

Date of Approval: October 1, 2009

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-302

EAZI-BREED CIDR Sheep Insert

Progesterone
Solid Matrix
Sheep (ewes)

For induction of estrus in ewes (sheep) during seasonal anestrus

Sponsored by:

Pharmacia & Upjohn Company, A Division of Pfizer Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION:	1
II. EFFECTIVENESS:	3
A. Dosage Characterization:	3
B. Substantial Evidence:	4
C. Study #1998-1:	9
III. TARGET ANIMAL SAFETY:	11
IV. HUMAN FOOD SAFETY:	16
A. Toxicology:	16
B. Residue Chemistry:	16
C. Microbial Food Safety:	19
D. Analytical Method for Residues:	19
V. USER SAFETY:	19
VI. AGENCY CONCLUSIONS:	19
A. Marketing Status:	20
B. Exclusivity:	20
C. Patent Information:	20
VII. ATTACHMENTS:	20

I. GENERAL INFORMATION:

A. File Number:	NADA 141-302
B. Sponsor:	Pharmacia & Upjohn Co., a Division of Pfizer, Inc. 235 East 42 ^d St. New York, NY 10017
	Drug Labeler Code: 000009
C. Proprietary Name:	EAZI-BREED CIDR Sheep Insert
D. Established Name:	Progesterone

- E. Pharmacological Category:** Steroid Hormone
- F. Dosage Form:** Solid Matrix
- G. Amount of Active Ingredient:** Each insert contains 0.3 gram of progesterone in molded silicone over a flexible nylon spine.
- H. How Supplied:** 20 inserts per polyethylene bag
- I. How Dispensed:** OTC
- J. Dosage:** 0.3 gram progesterone/insert, one insert per ewe for five days
- K. Route of Administration:** Intravaginal
- L. Species/Class:** Sheep, ewes
- M. Indication:** For induction of estrus in ewes (sheep) during seasonal anestrus.

II. EFFECTIVENESS:

The data summarized in this section were compiled by the National Research Support Project No. 7 (NRSP-7) and are publicly available and contained in Public Master File 005-947.

A. Dosage Characterization:

Reports in published literature demonstrated that treatment of seasonally-anestrous ewes with progestogens for periods of 6 to 14 days induced estrus (Christenson, 1976; Hamra et al., 1989; Wheaton et al., 1992; Safranski et al., 1992; Jabbar et al., 1994, Powell et al., 1996; Rodriguez Iglesias et al., 1996). One of these reports (Wheaton et al., 1992) used, during a 12 day treatment period, the intravaginal progesterone releasing insert (0.3 gram progesterone per insert) used for the current application (EAZI-BREED CIDR Sheep Insert, CIDR). This report provided a scientific basis for the dose and formulation of progesterone tested in the sponsor's effectiveness study (Study #1999-1, see Section II.B below).

In the reports cited in the previous paragraph, progestogen treatment durations of approximately 12 days were most common, though a treatment period as short as six days was effective for inducing estrus in anestrous ewes. In another study (Study #1998-1, see Section II.C below), the sponsor compared treatment with an experimental, intravaginal progesterone releasing insert for 5 or 12 days. The experimental insert contained 0.82 g progesterone in a polycaprolactone (PCL) coating. The physical characteristics (i.e., configuration, dimensions) were the same as the CIDR insert. They found that the 5-day treatment period was equally effective as the 12-day treatment period for induction of estrus in seasonally anestrous ewes. Though this study was not conducted with the same insert as the one for which the sponsor sought approval, it substantiated that administration of progesterone to anestrous ewes via an intravaginal insert for five days induced fertile estrus. Thus, the sponsor chose in their effectiveness study to treat anestrous ewes with the CIDR for 5 days (Study #1999-1, see Section II.B below).

A common concern relative to progestogen-induced estrus in seasonally anestrous ewes relates to reduced ovulation rate and thus reduced prolificacy (number of lambs born per ewe lambing). To this end, researchers have included exogenous gonadotropins (Christenson, 1976; Hamra et al., 1989; Safranski et al., 1992; Jabbar et al., 1994) to help offset reduced ovulation in ewes induced into estrus during the non-breeding season vs. ovulation rate in spontaneously-cycling ewes during the natural breeding season. As part of the sponsor's initial investigations (Study #1998-1, see Section II.C below), treatment of anestrous ewes with progesterone alone was compared to ewes treated concurrently with progesterone and follicle stimulating hormone (FSH). While there were no significant differences between ewes treated with progesterone alone vs. ewes treated concurrently with progesterone and FSH, there were non-significant trends towards improvements in ovulation rate and prolificacy in ewes treated concurrently with progesterone and FSH vs. ewes given progesterone alone. This provided impetus for the sponsor to include as part of the experimental design in their effectiveness study Study #1999-1 (see Section II.B. below) a treatment group for the concurrent use of progesterone and FSH.

Literature Cited

Christenson, R.K. 1976. Effect of short-term progestogen treatment on induction of estrus and lambing in anestrus ewes. *J. Anim. Sci.* 43:795-801.

Hamra, A.H., J.W. McNally, J.M. Marcek, K.M. Carlson and J.E. Wheaton. 1989. Comparison of progesterone sponges, cronolone sponges, and controlled internal drug release dispensers on fertility in anestrus ewes. *Anim. Reprod. Sci.* 18:219-226.

Jabbar, G., S.H. Umberger and G.S. Lewis. 1994. Melengestrol acetate and norgestomet for the induction of synchronized estrus in seasonally anovular ewes. *J. Anim. Sci.* 72:3049-3054.

Powell, M.R., M. Kaps, W.R. Lamberson and D.H. Keisler. 1996. Use of melengestrol acetate-based treatments to induce and synchronize estrus in seasonally anestrus ewes. *J. Anim. Sci.* 74:2292-2302.

Rodriguez Iglesias, R.M., N.H. Cicciooli, H. Irazoqui and C. Giglioli. 1996. Ovulation rate in ewes after a single oral glucogenic dosage during a ram-induced follicular phase. *Anim. Reprod. Sci.* 44:211-221.

Safranski, T.J., W.R. Lamberson and D.H. Keisler. 1992. Use of melengestrol acetate and gonadotropins to induce fertile estrus in seasonally anestrus ewes. *J. Anim. Sci.* 70:2935-2941.

Wheaton, J.E., H.F. Windels and L.J. Johnston. 1992. Accelerated lambing using exogenous progesterone and the ram effect. *J. Anim. Sci.* 70:2628-2635.

B. Substantial Evidence:

Clinical Field Study #1999-1

Study #1999-1 was conducted on seven commercial farm flocks in West Virginia and Pennsylvania. The objective of the study was to evaluate the effectiveness of the CIDR administered for five days, to induce a fertile estrus in ewes during seasonal anestrus. The names and locations of the investigators, and the study locations are provided below:

Name and Address of Investigators:

Drs. Keith Inskeep & Paul Lewis
West Virginia University
Morgantown, West Virginia

Study Locations:

West Virginia: Preston County, Randolph County, Terra Alta and Elkins
Pennsylvania: Waynesburg

General Design:

This study was conducted on seven commercial farm flocks during May to August 1999, using a common protocol. Data were pooled across all locations for statistical analyses. Healthy, non-lactating ewes (n = 759) of mixed breeding (primarily Suffolk and Dorset) were enrolled in the study. Ewes were managed on mixed grass pastures, but brought into barns or holding lots to initiate treatment and during the synchronized estrus/first service period. In general, animals were managed in a manner typical of commercial farm flocks in the Eastern U.S.

A single blood sample was taken via jugular venipuncture three days prior to treatment start for measurement of the concentration of progesterone in serum to determine cyclic status. Ewes with serum progesterone values of < 0.6 ng/mL were classified as anestrus ewes and were included in statistical analyses (n = 653). Ewes with progesterone concentrations of > 0.6 ng/mL were excluded from statistical analyses (n = 101). Five ewes were excluded due to serious health abnormalities or poor body condition.

Ewes were randomly assigned to three treatment groups:

- 1) Control (C, n=125)
- 2) CIDR (0.3 g progesterone) for 5 days (P5, n=257)
- 3) CIDR for 5 days and 55 mg (NIH-FSH-P1 equivalent) FSH in saline: propylene glycol (1:4) 24 hours before insert removal (P5F, n=271)

The time of CIDR removal was identified as Study Day 0, with times reported as study days relative to Study Day 0.

All ewes received ram exposure (ewe: ram ratio not exceeding 15:1), beginning at the time of CIDR removal. Rams were maintained at the 15:1 ewe: ram ratio through Study Day 3. Beginning on Study Day 1, ewes were observed for estrus every day for three days (synchronized breeding period or first service period). Rams were raddled (briskets painted), and ewes marked with paint were considered to be in estrus and mated. After each estrous observation period, the briskets of rams were repainted to ensure that mounted ewes were clearly detectable. After Study Day 3, rams remained with ewes through Study Days 26-30 at a ewe: ram ratio not exceeding 25:1 (second service period).

Transrectal ultrasonography was used for pregnancy diagnoses, performed at Study Days 26-31, and Study Days 46-51. These periods corresponded to pregnancies that would occur after the first and second service periods. At Study Days 10-14, ewes mated during the first service period were subjected to transrectal ultrasound to determine the number of corpora lutea as the indicator of ovulation rate immediately post-treatment.

Key Variables:

1. Retention of CIDR inserts = The number of ewes that retained the CIDR inserts for the five-day treatment period as a percentage of ewes treated with inserts.

2. Ewes in estrus (treatment-induced estrus) = The number of ewes marked by raddled rams during Study Days 1 to 3 as a percentage of all ewes treated.
3. Ovulation rate = The number of corpora lutea on ovaries, detected by ultrasound on Study Days 10 to 14, of ewes in estrus during Study Days 1 to 3.
4. Conception rate = The number of ewes diagnosed as pregnant at Study Days 26 to 31 as a percentage of ewes exhibiting estrus.
5. Pregnancy rate:
 - a. To first service period = The number of ewes diagnosed as pregnant on Study Days 26 to 31 as a percentage of all ewes treated.
 - b. To second service period = The number of ewes diagnosed as pregnant on Study Days 46 to 51 expressed as a percentage of ewes not pregnant on Study Days 26 to 31.
6. Percent ewes lambing = The number of ewes lambing as a percentage of ewes in all treatments for: a) the first service period; and b) both service periods.
7. Lambing rate = The number of lambs born per ewes exposed to rams for: a) the first service period; and b) both service periods.
8. Prolificacy = The number of lambs born per ewe lambing for: a) the first service period; b) the second service period; and 3) both service periods (overall).

Variables 1, 2, 5, 6, 7, and 8 were primary response variables for determining effectiveness and animal safety, while Variables 3 and 4 were used as supportive evidence for conclusions made relative to the primary response variables. Results for variables 2 through 8 are provided in Table 1 below.

Statistical Analysis:

Data were analyzed using generalized linear mixed models (GLIMMIX procedures of SAS). Treatment was a fixed effect and farm was a random effect in the model. Logit link with binomial error was chosen for binary responses and log link with Poisson error was chosen for count responses. Least squares means of treatment groups were compared to each other.

Results:

The retention rate of CIDR inserts was 97.3%, with 514 of 528 ewes retaining the inserts for the five day treatment period. Thus, the rate of insert loss was only a minor concern for this study.

The number of ewes per treatment, and analysis results for key reproductive variables are summarized in Table 1.

The purpose for including FSH as part of a treatment regimen was based on the concern that induced estrus during seasonal anestrus, while fertile, may result in reduced prolificacy (see Section II.A above). However, based on results of this study, concurrent use of FSH with CIDR inserts did not improve responses when compared to treatment with the inserts alone. No differences were noted between the P5 and P5F treatment groups for indicators that FSH had the intended effect: ovulation rate, lambing rate, and prolificacy. Therefore, results from this study do not support use of FSH as part of the treatment regimen with the CIDR insert for inducing estrus in seasonally anestrous ewes.

Treatment of ewes with CIDR inserts increased the percentage of ewes in estrus within three days of insert removal and ram exposure, when compared to control ewes subjected to ram exposure only. Only 19% of C ewes were in estrus during Study Days 1 to 3, compared to 77 and 79% of P5 and P5F ewes that were in estrus during this time period ($P < 0.05$). In addition, conception rate to the first service mating was greater in P5 and P5F vs. C ewes, as the conception rate in C ewes was 0%. Similarly, pregnancy rate to the first service mating was greater in P5 and P5F vs. C ewes, though pregnancy rate to the second service mating was similar among the three treatment groups. Percentage of ewes lambing was greater in P5 and P5F vs. C ewes, when considering matings for the first service period and for both service periods together.

Lambing rate was greater in P5 and P5F vs. C ewes, when considering matings for the first service period, and both service periods together. Prolificacy did not differ between P5 and P5F ewes when considering matings for the first service period, or among all three treatment groups when considering the second service period and both service periods.

Conclusions:

Treatment of seasonally anestrous ewes with the CIDR insert for 5 days, in conjunction with ram exposure, was effective for inducing fertile estrus. CIDR insert loss during the five-day treatment was a minor concern, given insert loss was less than 3%. In addition, use of the CIDR insert did not compromise reproductive function, using the indices of fertility and prolificacy provided in Table 1. Use of FSH as part of the treatment regimen did not improve ovulation rate, lambing rate or prolificacy. Thus, the results of this study do not support concurrent use of FSH with the CIDR insert and ram exposure for induction of estrus in seasonally anestrous ewes.

The results of this study support the proposed use of the CIDR alone for five days for “induction of estrus in ewes (sheep) during seasonal anestrus.” The directions for use should indicate a five day treatment period with the CIDR insert, and that ewes be exposed to rams from the time of insert removal.

Table 1. Summary of reproductive performance of anestrus ewes in response to ram introduction (C), or ram introduction + 5-day CIDR pre-treatment without FSH (P5) or with FSH (P5F).

Variable/Treatment	C	P5	P5F
Total number of ewes	125	257	271
No. of ewes in estrus (%)	24(19) ^a	198(77) ^b	214(79) ^b
Ovulation rate	-- ¹	1.97 ^a	1.94 ^a
Conception rate, %	-- ²	72 ^a	67 ^a
Pregnancy rate, %			
First service period	NA	53 ^a	52 ^a
Second service period	58 ^a	47 ^a	57 ^a
Percent ewes lambing, %			
First service period	NA	46 ^a	46 ^a
Both service periods	47 ^a	66 ^b	69 ^b
Lambing rate, (mean ± SE)			
First service period	NA	0.69 ^a ± 0.07	0.76 ^a ± 0.08
Both service periods	0.70 ^a ± 0.09	0.96 ^b ± 0.10	1.08 ^b ± 0.11
Prolificacy, (mean ± SE)			
First service period	NA	1.49 ^a ± 0.07	1.66 ^b ± 0.08
Second service period	1.49 ^a ± 0.09	1.43 ^a ± 0.09	1.46 ^a ± 0.09
Overall	1.48 ^a ± 0.09	1.46 ^a ± 0.07	1.59 ^a ± 0.07

¹Ovulation rate for the control was not included, as only ovulation was detected in 3 control ewes vs. 155 and 175 ewes with detected ovulations in the P5 and P5F groups.

²Conception rate to first service in control ewes was zero. Therefore, subsequent first service period analyses based on pregnancy conducted without the control group. NA = Not Applicable

^{a,b}Pairwise comparisons were conducted. Treatments with common superscript did not differ from each other; treatments with different superscripts differed ($P < 0.05$).

C. Study #1998-1

Name and Location of Investigators:

Drs. Keith Inskeep & Paul Lewis
West Virginia University
Morgantown, West Virginia

Study #1998-1 was conducted on six farms in West Virginia. The objective of the study was to evaluate, in anestrus ewes, the effectiveness of an experimental intravaginal progesterone releasing insert (PCL insert) administered for 5 days or 12 days with and without FSH to induce a fertile estrus. The experimental insert contained 0.82 g progesterone in a polycaprolactone (PCL) coating. The physical characteristics (i.e., configuration, dimensions) were the same as the CIDR insert.

This study was conducted on six farms during May to July 1998, using a common protocol. Data were pooled across all locations for statistical analyses. Healthy, non-lactating ewes of mixed breeding (primarily Suffolk, Dorset, and North Country Cheviot) were enrolled in the study. Ewes were managed on mixed grass pastures, but brought into barns or holding lots to initiate treatment and during the synchronized estrus/first service period. In general, animals were managed in a manner typical of commercial farm flocks in the Eastern U.S.

Healthy, non-lactating ewes were selected for the study. Ewes were confirmed to be anestrus with the measurement of serum progesterone concentrations in two pre-study blood samples collected three days apart. If either of the two samples from a given ewe had serum concentrations of progesterone of > 0.6 ng/mL, that ewe was deemed as estrual and was not used in the study.

All ewes received ram exposure (ewe: ram ratio not exceeding 15:1), beginning at the time of PCL insert removal (Study Day 0).

- 1) Negative control (C; n = 73)
- 2) PCL insert (0.82 g progesterone) for 12 days (P12; n = 73)
- 3) PCL insert for 12 days with 55 mg FSH (NIH-FSH-P1 equivalent) on day 11 (P12F; n = 71)
- 4) PCL insert for 5 days with 55 mg FSH on day 4 (P5F; n = 77)

The time of insert removal was identified as Study Day 0, with times reported as study days relative to Study Day 0.

Beginning on Study Day 1, ewes were observed for estrus every 12 hours for 5 days. Raddled rams (briskets painted) were used, and when ewes had raddle marks, they were considered in estrus and mated. After each estrous observation period, the briskets of rams were repainted to ensure that mounted ewes were clearly detectable. After synchronized breeding, rams remained with ewes through Study Days 26-30 after insert removal at a ewe: ram ratio not exceeding 25:1.

Transrectal ultrasonography was used for pregnancy diagnoses, performed at Study Days 26-30 and Study Days 46-51 after insert removal. These periods corresponded to pregnancies that would occur after the first and second service periods. At the Study Day 26-30 diagnosis, the number of corpora lutea was determined as the indicator of ovulation rate.

Results:

A low rate of insert loss during the 5- or 12-day treatment period was observed (2 of 221 inserts lost, \approx 0.9%). Therefore, insert loss was not of concern for this study.

The definitions for variables: ewes in estrus (treatment-induced estrus), pregnancy rate, conception rate, percent ewes lambing, lambing rate, ovulation rate, and prolificacy were the same as those for Study #1999-1 (see Section II.B above).

Treatment of anestrus ewes with the inserts for 5 or 12 days increased the number of ewes in estrus vs. C ewes, though there were no differences among the P12, P12F, and P5F treatment groups. This indicates that progesterone treatment for five days with FSH administration was equally as effective as a twelve-day progesterone treatment, with or without FSH administration, for inducing estrus in seasonally anestrus ewes. In addition, there were no differences in pregnancy and conception rates to first and second services among the three groups given inserts, though C ewes had reduced conception and pregnancy rates to first service vs. insert-treated ewes. The number of mated ewes lambing at the first service period or across both service periods was greater in P12, P12F, and P5F vs. C ewes.

Ovulation rate after the first service estrus did not differ among the P12, P12F, and P5F treatment groups, though there was a tendency for an increase in P12F and P5F ewes. Lambing rate (lambs born per ewe in treatment group) and prolificacy (lambs born per ewe lambing) did not differ among ewes in the P12, P12F, and P5F treatments. Prolificacy was similar among P12, P12F, and P5F ewes. Lambing rate was less in C vs. P12, P12F, and P5F ewes.

Based on these results, treatment of seasonally anestrus ewes with progesterone via intravaginal inserts for five or twelve days was equally effective for inducing fertile estrus. While this study was not conducted with the same product the sponsor intends to market, it supported the approval in that it demonstrated that administration of progesterone to ewes in seasonal anestrus elicited fertile estrus.

III. TARGET ANIMAL SAFETY:

The data summarized in this section were compiled by the National Research Support Project No. 7 (NRSP-7) and are publicly available and contained in Public Master File 005-947.

Target Animal Safety Study #03-258-TAS

Study #03-258-TAS was conducted at the University of California at Davis. The objective of the study was to evaluate the target animal safety of the CIDR administered for fourteen days to exceed the expected treatment period (5 or 12 days) to induce a fertile estrus in ewes during seasonal anestrus. The name and location of the investigator, and the study location are provided below:

Name and Address of Investigator:

Dr. Joan Dean Rowe
Population Health and Reproduction: Veterinary Medicine
University of California at Davis
Davis, California

Study Location:

Sheep Research Facility
University of California at Davis
Davis, California

General Design of the Investigation:

This study was conducted during March and April 2003. Healthy ewes of mixed breeding (Polypay type) were enrolled in the study. All ewes were at least 45 days post lambing, had no signs of systemic illness, and had a normal vaginal exam (speculum) at the time of enrollment. Ewes were housed outside in a dirt pen and had access to loose housing in a barn area. Ewes were fed 5 lbs. alfalfa hay once daily, with mineral/salt mix and water available for *ad libitum* consumption.

On Day -14, ewes were given a pre-enrollment physical and vaginal examination. Twenty ewes were randomly assigned to a treatment or a control group (n = 10 per group). CIDR were inserted in ewes in the treatment group. Animals were observed twice each day for adverse effects and the results recorded for each individual animal. Barn temperatures were also read and recorded. CIDR inserts were removed on Day 0. Ewes were given a physical and vaginal exam. These exams were repeated 2 days later (Day 2) and again 5 days after that (Day 7).

Key Variables:

- Body weights (Days -14, 0, 2, and 7 of CIDR removal)
- Clinical health observations (Daily)

- Physical exams (heart rates, respiration rates, body temperatures; Days -14, 0, 2, and 7 of CIDR removal)
- Vaginal examinations and vaginal mucous scores (using vaginal speculum; Days -14, 0, 2, and 7 of CIDR removal)

At each observation period vaginal erosion/ulcer scores were recorded according to the following system:

- 0 = normal or no erosion(s) detected
- 1 = healing erosion(s)
- 2 = one erosion or ulcer
- 3 = two or more erosions or ulcers

At each observation period, mucous scores were recorded according to the following system:

- 1 = no mucus
- 2 = clear mucus
- 3 = cloudy mucus
- 4 = yellow mucus
- 5 = brown or red mucus

Statistical Analysis:

Continuous data (body weight, heart rate, respiration rate, and body temperature) were analyzed using repeated measures analysis of covariance using a spatial power covariance matrix to account for the unequal spacing between times of measurement. The response variable at Day -14 was used as the covariate and with the independent variables day, treatment, and day by treatment.

Categorical data (vaginal erosion/ulcer and mucous scores) were analyzed via exact methods.

Results:

Daily clinical observations revealed a small number of non-specific and minor health anomalies, with no adverse events noted in the conduct of the study. No ewes died during the conduct of the study.

Results of physical examination records are provided in Table 2. Heart rate did not differ between treatments on Days 0 and 2 after CIDR removal. On Day 7, heart rate decreased in both treatment groups; there was a greater reduction in control vs. CIDR ewes ($P < 0.10$). Respiration rate was reduced from baseline in both treatments on Day 0. There was a greater reduction in control vs. CIDR ewes ($P < 0.01$). Respiration rate increased in control vs. CIDR ewes on Day 2 ($P < 0.10$). No differences in respiration rate were noted on Day 7. The fluctuations in heart and respiration rates were within normal ranges and were not deemed to be clinically relevant.

There were no differences in body weights during the course of the study (Table 2).

For all ewes in both treatments at all observation times, vaginal erosion/ulcer scores were zero (data not shown). Thus no data analyses were conducted. There were no reports of red/brown mucus in any ewe at any time point of the study. No differences between treatments were noted in vaginal mucous scores on Days -14 and 7 of CIDR removal. On Day 0, there tended to be a greater number of CIDR vs. control ewes that had mucous scores of 4 (yellow mucus). Subsequently on Days 2 and 7, however, there were no treatment differences at mucous scores greater than 3. This indicated that vaginal irritation caused by the CIDR was transient in nature, and cleared by the likely time of breeding (2-7 days after CIDR removal). On Day 2, there was a higher proportion of CIDR ewes with a vaginal mucous score of 2 (clear mucus) than control ewes (Table 3), with a concomitant reduction in CIDR ewes with mucous scores of 1 (no mucus). Ewes nearing or in estrus naturally exhibit an increase in the secretion of clear vaginal mucus. Thus, the increase in clear vaginal mucus in CIDR ewes was a normal biological response when progesterone treatment was used for induction of estrus.

Conclusions:

Results of this study indicated that treatment of ewes with CIDR for up to 14 days caused transient, mild vaginal irritation, based on presence of yellow mucus on the day of CIDR removal which cleared by Day 2 after CIDR removal. No vaginal erosions or ulcerations were detected via speculum observation. No concerns were raised from data collected during physical examinations or during daily observations. In addition, no concerns with respect to negative effects on reproductive performance were noted from the results of the effectiveness study (Section II.B, Table 1). When used according to label directions for induction of estrus in seasonally-anestrous ewes, the CIDR has no animal safety concerns.

Table 2. Deviations from baseline for variables showing a significant interaction between treatment and day. Where significant differences exist, the treated group is more similar than the negative control group to its baseline measurement at day -14. Variables are heart rate (HR), respiration rate (RR), and weight (Wt).

Variable	Time (Day)	Baseline Value (Day -14)		Negative Control Deviation from Baseline	CIDR Treated Deviation from Baseline
		Control (n = 10)	CIDR (n = 10)		
Heart Rate (per min)	0	130.0	126.6	-11.0	-3.6
	2			-2.8	5.6
	7			-51.8	-31.8 ^a
Respiration Rate (per min)	0	32.8	38.2	35.2	17.0 ^b
	2			11.4	-0.4 ^a
	7			4.6	-2.0
Body Weight (kg)	0	84.5	77.9	3.7	4.1
	2			5.5	1.7
	7			-1.2	-2.2

P-values for difference between negative control and CIDR treated deviations from baseline: ^a indicates $P < 0.10$,

^b indicates $P < 0.01$. All other P-values > 0.10 .

Table 3. Mucous score^a frequency for control (n = 10) and CIDR-treated (n = 10) ewes on Days -14, 0, 2, and 7 of the Study.

Study Day	Treatment	Mucous Score ^a				
		1	2	3	4	5
Day -14	Control	8	2	0	0	0
	CIDR	9	1	0	0	0
Day 0	Control	6	2	0	2	0
	CIDR	2	3	1	4	0
Day 2 ^b	Control	6	1	0	3	0
	CIDR	1	8	0	1	0
Day 7	Control	7	2	0	1	0
	CIDR	9	1	0	0	0

^aMucous scores: 1 = no mucus; 2 = clear mucus; 3 = cloudy mucus; 4 = yellow mucus; 5 = brown or red mucus

^bP < 0.01, Control vs. CIDR ewes for mucous scores of 1 and 2

IV. HUMAN FOOD SAFETY:

A. Toxicology:

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 increments above the concentrations of progesterone naturally present in untreated animals of steers and calves: 3 ppb for muscle, 6 ppb for liver, 9 ppb for kidney and 12 ppb for fat. However, these values were calculated based on old daily consumption values. The daily consumption values have been revised since 1994 (59 FR 37499). Therefore, CVM has updated the incremental increase limits based on the revised daily consumption values. The following table (Table 4) summarizes the allowable incremental increase limits for residues of progesterone in edible tissues based on the old and revised daily consumption values:

Table 4. Allowable incremental increase limits calculated based on the old and revised daily consumption values

Edible Tissue	Old Daily Consumption Values (g)	Codified Allowable Incremental Increase Limits (ppb)	Revised Daily Consumption Values (g)	Updated Allowable Incremental Increase Limits (ppb)
Muscle	500	3	300	5
Liver	250	6	100	15
Kidney	167	9	50	30
Fat	125	12	50	30

B. Residue Chemistry:

The data summarized in this section were compiled by the National Research Support Project No. 7 (NRSP-7) and are publicly available and contained in Public Master File 005-947.

1. Summary of Residue Chemistry Studies

Progesterone Residue Concentrations in Edible Tissues of Ewes with or without Treatment with Progesterone-Impregnated Controlled Intravaginal Drug Release (CIDR) Device -- ADR Number: 258, NMSU Study No. 03-01

1) Objective of the Study:

To compare progesterone concentrations in liver and muscle tissue samples of ewes in the control group and groups treated with the CIDR containing 0.3 g

progesterone for a 5-day and a 14-day implantation, respectively. The study used ewes, as they represented the target species for the CIDR. The dose examined was the proposed commercial dose level.

2) Study Director and Laboratory:

Dennis Hallford
Department of Animal & Range Sciences
New Mexico State University
Las Cruces, New Mexico

3) Test Animals:

18 Rambouillet ewes, 2 to 6 years of age, weighing 58.5 to 96.6 kg on the day before device insertion

4) Test Material:

CIDR contain 0.3 g progesterone per device

5) Treatment Duration and Sample Collections:

A single insertion for a 5-day and a 14-day implantation, respectively

- Day 0: November 20, 2003 -- Insert the CIDR in 6 ewes for a 14-day treatment
- Day 9: November 29, 2003 -- Insert the CIDR in an additional 6 ewes for a 5-day treatment
- Day 14: December 4, 2003 -- Remove the CIDR from all ewes in both treatment groups
- Day 15: December 5, 2003 -- Collect tissue samples from control and treated animals

Entire liver and 1 kg composite of skeletal muscle were collected, weighed, ground, packaged, and stored frozen at approximately -20°C until being analyzed for progesterone.

6) Sample Analysis:

Progesterone concentrations in liver and muscle tissue samples were analyzed using a validated radioimmunoassay.

7) Results:

Table 5. Progesterone concentrations in muscle tissue samples from control group and groups treated with the CIDR for 5 days (CIDR 5 D) and 14 days (CIDR 14 D), respectively, and slaughtered at one day after the device removal

Animals Sample Number	Treatment	Muscle (ng/g)
142 (1)	Control	3.2
128 (6)	Control	2.4
013 (7)	Control	2.8
72C (8)	Control	0.5
71E (11)	Control	0.5
147 (14)	Control	0.6
Average ± SD		1.67 ± 1.27
075 (3)	CIDR 5 D	5.4
118 (4)	CIDR 5 D	1.1
160 (12)	CIDR 5 D	1.2
184 (13)	CIDR 5 D	0.7
72J (16)	CIDR 5 D	0.7
875 (17)	CIDR 5 D	4.6
Average ± SD		2.28 ± 2.13
809 (2)	CIDR 14 D	0.9
183 (5)	CIDR 14 D	0.7
11K (9)	CIDR 14 D	0.7
773 (10)	CIDR 14 D	0.6
876 (15)	CIDR 14 D	0.6
743 (18)	CIDR 14 D	0.6
Average ± SD		0.68 ± 0.12

The residue depletion study data from both the 5-day and 14-day treatment groups showed that the progesterone concentrations in the muscle samples at one day after the device removal did not exceed the updated allowable incremental increase limit of 5 ppb for muscle. Although the muscle samples for the study were not collected at the nominal zero-day withdrawal of 8-12 hours after the device removal, we find that the sampling time for the muscle tissue in the study reflected the normal animal husbandry management practices for the breeding of the sheep.

Due to rapid metabolism of progesterone in liver, progesterone is inherently unstable in liver samples *in vitro*, even under fastidious handling. Therefore, the liver tissue progesterone residue data were not used for making human food safety decisions. Residue data from other edible tissues were not required.

2. Target Tissue and Marker Residue Assignment

Progesterone is regulated based on allowable increments. No target tissue or marker residue assignment is needed for this approval.

3. Tolerance Assignments

Sheep are considered a minor species for human food safety assessment, and the updated allowable incremental increase limits based on the revised daily consumption values are applicable to sheep. A tolerance is not established for residues of progesterone in sheep.

4. Withdrawal Time

A withdrawal time is not required for the use of the CIDR in sheep.

C. Microbial Food Safety:

Progesterone is not considered to be an antimicrobial agent. FDA has determined that an assessment of microbial food safety for the use of progesterone in sheep is not necessary at this time.

D. Analytical Method for Residues:

A regulatory method is not required for the approval of the CIDR in sheep.

V. USER SAFETY:

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

“Avoid contact with skin by wearing protective gloves when handling the inserts. Keep this and all medications out of the 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 the EAZI-BREED CIDR Sheep Insert, when used according to the label, is safe and effective for induction of estrus in ewes (sheep) during seasonal anestrus. Additionally, data demonstrate that residues in food products derived from sheep treated with the EAZI-BREED CIDR Sheep Insert will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

Under section 573(c) of the Federal Food, Drug and Cosmetic Act (the act), this approval qualifies for SEVEN years exclusive marketing rights beginning on the date of approval because the new animal drug has been declared a designated new animal drug by FDA under section 573(a) of the act.

C. Patent Information:

The EAZI-BREED CIDR Sheep Insert is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
6,423,039	June 22, 2017
6,663,608	June 22, 2017

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

VII. ATTACHMENTS:

Facsimile Labeling:
Package Outsert
Carton Label
Shipping Label