Approval Date: July 29, 2003

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-200

Progesterone

EAZI-BREED™ CIDR®
Cattle Insert

For Synchronization of the Return to Estrus in Lactating Dairy Cows Inseminated at the Immediately Preceding Estrus

SPONSORED BY:

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001-0199

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FREEDOM OF INFORMATION SUMMARY

EAZI-Breed™ CIDR® Cattle Insert (progesterone)

1. GENERAL INFORMATION:

a. File Number:	NADA 141-200
b. Sponsor:	Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, MI 49001-0199 Drug Labeler Code: 000009
c. Established Name:	Progesterone
d. Proprietary Name:	EAZI-Breed™ CIDR® Cattle Insert
e. Dosage Form:	Intravaginal Insert
f. How Supplied:	10 Inserts per Polyethylene Bag
g. How Dispensed:	OTC
h. Amount of Active Ingredient:	Each insert contains 1.38 grams progesterone in molded silastic over a nylon spine.
i. Route of Administration:	Intravaginal
j. Species/Class:	Bovine/Lactating Dairy Cows
k. Recommended Dosage:	One Insert (1.38 grams progesterone)
l. Pharmacological Category:	Steroid Hormone
m. Indications:	For synchronization of the return to estrus in lactating dairy cows inseminated at the immediately preceding estrus
n. Effect of Supplement:	The supplement provides for the synchronization of the return to estrus in lactating dairy cows inseminated at the immediately preceding estrus.

2. EFFECTIVENESS:

A. Dosage Characterization:

Previous information submitted to support the original approvals in beef cows, beef heifers and dairy heifers (NADA 141-200; original approval date of May 2, 2002) provided the scientific basis for the dose (1.38 g progesterone) of the intravaginal progesterone insert (CIDR insert) selected for the current use in lactating dairy cows.

For synchronization of the return to estrus in lactating dairy cows, CIDR inserts are administered on day 14±1 after insemination and removed 7 days later. This duration of administration is consistent with practical application. Estrous cycle lengths of 18 to 24 days (mean of 21 days) are considered normal for dairy cows. Therefore, administration of CIDR inserts on day 14±1 after insemination prevents a "shortened" return to estrus. Removal 7 days later on day 21±1 after the previous insemination allows for a luteal phase of normal length in those animals that spontaneously regress their corpus luteum during the administration period. This also prevents the development of persistent follicles and the ovulation of senescent ova (Mihm et al., 1994) and increased embryonic death (Ahmad et al., 1995). Removal on day 21±1 after insemination allows cows with spontaneous estrous cycle lengths of 22 to 25 days to have their return to estrus synchronized with those animals that spontaneously regress their corpus luteum during the CIDR insert administration period and return to estrus after removal of the insert. Furthermore, use of a 7 day administration period is of practical value for producers as it allows for administration and removal of CIDR inserts on the same day of the week.

References Cited

Ahmad, N. R., N. Schrick, R. L. Butcher and E. K Inskeep. 1995. Effect of persistent follicles on early embryonic losses in beef cows. Biol. Reprod. 52: 1129-1135

Mihm, M., N. Curran, P. Hyttel, M. P. Boland and J. F. Roche. 1994. Resumption of meiosis in cattle oocytes from preovulatory follicles with a short and long duration of dominance. J. Reprod. Fertil. Abstr. Series 13: 14.

B. Substantial Evidence:

A study was conducted at eight commercial dairy farms (Table 1). The objectives of the study were to determine the effect of the CIDR inserts, given to lactating dairy cows from 14 ± 1 to 21 ± 1 days after insemination, on synchrony of returns to estrus and fertility to inseminations immediately prior to and after treatment.

Table 1. List of Principal Investigators and Trial Sites

Site Identification	Principal Investigator	Trial Site Location
A	Paul Busman DVM Deer Creek Veterinary Services Coopersville, MI	Meadow Rock Dairy Greenville, MI
B	Darrel Kesler PhD University of Illinois Urbana, IL	Inwood Dairy Elmwood, IL
C	Steve Carlson DVM Central Valley Large Animal Services Tipton, CA	Bayou Vista Dairy Tipton, CA
D	Jose Santos DVM, PhD UC Davis, VMTRC Tulare, CA	River Ranch Hanford, CA
E	Phillip Jardon DVM Visalia, CA Currently residing: Carroll, IA	Dover Dairy Hanford, CA
F	Arthur Sherman DVM Keseca Veterinary Clinic Geneva, NY	Willow Bend Farm Clifton, NY
G	Anthony Wiseley DVM Perry Veterinary Clinic Perry, NY	Mount Morris Dairy Farm Mount Morris, NY
H	James P. Garlough Okeechobee, FL	Larson Dairy Okeechobee, FL

General Design:

This study was conducted at 8 commercial dairies (trial sites; see Table 1) using a common protocol. Data were pooled across all locations for statistical analyses. Lactating Holstein dairy cows at either their first service following the voluntary wait period or found not pregnant to a previous insemination (determined by rectal palpation or return to estrus) were eligible for participation in this study. Cows ≥ 40 days or ≤ 150 days after calving, with fewer than 4 inseminations in the current lactation, and clinically healthy as determined by a physical examination, were eligible for enrollment. CIDR inserts were administered intravaginally on day 14 ± 1 after artificial insemination (AI). To maintain better control of the study, cows meeting the enrollment criteria had their pre-enrollment estrus synchronized with dinoprost tromethamine (5 mL LUTALYSE® Sterile Solution; day of injection = study day 0). Animals inseminated on study days 2, 3, and 4 (pre-enrollment period)

were enrolled in the study and were assigned randomly in replicates to one of the two treatment groups: 1) control, no further treatment, or 2) administration of a CIDR insert on study day 17 (day 14 ± 1 after insemination). CIDR inserts were removed 7 days later (study day 24, day 21 ± 1 after insemination). At the time of CIDR insert removal, the vaginal mucus adhering to each insert was observed and a mucus score was recorded; score 1 = no mucus observed, 2 = clear mucus, 3 = cloudy mucus, 4 = yellow mucus and 5 = red or brown mucus.

Each cow was observed for signs of estrus using site specific Standard Operating Procedures (SOPs) on study days 21 to 29 (18±1 to 26±1 days after the pre-enrollment insemination), herein called the re-synchronization of estrus period. Cows deemed to be in estrus (heat) were artificially inseminated following SOPs at each location. Cows not observed in estrus during the re-synchronization of estrus period were assumed to be pregnant and were not inseminated. In addition, each cow was observed for general health status daily on study days 17 to 29 (CIDR insert administration period plus the 5 days after insert removal).

Pregnancy status of cows was determined via rectal palpation or ultrasonography 35 to 45 days after the pre-enrollment insemination (approximate interval of study days 37 to 49) and again 35 to 45 days after inseminations conducted during the re-synchronization of estrus period (approximate interval of study days 56 to 74).

Decision Variables:

Effectiveness: The primary variable for statistical analysis for effectiveness was the number of cows with a synchronized return to estrus on study days 25, 26, and 27; corresponding to the 3 days after CIDR insert removal and the 3 consecutive days with the highest number of cows in estrus in the control group. Cows subsequently determined to be pregnant to artificial insemination during the pre-enrollment estrus were not included in analyses for synchronization of the return to estrus.

Ancillary statistical analysis for return to estrus was conducted on all control cows in estrus during the entire 9-day re-synchronization of estrus observation period (study days 21 to 29) vs. number of CIDR insert treated cows in estrus on study days 26 to 29.

Median time to estrus during the re-synchronization period also was evaluated as an ancillary variable. This variable was defined as the number of days from removal of the insert to observed estrus for the CIDR insert group and as the number of days starting on study day 21 to observed estrus for the control group.

Fertility: Conception rates (CR) and pregnancy rates (PR) were used to assess treatment effects on fertility, as measurements of safety for the use of CIDR inserts. The following variables were evaluated:

PR of all cows inseminated during the pre-enrollment period (all cows enrolled): This evaluated the potential effect of CIDR insert administration in animals that conceived to the pre-enrollment inseminations (effect of CIDR insert administered to pregnant animals).

- PR = [# pregnant ÷ (# in treatment group – # with unknown pregnancy status)] X 100.

CR and PR for all inseminations were conducted during the 9-day re-synchronization of estrus period (study days 21 to 29). These variables evaluated the potential effect of CIDR insert administration on CR and PR to inseminations immediately following insert removal.

- CR = [# pregnant to inseminations during the re-synchronization of estrus period ÷ (# inseminated during the re-synchronization of estrus period - # with unknown pregnancy status)] X 100.
- PR = [# pregnant ÷ (# enrolled - # pregnant to the pre-enrollment inseminations - # with unknown pregnancy status)] X 100.

An ancillary fertility variable evaluated was the cumulative PR to inseminations during the pre-enrollment synchronization and re-synchronization of estrus periods.

Statistical Analysis:

The synchronization of the return to estrus, pregnancy rates and conception rates were analyzed using a mixed logistic regression analysis. The model included terms for the random effects of location, block within location (when reasonable), location by treatment interaction, and the fixed effect of treatment. Covariates considered for inclusion in the models were parity (first lactation vs. all others combined), days post-partum at time of enrollment, body condition score, days from Lutalyse administration to insemination (during pre-enrollment estrus synchronization period), and month of enrollment (grouped as March/April, May/June, and July/August/September). Covariates were retained in the model if either the main effect or their interaction with treatment was significant (α=0.10).

Survival analysis methods (proportional hazards regression analysis) were used to evaluate median time to estrus.

Level of significance:

The synchronization of the return to estrus was tested using a one-sided test (α=0.05) of the hypothesis that the CIDR insert group had higher rates of return to estrus than the control. For the primary measurements of fertility, pregnancy rates and conception rate over the 9-day re-synchronization period, a one-sided test (α=0.10) of the hypothesis that the insert group is less than the control was used. For the

ancillary measurement of cumulative pregnancy rates, and conception rates over study days 21-29 for the control and study days 26-29 for the insert group, a two-sided test (α=0.05) of the hypothesis that the insert group is different than the control was used. Estrus detection and pregnancy rates over these intervals (study days 21-29 for the control and study days 26-29 for the insert group) were tested with a one-sided test (α=0.05) of the hypothesis that insert group is greater than the control.

Results:

During the course of the study, 1893 cows were enrolled into the study (945 control and 948 CIDR insert cows); however, 1754 were included in the analysis (867 control and 887 CIDR insert cows). Total number of animals enrolled and documentation when animals were removed from the study are presented in Table 2.

Table 2. Number of Cows Enrolled and Censored (Not Included in Statistical Analyses) for Primary Decision Variables [Synchronization of the Return to Estrus, Pregnancy Rate (PR) to Artificial Inseminations (AI) During the Pre-enrollment Period, and PR and Conception Rate (CR) During the Re-synchronization of Estrus Period]

Location	Treatment Group	Number Enrolled[a]	Number Completely Censored[b]	Total Number in SAS Data Set[c]	Primary Decision Variables (Number of Cows Censored)[d]			
					PR to AI in Pre-enrollment Period	Synchronization of Returns to Estrus	CR to AI in the Re-synchronization of Estrus Period	PR to AI in Re-synchronization of Estrus Period
A	Control	127	7	120	0	0	2	2
	CIDR	170	46	124	1	2	4	4
B	Control	125	6	119	0	4	4	4
	CIDR	125	1	124	1	5	6	6
C	Control	110	2	108	0	1	2	2
	CIDR	111	2	109	0	0	1	1
D	Control	125	3	122	0	0	0	0
	CIDR	125	2	123	1	0	0	0
E	Control	119	14	105	0	0	0	0
	CIDR	119	12	107	1	3	4	4
F	Control	77	1	76	0	0	0	0
	CIDR	78	2	76	0	1	1	1
G	Control	121	7	114	2	2	3	3
	CIDR	121	7	114	1	1	1	1
H	Control	120	17	103	2	1	2	2
	CIDR	120	10	110	1	0	1	1
Total	Control	924	57	867	4	8	13	13
	CIDR	969	82	887	6	12	18	18

[a] Cows entered on the Randomization and Treatment Administration Record
[b] Cows removed from consideration for all analyses
[c] Difference of number enrolled and completely censored
[d] Not included in statistical analyses of primary decision variables; these censored cows are in addition to those cows completely censored

Over all locations 97.3% (863/887) of the CIDR inserts administered were retained for the scheduled 7-day administration period. Retention rates ranged from a low of 91.9% at one trial site to a high of 100% at two locations.

Effectiveness: In the CIDR insert group 34.1% of cows were observed in estrus during study days 25, 26, and 27 compared to 19.3% of cows in the control group observed in estrus on these study days (Table 3). Thus the CIDR inserts were effective for synchronization of the return to estrus in lactating dairy cows inseminated at the immediately preceding estrus.

Table 3. Synchronization of returns to estrus, percent seen in estrus over study days 25, 26, and 27, and logistic regression analysis[a]

Treatment	Percent	(# Estrus/ # Available)	Logit Means	SE	DF	95% Confidence Interval	One-sided P-Value
Control	19.3%	(105/544)	-1.91	0.19	7	(-2.35,-1.47)	
CIDR[b]	34.1%	(201/589)	-0.69	0.14	7	(-1.02,-0.36)	
Difference	14.8%		-1.22	0.21	7	(-1.71,-0.74)	0.001

	Percent Observed in Estrus (# Available)						
Treatment	Body Condition Score[c]				Day of AI[d]		
	≥ 2.0- ≤ 2.5	>2.5- ≤3.0	>3.0- ≤3.5	>3.5- ≤4.0	2[e]	3	4
Control	16% (147)	22% (238)	20% (131)	14% (28)	12% (86)	21% (304)	21% (154)
CIDR	44% (146)	31% (259)	30% (143)	32% (41)	46% (94)	34% (325)	28% (170)

a Variance Components: trial = 0.0238; block(trial) = 1.8816; trial*treatment = 0; Extra-dispersion = 0.6219.
Model included Covariates: Body condition score (grouped as above; main effect p=0.656 interaction with treatment p=0.008); day of AI (grouped as above; main effect p=0.610 interaction with treatment p=0.002).

b CIDR cows given intravaginal progesterone inserts on study days 17-24.

c Body condition scores assigned on scale of 1 to 5; 1 = very thin, and 5 = obese.

d Pre-enrollment artificial insemination (AI) of cows was on study days 2, 3, and 4.

e Includes two cows that were also inseminated on day 1

During the re-synchronization of estrus period, the median time to estrus was 5 days from study day 21 for the control group and 3 days from study day 24 for the CIDR insert group. These times corresponded to study days 26 and 27, respectively, in the control and CIDR insert treatment groups. Significantly more (P = 0.031) cows in the CIDR insert treatment group (43%) were observed in estrus over study days 26 to 29 than in the control group over study days 21 to 29 (36%).

Fertility: Pregnancy rate to inseminations conducted during the pre-enrollment period was reduced for cows in the CIDR insert vs. control treatment group (32.7% vs. 36.7%, Table 4). This indicated that the administration of a CIDR insert to cows inseminated at the estrus immediately prior to treatment resulted in a loss of pregnancy in an estimated 11% [100(36.7-32.7)/36.7] of pregnant animals.

Table 4. Pregnancy rate to pre-enrollment AI[a], percent pregnant, and logistic regression analysis[b]

Treatment	Percent	(# Pregnant/ # AIed)	Logit Means	SE	DF	95% Confidence Interval	One-sided P-Value
Control	36.7%	(317/863)	-0.57	0.13	7	(-0.88,-0.26)	
CIDR[c]	32.7%	(288/881)	-0.76	0.13	7	(-1.08,-0.45)	
Difference	4.0%		0.19	0.10	7	(-0.04,0.43)	0.044

	Percent Pregnant (#AIed)								
	Parity		Body Condition Score[d]				Day of AI		
Treatment	1	≥2	≥ 2.0-≤ 2.5	>2.5-≤3.0	>3.0-≤3.5	>3.5-≤4.0	2[e]	3	4
Control	41% (307)	35% (556)	28% (203)	39% (392)	38% (210)	52% (58)	35% (133)	35% (469)	41% (261)
CIDR	35% (325)	31% (556)	27% (202)	34% (397)	30% (207)	45% (75)	27% (129)	31% (475)	38% (277)

a Pre-enrollment artificial insemination (AI) of cows was on study days 2, 3, and 4.

b Variance Components: trial = 0.0989; block(trial) = 0.2979 ; trial*treatment = 0; Extra-dispersion = 0.9123.
Model included Covariates: Parity (1 and ≥2; p=0.108), Body Condition Score (continuous; p = 0.002), and Day of insemination (continuous; p = 0.034); none of the covariates interacted significantly with treatment.

c CIDR cows given intravaginal progesterone inserts on study days 17-24.

d Body condition scores assigned on scale of 1 to 5; 1 = very thin and 5 = obese.

e Includes four cows that were inseminated on day 1.

Mucous scores were obtained for 863 cows in the CIDR insert treatment group: score 1 = 7%, 2 = 26%, 3 = 38%, 4 = 27%, and 5 = 2%. Thus, a majority of cows (scores 3 + 4, 65%) had evidence of localized irritation and only 2% of cows had a score of 5 suggestive of severe irritation or vaginitis. For the majority of cows in the CIDR insert treatment group, vaginal irritation was likely transient in nature since the fertility of untreated and treated cows to post-treatment inseminations was not different.

Conception rate to inseminations during the 9-day re-synchronization of estrus period were similar in the control vs. CIDR insert treatment groups (30.9% vs. 26.7%; Table 5). Therefore, under the conditions of this study, treatment of cows with the CIDR insert did not reduce the conception rate to inseminations immediately following insert removal.

Table 5. Conception rate to AI[a] conducted at returns to estrus, percent pregnant, and logistic regression analysis[b]

Treatment	Percent	(# Pregnant/ # AIed)	Logit Means	SE	DF	95% Confidence Interval	One-sided P-Value
Control	30.9%	(60/194)	-0.79	0.23	7	(-1.34,-0.25)	
CIDR[c]	26.7%	(71/266)	-0.99	0.22	7	(-1.51,-0.48)	
Difference	4.2%		0.20	0.32	7	(-0.55,0.95)	0.271

	Percent pregnant (# AIed)	
	Parity	
Treatment	1	≥2
Control	35% (72)	29% (122)
CIDR	33% (105)	22% (161)

a Artificial insemination (AI) conducted at returns to estrus during study days 21 to 29.

b Variance Components: trial = 0; block(trial) excluded from the model; trial*treatment = 0.2176; Extra-dispersion = 0.9780. Model included Covariate: Parity (1 and ≥2; p=0.055).

c CIDR cows given intravaginal progesterone inserts on study days 17-24.

Similarly, pregnancy rate to inseminations during the 9-day re-synchronization of estrus period were similar between treatments (11.1% vs. 12.2% in the control and CIDR insert treatment groups; Table 6). Therefore, under the conditions of this study treatment of cows with the CIDR insert did not reduce the pregnancy rate to inseminations immediately following insert removal.

Table 6. Pregnancy rate to AI[a] conducted at returns to estrus, percent pregnant, and logistic regression analysis[b]

Treatment	Percent	(# Pregnant/ # In Group)	Logit Means	SE	DF	95% Confidence Interval	One-sided P-Value
Control	11.1%	(60/540)	-2.06	0.22	7	(-2.58,-1.55)	
CIDR[c]	12.2%	(71/583)	-1.96	0.21	7	(-2.46,-1.46)	
Difference	-1.1%		-0.10	0.24	7	(-0.67,0.47)	0.350

	Percent pregnant (# in Group)	
	Parity	
Treatment	1	≥2
Control	14% (182)	10% (358)
CIDR	17% (209)	10% (374)

a Artificial insemination (AI) conducted at returns to estrus during study days 21 to 29.

b Variance Components: trial = 0.1343; block(trial) excluded from the model; trial*treatment = 0.0921; Extra-dispersion = 0.9547. Model included Covariate: Parity (1 and ≥2; p=0. 009).

c CIDR cows given intravaginal progesterone inserts on study days 17-24.

In addition, the cumulative pregnancy rate for the control group was 44.0%, compared to 41.2% for the CIDR insert group (p=0.277).

Health Observations: No general health observations or medical events were noted that would suggest a detrimental effect that could be attributed to use of CIDR inserts as described in this study. A total of two adverse reactions related to abnormal reproductive tract discharge during CIDR insert treatment were noted: One of these cows had an insert that was turned 90 degrees to expected orientation within the vagina. In both cows, the vaginal discharge appeared to be self-limiting as no discharge was noted during post-treatment observations. Based on mucous scores recorded at the time of insert removal, a majority of cows experienced some degree of vaginal irritation, but appeared also to be self-limiting as post-treatment conception and pregnancy rates were not different between treatments.

Conclusions:

When using proper administration techniques, retention of CIDR inserts in lactating dairy cows was 97.3%. Administration of CIDR insert to lactating dairy cows on day 14±1 after insemination and removed 7 days later (day 21±1 after insemination) effectively synchronized their return to estrus. Cows in the CIDR insert treatment group had a reduced pregnancy rate to inseminations at estrus immediately preceding treatment when compared to cows in the control group. No difference was detected between treatment groups for conception rate or pregnancy rate to inseminations conducted during the 9-day re-synchronization of estrus period (i.e. following insert removal).

3. TARGET ANIMAL SAFETY:

A target animal safety study, performed according to Good Laboratory Practices regulations (GLP, 21 CFR 58), supported the original approval (NADA 141-200, approval date - May 2, 2002) of the CIDR insert in suckled beef cows and replacement beef and dairy heifers. Information provided with that target animal safety study also support the current supplemental new animal drug application for lactating dairy cows.

Animal safety data were collected during the conduct of the clinical effectiveness study described in Section 2 above. This study provided observations on general health and fertility of cows during and following removal of CIDR inserts. Administration of CIDR inserts on day 14±1 after insemination and removal 7 days later resulted in a reduction in pregnancy rates to inseminations immediately prior to administration of the inserts when compared to the control group. Conception rates and pregnancy rates to inseminations following CIDR insert removal were similar between treatment groups. Localized vaginal irritation was present in a large portion of cows administered CIDR inserts. This irritation was self-limiting and did not affect subsequent fertility. Two adverse reactions were noted relative to reproductive tract discharge during treatment: One animal had an insert that was turned 90 degrees to expected orientation within the vagina. For these two cows, the vaginal discharge appeared to be self-limiting as no discharge was noted during post-treatment observations.

4. HUMAN SAFETY:

Adequate data have been submitted previously to NADA 141-200 to establish a withdrawal period for use of intravaginal progesterone inserts in beef cattle and dairy heifers; see the FOI for NADA 141-200 dated May 2, 2002.

- **Residue Depletion Studies**

Progesterone Study in Milk

Title of study:

Determination of concentration of progesterone in milk of untreated pregnant cows and estrous cycling cows with and without a CIDR™ 1380 progesterone-releasing insert.

Name of Study Director:

Rex E. Hornish, Ph.D.
Research Advisor
Preclinical Development
Pharmacia Animal Health,
Pharmacia Corporation
Kalamazoo, MI 49001

Location of the study:

The animal phase of the study was conducted at a commercial dairy in Banfield, MI. The analysis of the milk samples for progesterone concentration was performed in the laboratories of Pharmacia Animal Health.

Brief outline of the protocol:

In this GLP-compliant study, milk samples were collected from untreated pregnant dairy cows, untreated estrous cycling cows, and cycling cows administered an intravaginal progesterone insert (EAZI-BREED CIDR™ Cattle Insert; CIDR insert) containing 1.38 g of progesterone. CIDR inserts were administered intravaginally 14±1 days after estrus and were removed 7 days later.

The Coat-A-Count® Progesterone RIA kit, manufactured by Diagnostic Products Corporation (DPC), Los Angeles, CA, was used to determine the progesterone concentration in skim milk samples collected in this study. The kit was modified and validated by Pharmacia Animal Health to assay bovine milk samples.

Number of animals:

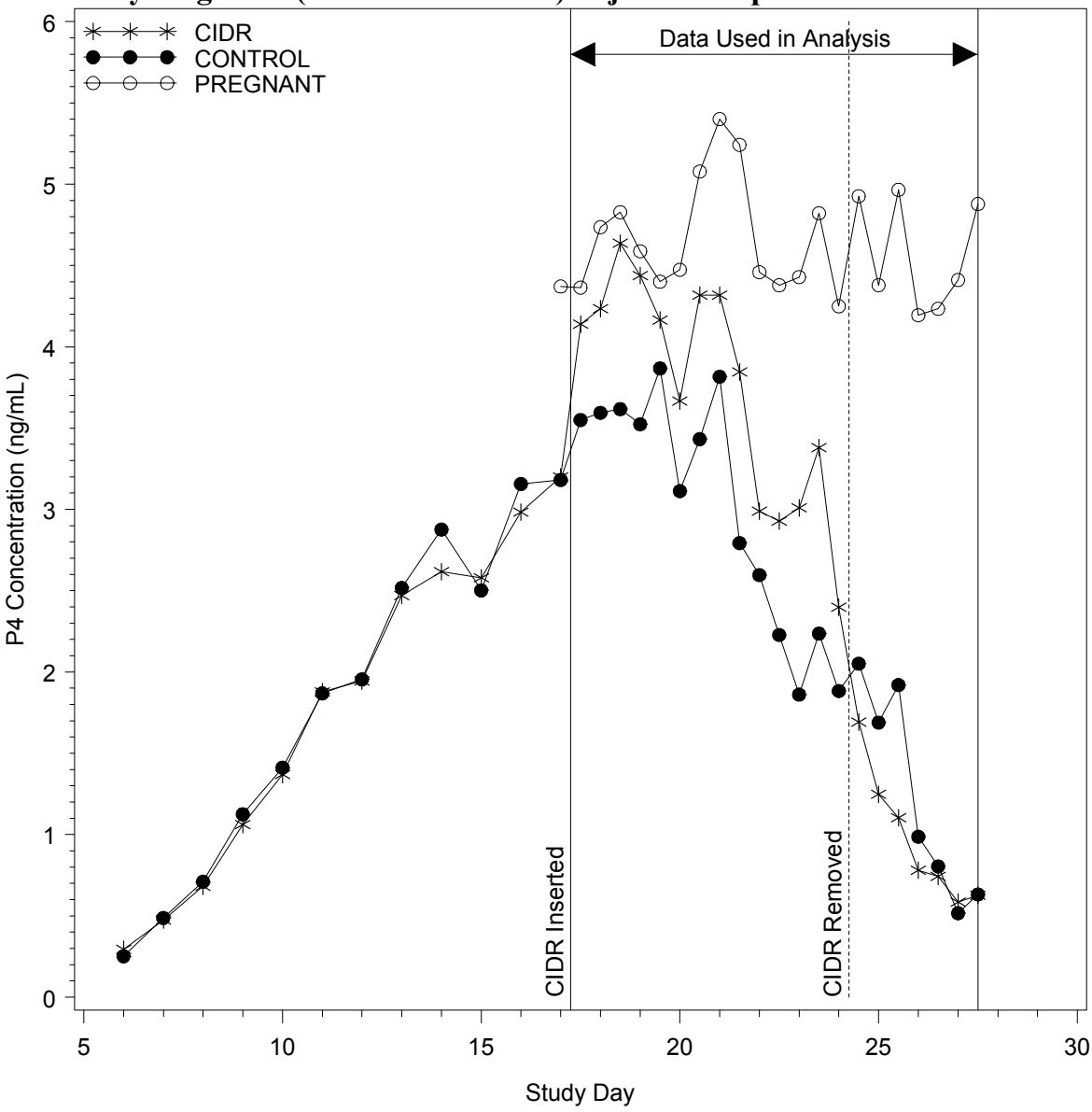
Pregnant cows, 10.
Estrous cycling cows, control, 10 assigned, 1 removed from statistical analyses.
Estrous cycling cows administered CIDR insert, 10 assigned, 1 removed from statistical analyses.

Study results:

Within each individual sample period the mean milk progesterone concentration of cows administered CIDR inserts never exceeded that observed for the pregnant cows (Figure 1).

The statistical analyses of the AUC data indicated that the use of the CIDR insert caused an increase in milk progesterone concentration that was significantly less (α=0.05) than the increase resulting from pregnancy. Within the average milking herd, many cows are pregnant. It is concluded that use of a CIDR insert in lactating dairy cows does not compromise human food safety; therefore, such use does not require a milk discard period, either during or after the CIDR insert administration period.

Figure 1. Average milk progesterone over time for cycling control cows (CONTROL; n = 9), cycling cow administered CIDR (CIDR; 1.38 g progesterone; n = 9), and untreated pregnant cows (PREGNANT; n = 10) with cycling cows (control and CIDR) adjusted for pre-treatment differences



- **Tolerance and Withdrawal Time**:
  Based on this study, there is no need to codify a tolerance for progesterone in milk (21 CFR 556.540) and there is no milk discard requirement.

- **Regulatory Method for Residues:**
  Based on this study, there is no method requirement for this product.

- **User Safety Concerns:**
  The product labeling contains the following statements:

  1. "Human Warning: Avoid contact with skin by wearing latex gloves when handling the inserts. Keep this and all medications out of reach of children."

  2. "For Use in Animals Only."

5. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that the use of the Intravaginal Progesterone Insert, when administered according to the label, is safe and effective for the claim indicated in section 1 of this FOI Summary.

The allowable increments of progesterone concentrations in edible tissues are codified under 21 CFR 556.540: 3 ppb for muscle, 6 ppb for liver, 9 ppb for kidney and 12 ppb for fat. Based on the residue depletion study of progesterone in milk, there is no need to codify a tolerance for progesterone in milk (21 CFR 556.540), and there is no milk discard requirement. There is also no method requirement for this product.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions are accompanied by pictorial diagrams and detailed instruction in plain language. The drug is not a controlled substance. Thus, the product is assigned OTC status, and the labeling is adequate for the intended use.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug and Cosmetic Act, this 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 use of the product (EAZI-Breed™ CIDR® Cattle Insert) containing 1.38 grams progesterone in molded silastic over a nylon spine for synchronization of the return to estrus in lactating dairy cows inseminated at the immediately preceding estrus for which this supplemental application is approved.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

There were no patents submitted with this application.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Primary Package Label (Front Panel)
Primary Package Label (Back Panel)
Carton Label