei* (Blackleg), possibly due to intramuscular injection. Cause of the other three deaths could not be determined. Four additional reports involved apparent lack of effectiveness or lower than anticipated pregnancy rates. The low frequency of these adverse events and questionable relationship to the drug do not raise target animal safety concerns.

V. HUMAN FOOD SAFETY:

A. Microbial Food Safety (Antimicrobial Resistance):

The use of GONABREED injectable solution for the treatment of ovarian follicular cysts in dairy cattle, and the use of GONABREED injectable solution with cloprostenol sodium to synchronize estrous cycles to allow fixed time artificial insemination in lactating dairy and beef cows are not thought to nor have been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated animals. FDA determined that an assessment of the microbial food safety (antimicrobial resistance) associated with the use of GONABREED injectable solution in dairy cattle and the use of GONABREED injectable solution with cloprostenol sodium in lactating dairy and beef cows was not necessary at this time.

B. Impact of Residues on Human Intestinal Flora:

Residues and metabolites of GONABREED injectable solution or cloprostenol sodium in or on the edible tissues of treated dairy cattle, and treated lactating

dairy and beef cows are not thought to nor have been reported to impact the intestinal flora of human consumers. FDA determined that an assessment of the impact of residues or metabolites of GONABREED injectable solution or cloprostenol sodium in the edible tissues of treated dairy cattle, and treated lactating dairy and beef cows on human intestinal flora was not necessary at this time.

C. Toxicology:

Summary of Toxicology Studies

No additional toxicology studies were required for the evaluation of human food safety to support the approval of GONABREED injectable solution as a generic copy of the Reference Listed New Animal Drug (RLNAD), CYSTORELIN (NADA 098-379). Increasing of the dose for GONABREED injectable solution to 100 mcg gonadorelin from the labeled dose of 86 mcg gonadorelin in the RLNAD does not change the toxicological conclusion.

Cloprostenol sodium is the active ingredient in severalapproved new animal drug products. Based on the rapid depletion of gonadorelin and cloprostenol residues from cattle, the use of GONABREED injectable solution with cloprostenol sodium does not cause additional toxicological concerns for human food safety, and no additional toxicology studies were required for the approval.

D. Assignment of the Final Acceptable Daily Intake (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:

1. Summary of Residue Chemistry Studies

No additional residue chemistry studies were required for the evaluation of human food safety to support the approval of GONABREED injectable solution containing 100 mcg gonadorelin/mL as a generic copy of the RLNAD, CYSTORELIN (NADA 098-379), for the treatment of ovarian follicular cysts in dairy cattle. A tissue residue study to establish the withdrawal period for the generic product is not needed because a waiver from the requirement to conduct an *in vivo* bioequivalence study for the generic GONABREED injectable solution was granted. The withdrawal period and milk discard time for the generic product are those previously assigned to the RLNAD. Neither a withdrawal period nor a milk discard time for generic GONABREED injectable solution is required because it was not required for the RLNAD. The tolerances established for the RLNAD apply to the generic product. A tolerance for gonadorelin is not required because it was not required for the RLNAD. A regulatory method for gonadorelin is not required because it was not required for the RLNAD.

No additional residue chemistry studies were required for the approval of GONABREED injectable solution at a dose of 100 mcg gonadorelin for the treatment of ovarian follicular cysts in dairy cattle. This dose is 1.2 times the dose for GONABREED injectable solution as a generic copy of the RLNAD. Because gonadorelin is known to be metabolized rapidly and has a very short half-life in cattle, FDA concluded that the use of GONABREED injectable solution at a dose of 100 mcg gonadorelin does not cause additional residue chemistry concerns beyond those that have already been addressed for the generic GONABREED injectable solution.

No additional residue chemistry studies were required for the approval of GONABREED injectable solution at a dose of 100 mcg gonadorelin with 500 mcg cloprostenol (as cloprostenol sodium), which is the active ingredient in several approved new animal drug products. Based on the rapid depletion of gonadorelin and cloprostenol residues in cattle, the use of GONABREED injectable solution at a dose of 100 mcg gonadorelin with the approved cloprostenol sodium products does not cause additional residue chemistry concerns beyond those that have already been addressed for the individual approvals of GONABREED injectable solution at a dose of 100 mcg gonadorelin and the cloprostenol sodium products.

2. Target Tissue and Marker Residue

It is not necessary to assign a target tissue or a marker residue for gonadorelin residues in cattle.

3. Tolerances

Tolerances for gonadorelin in edible tissues or milk of cattle are not required.

4. Withdrawal Period and Milk Discard Time

The approved use of GONABREED injectable solution at a dose of 100 mcg gonadorelin in dairy cattle does not require a withdrawal period (i.e., zero withdrawal) or a milk discard time (i.e., zero milk discard).

The approved use of GONABREED at a dose of 100 mcg gonadorelin with 500 mcg cloprostenol (as cloprostenol sodium) in lactating dairy and beef cows does not require a withdrawal period (*i.e.*, zero withdrawal) or a milk discard time (*i.e.*, zero milk discard).

G. Analytical Method for Residues:

A regulatory method for monitoring gonadorelin residues in cattle is not required.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The labeling for GONABREED contains the following user safety warning regarding safety to humans handling, administering or exposed to GONABREED:

"Not for use in humans. Keep this and all drugs out of the reach of children."

The labeling for cloprostenol sodium contains the following user safety warning regarding safety to humans handling, administering, or exposed to cloprostenol sodium:

"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. [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."

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of sections 512(n) and 512(b)(1) of the act and demonstrates that GONABREED, when used according to the label, is safe and effective.

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 cloprostenol sodium, which also has Rx marketing status.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the act, the 512(b)(1) supplemental approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new use of GONABREED with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.

C. Patent Information:

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