

Date of Approval: December 19, 2013

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-200

EAZI-BREED CIDR Cattle Insert

Progesterone intravaginal insert

Anestrous Lactating Dairy Cows

This supplement provides for the addition of a new indication for induction of estrous cycles in anestrous lactating dairy cows.

Sponsored by:

Zoetis Inc.

Table of Contents

I.	GENERAL INFORMATION	3
	A. File Number.....	3
	B. Sponsor	3
	C. Proprietary Name	3
	D. Established Name.....	3
	E. Pharmacological Category	3
	F. Dosage Form:	3
	G. Amount of Active Ingredient	3
	H. How Supplied	3
	I. Dispensing Status	3
	J. Dosage Regimen	3
	K. Route of Administration	3
	L. Species/Class	3
	M. Indication.....	4
	N. Effect of Supplement	4
II.	EFFECTIVENESS.....	4
	A. Dosage Characterization	4
	B. Substantial Evidence	4
III.	TARGET ANIMAL SAFETY:.....	8
IV.	HUMAN FOOD SAFETY:	9
	A. Antimicrobial Resistance:	9
	B. Impact of Residues on Human Intestinal Flora:	9
	C. Toxicology:	9
	D. Residue Chemistry:	9
	E. Analytical Method for Residues:	10
V.	USER SAFETY:	10
VI.	AGENCY CONCLUSIONS:.....	10
	A. Marketing Status:	10
	B. Exclusivity:.....	10
	C. Supplemental Applications:	10
	D. Patent Information:	10

I. GENERAL INFORMATION

A. File Number

NADA 141-200

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

EAZI-BREED CIDR Cattle Insert

D. Established Name

Progesterone intravaginal insert

E. Pharmacological Category

Steroid hormone

F. Dosage Form:

Insert

G. Amount of Active Ingredient

Each insert contains 1.38 grams progesterone

H. How Supplied

Ten inserts per polyethylene bag

I. Dispensing Status

OTC

J. Dosage Regimen

Administer one EAZI-BREED CIDR Cattle Insert per anestrous cow and remove 7 days later.

K. Route of Administration

Intravaginal

L. Species/Class

Anestrous lactating dairy cows

M. Indication

For induction of estrous cycles in anestrus lactating dairy cows

N. Effect of Supplement

This supplement provides for the addition of a new indication for induction of estrous cycles in anestrus lactating dairy cows.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-200 dated May 2, 2002, and the supplemental approval dated July 29, 2003, respectively, contain dosage characterization information for beef cows, beef and dairy heifers, and lactating dairy cows.

B. Substantial Evidence

1. Field Effectiveness Study

a. Title:

Pivotal Field Efficacy Study for Use of the EAZI-BREED CIDR Cattle Insert (Progesterone Releasing Intravaginal Insert) for Induction of Estrous Cycles in Postpartum Dairy Cows.

b. Investigators and Locations

The study was conducted at nine commercial dairies: two in California and Wisconsin, and one each in Florida, Idaho, Illinois, Michigan, and Minnesota. Although two dairies were involved in Wisconsin, they were both under the same management, and were treated as a single site in the statistical analysis. Site selection covered a broad range of management and environmental conditions representative of the U.S. dairy industry. Locations and associated clinical investigators are listed in Table 1.

Table 1. Clinical investigators and study locations

Investigator	Location
Clint Walhof, DVM	Woodville, CA
Paul Busman, DVM	Bailey, MI
Darrel Kessler, PhD	Mansfield, IL
David Kolb, DVM	DeForest, WI Arlington, WI
Paul Bos, DVM	Escalon, CA
Andrew Borrowman, DVM	Marsing, ID
Jose Santos, DVM	Trenton, FL
Ricardo Chebel, DVM	Nicollet, MN

c. Study Design:

(1) Objective:

To evaluate the effectiveness and field safety of the EAZI-BREED CIDR Cattle Insert for induction of estrous cycles in anestrus lactating dairy cows.

(2) Experimental Design:

This study was conducted in accordance with Good Clinical Practices (CVM Guidance No. 85 (VICH GL9)). Cows were randomized to treatment in blocks of two within a pen. Cows were assigned to pens according to routine farm management (e.g., high production group, first lactation group), and study cows were co-housed with non-study cows. If there were not enough eligible cows to complete a block within a pen, then the block was left incomplete and a new block started in the next pen. Pens contained animals from both treatment groups, so that cow was the experimental unit. The majority of the personnel involved in the study were masked to treatment. Only the Treatment Administrator and Treatment Administrator Assistant were aware of treatment assignments and were not allowed to collect study data.

(3) Study Animals, Housing, and Management

A total of 1,132 cows were enrolled, of which 856 cows were included in the analysis for effectiveness. The predominant breed was Holstein, although some Jersey and Holstein-Jersey crossbreeds were also included in the study. 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 and were at least 42 days in lactation prior to study initiation. To qualify as anestrus, cows could not have a functional corpus luteum (CL), shown signs of estrus, or have a plasma progesterone value greater than 1 ng/mL on either Study Day - 7 or Study Day 0. Cows were allotted to treatment groups on Study Day 0.

Two hundred seventy-six cows were excluded from the study after enrollment. The main reason for removal was due to elevated progesterone levels (greater than 1 ng/mL) indicating the cow was estrous cycling by Study Day 0. This was unavoidable, due to the time needed to assay the large volume of samples. Reasons for exclusion are in Table 2.

Table 2. Cows removed from study after enrollment

Reason for Removal	Number of Cows
High progesterone	239
Did not meet criteria	16
Protocol deviations	11
Culled/sold/death	10
Total	276

(4) Treatment Groups:

The study consisted of two treatment groups: 1) negative control, and 2) EAZI-BREED CIDR Cattle Insert (CIDR) for seven days. The CIDR contained 1.38 grams progesterone in a solid matrix.

(5) Drug Administration:

Cows in treatment group 2 received one CIDR on Study Day 0, which was removed on Study Day 7. Control cows were untreated.

(6) Measurements and Observations:

Cows were observed daily beginning on Study Day -7 for general health and signs of estrus according to typical herd procedures. Cows were bred on observed estrus. Cows were examined on Study Days 7, 14, 21, 28, 35 and 42 by transrectal ultrasound for presence of a CL.

Demonstration of induction of estrous cycles was based on ultrasound observations and defined as identification of a functional CL by Study Day 21 and any one of the following six criteria:

1. Continued estrous cycles based on ultrasound evaluation of ovaries and the following observations:
 - a. Regression of the original CL detected on Study Day 7, 14 or 21, and
 - b. Presence of at least one new CL by Study Day 42, and
 - c. During Study Days 7 to 42 at least one incidence of a CL detected on the same ovary for a minimum of two consecutive ultrasound observations.
2. Evidence of continued estrous cycles based on ultrasound evaluation of ovaries defined as presence of at least one new CL on the ovary opposite the initial CL by Study Day 42 without evidence of regression of the initial CL.
3. For cows inseminated during days 1 to 21, either:
 - a. Continued presence of the original CL, with pregnancy determined at 30 ± 3 days post insemination; or
 - b. Continued estrous cycles as defined in criterion 1 for animals not conceiving to the initial insemination; or
 - c. Continued presence of the original CL for 4 or more weeks, without subsequent estrus and found to be not pregnant at 30 ± 3 days post insemination. These animals were considered to have early embryo mortality with extension of luteal lifespan.
4. Animals with consistent detection of a CL on the same ovary for 4 or more weeks with an estrus detected during this interval. These animals were considered to have developed a new CL on the same ovary as the initial CL, without detection of regression of the initial CL.
5. Animals with consistent detection of a CL on the same ovary for 4 or more weeks, without detected estrus during this 4 or more week interval. These cows were assumed to have had a silent heat. [This is consistent with incidence of a CL detected on the same ovary for several weeks and appearance of a new CL on

the opposite ovary without an intervening week with no CL detected.]

6. Animals with two detected estrous periods, occurring at an 18 to 25 day interval, with at least two observations of functional CL on the same ovary within the interval of the two detected estruses.

(7) Statistical Methods:

The primary effectiveness variable is rate of induction of estrous cycles, defined by the following equation:

$$\text{Rate of Induction of Estrous Cycles} = \frac{\text{number of animals induced to cycle}}{\text{number of animals enrolled} - \text{animals withdrawn or removed from analyses}} \times 100$$

The data were analyzed by a generalized linear mixed model with a binomial error distribution and a logit link. The model included treatment and parity as fixed effects. Parity was used as a covariate as it had not been a factor in the randomization. Random effects in the model were: site, site by treatment, cohort within site, and the residual term. A 0.05 alpha level two-sided test was used for induction rate and the associated 95% confidence intervals for the percent induction in each treatment group were provided.

d. Results

A total of 856 cows were available for analysis of effectiveness. Table 3 presents the cows per site and total numbers and percentages of cows meeting the criteria for induction of estrous cycles. Use of CIDR resulted in a significant increase in return to estrous cycling compared to control (62.0 vs. 45.1¹ %; p<0.0001).

Table 3. Number and percent of cows meeting criteria for effectiveness

Site	Control	Control	CIDR	CIDR
	N	%	N	%
A	18/59	30.5	44/56	78.6
B	28/76	36.8	40/71	56.3
C	15/25	60.0	17/23	73.9
D	12/25	48.0	19/26	73.1
E	14/43	32.6	24/49	49.0
F	22/58	37.9	35/57	61.4
G	42/78	53.9	53/77	68.8
H	46/66	69.7	50/67	74.6
Total	197/430	45.1	264/426	62.0

¹ Percent based on results of statistical analysis rather than arithmetic mean

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-200 dated May 2, 2002, and supplemental approval dated July 29, 2003, contain a summary of target animal safety studies for beef cows, beef and dairy heifers, and lactating dairy cows.

Reproductive safety was assessed as part of the field effectiveness study. Reproductive safety variables were conception rate and pregnancy rate, defined as:

$$\text{Conception Rate} = \frac{\text{Number of cows diagnosed pregnant to inseminations on Days 1 to 21}}{\text{Number of cows inseminated on Days 1 to 21} - \text{number of inseminated cows withdrawn or removed}} \times 100$$

$$\text{Pregnancy Rate} = \frac{\text{Number of cows diagnosed pregnant to inseminations on Days 1 to 21}}{\text{Number of cows enrolled} - \text{number of cows withdrawn or removed}} \times 100$$

Data on conception rate and pregnancy rate were analyzed the same as for the effectiveness variable. For conception rate and pregnancy rate, 80% confidence intervals were provided to estimate the decrease in rate associated with a 10% one-sided test.

Conception rates during Study Days 1 – 21 for cows receiving CIDR inserts were reduced compared to control cows (27.7 vs. 36.2%; p<0.083). Overall pregnancy rates were low (CIDR 9.0% vs. Control 8.2%) and did not differ between treatments (p=0.32). This low pregnancy rate may be due to a number of factors, including management and environment.

Because of the reduced conception rates but lack of effect on pregnancy rates in cows receiving CIDR inserts, package labeling will include the statement: "You May Notice: Reduced conception rates to inseminations conducted immediately following removal of the EAZI-BREED CIDR Cattle Insert when used for induction of estrous cycles in anestrus lactating dairy cows. Such reductions in conception rate are not expected to result in reduced pregnancy rates."

Relatively few animals developed health problems during the field effectiveness study. Health abnormalities noted during the study were considered typical for dairy cattle, and not related to treatment: mastitis, lameness, pneumonia. Table 4 contains the number of cows per treatment group that were observed with health abnormalities during the study.

Table 4. Health abnormalities observed during the effectiveness study

Health Abnormality	No. Control	No. CIDR	Total
Mastitis/udder abnormality	21	25	46

Health Abnormality	No. Control	No. CIDR	Total
Milk fever	1	0	1
Lameness	8	6	14
Pneumonia	5	3	8
Digestive	3	1	4
Injury	1	1	2

The cow diagnosed with milk fever also developed mastitis during the study. One cow died during the study due to hardware she had swallowed. Another cow died due to a displaced abomasum. Eight cows were culled or sold due to low milk production, injury, or chronic illness (Johne's Disease, pneumonia). None of these issues appear to have been related to treatment.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

EAZI-BREED CIDR Cattle Insert (containing 1.38 g progesterone) is not thought, or been reported, to promote antimicrobial resistance among bacteria of public health concern in or on treated lactating dairy cows; therefore, no additional microbial food safety (antimicrobial resistance) information or data are required for this proposed supplemental application to allow for treatment of lactating dairy cows with EAZI-BREED CIDR Cattle Insert at this time.

B. Impact of Residues on Human Intestinal Flora:

Residues and metabolites of EAZI-BREED CIDR Cattle Insert in the edible tissues and milk from treated lactating dairy cows are not thought, or been reported, to disrupt colonization or promote antimicrobial resistance among the intestinal flora of human consumers; therefore, no additional microbial food safety (impact on human intestinal flora) information or data are required for this supplemental application to allow for treatment of lactating dairy cows with EAZI-BREED CIDR Cattle Insert at this time.

C. Toxicology:

CVM did not require additional toxicology studies for this supplemental approval. Progesterone is regulated based on allowable incremental increase limits. As codified under 21 CFR 556.540, residues of progesterone are not permitted in excess of the following increments above the concentrations of progesterone naturally present in untreated cattle: 5 ppb for muscle, 15 ppb for liver, 30 ppb for kidney and 30 ppb for fat.

D. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-200, dated May 2, 2002, and the supplemental approvals of NADA 141-200, dated July 29, 2003, and July 22, 2010, contain summaries of residue chemistry studies for cattle.

E. Analytical Method for Residues:

The FOI Summaries for the original approval of NADA 141-200 dated May 2, 2002, and the supplemental approvals of NADA 141-200 dated July 29, 2003, and July 22, 2010, contain analytical method information for EAZI-BREED CIDR Cattle Insert in cattle.

A regulatory method for progesterone is not required.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to EAZI-BREED CIDR Cattle Insert:

Avoid contact with skin by wearing protective gloves when handling the inserts.
Not for use in humans. Keep out of reach of children.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that EAZI-BREED CIDR Cattle Insert, when used according to the label, is safe and effective for induction of estrous cycles in anestrous lactating dairy cows. Additionally, data demonstrate that residues in food products derived from species treated with EAZI-BREED CIDR Cattle Insert will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

The EAZI-BREED CIDR Cattle Insert can be marketed over-the-counter because the approved labeling contains adequate directions for the use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

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 new indication "for induction of estrous cycles in anestrous lactating dairy cows."

C. Supplemental Applications:

This supplemental NADA required a reevaluation of the safety data in the original NADA (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.