

NRSP-7 Program
Attention: Meg Oeller, D.V.M.
FDA Liaison to the NRSP-7
HFV-50, CVM/FDA
7519 Standish Place
Rockville, MD 20855

Re: Request for a Target Animal Safety Technical Section Complete Letter

Dear Dr. Oeller:

Based on the information in your submission dated September 7, 2007, and the information in INAD 011-389, the Division of Production Drugs considers the target animal safety technical section for the EAZI-BREED CIDR-G intravaginal progesterone releasing insert (CIDR) for synchronization of estrus in meat and dairy goat does during the breeding season to be complete. This technical section complete letter represents our finding that the laboratory studies essential to determining target animal safety are complete and accepted. We also evaluate target animal safety in our review of other technical sections, particularly the effectiveness and all other information technical sections.

The results of the target animal safety study in the current submission indicate the CIDR-G insert may cause transient vaginal irritation, and needs to be addressed on the product label. We proposed a similar such statement for the label in sheep based on the studies you conducted in sheep under INAD 010-321. A proposed modification to that statement to address goats is:

“Your May Notice:

Clear, cloudy or yellow mucus on the outside of EAZI-BREED CIDR Sheep and Goat Insert when removed from ewes or does. This is a result of mild irritation to the vaginal lining by the presence of the EAZI-BREED CIDR Sheep and Goat Insert, and generally clears between the time of removal and breeding. Such irritation does not affect fertility.”

This language may also be prepared specifically for goats, should the need arise (see draft language for Freedom of Information (FOI) Summary later in this letter). Results from the clinical effectiveness study in goats regarding mucous observations on the CIDR-G inserts at removal may lead to modifications to this statement as well. Also, the sentence *“Such irritation does not affect fertility”* does not currently apply to goats; fertility will need to be evaluated in the clinical effectiveness study before drawing such a conclusion in goats.

The draft language for the FOI Summary is provided below:

III. TARGET ANIMAL SAFETY:

Study #05-324-TAS was conducted at the University of California at Davis. The objective of the study was to evaluate the target animal safety of an intravaginal progesterone-releasing insert (CIDR-G) administered to does for nineteen days to reflect the longest treatment period used outside the U.S. 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 95616

Study Location:

UCD Goat Teaching and Research Facility
Department of Animal Science
University of California at Davis
Davis, California 95616

General Design of the Investigation:

This study was conducted during September and October 2005. Healthy dairy breed does (Alpine, LaMancha, Saanen, Toggenburg) were enrolled in the study. All does were nulliparous and of breeding age (12 to 27 months). Does were housed in an outside corral with dirt (no bedding) and had access to an open shelter. Does were fed a standard ration of approximately four lb. alfalfa hay once daily, with mineral/salt mix and water available for *ad libitum* consumption.

On Day -19, does were given a pre-enrollment physical and vaginal examination. Twenty does were randomly assigned to a treatment or a control group (n = 10 per group). CIDR-G devices were inserted in does in the treatment group. Due to the loss of the device from one treated doe, one additional doe was randomly assigned to the treatment group and one to the control groups on Day -11. 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-G inserts were removed on Day 0 and from the added does on Day 8. Does were given a physical and vaginal exam on Days 2 and 7 and on Days 10 and 15 for the added does.

Key Variables:

- Body weights (kg; Days -19, 0, 2, and 7 of CIDR-G removal)
- Clinical health observations (Daily)
- Physical exams (heart rates, respiration rates, rectal temperatures; Days -19, 0, 2, and 7 of CIDR-G removal)
- Vaginal examinations and vaginal mucous scores (using vaginal speculum; Days -19, 0, 2, and 7 of CIDR-G 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 recording according to the following system:

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

Statistical Methods:

Each safety variable was analyzed using repeated measures analysis of covariance, with treatment, baseline value, time, and time by treatment interaction, as fixed independent effects. Effects of treatment were evaluated at the 0.10 level of significance.

Results:

Twice daily clinical observations revealed that animals remained healthy throughout the study period with the exception of a transient loose stool in one doe in the control group which required no treatment. No adverse treatment effects were observed. No does died during the conduct of the study.

No significant effects of treatment were observed on vaginal erosion score, vaginal mucous score, pulse rate, respiration rate, and body weight (Table 1). Observed rectal temperatures, respiration rates, and pulse rates, were within physiologically normal ranges. Significant differences between treatment and control were observed on

temperature (control 102.3 °F, treatment 101.9 °F, $p=0.066$). One control doe's rectal temperature was 104.0 °F on Study Day 0, but was otherwise clinically normal. With the exception of one doe with a vaginal erosion score of 2 on Study Day 0 (which resolved by Study Day 2), all other vaginal erosion scores were zero. Though not statistically different, the modest increase in vaginal mucous score was indicative of transient vaginal irritation expected with the treatment of does with the CIDR-G. This is consistent with the increased frequency of does with vaginal mucous scores ≥ 3 at the time of CIDR-G removal (Study Day 0).

Table 1. Results of repeated measures analysis of covariance for rectal temperature (°F), body weight (kg), respiration rate (respirations/minute), pulse rate (beats/minute), and vaginal erosion and mucous scores.

Variable	p-value TRT	Control LSMean	Treatment LSMean	Notes
Rectal Temperature	0.066**	102.3	101.9	
Body Weight	0.194	59.4	60.4	
Respiration Rate	0.719	53.8	52.0	
Pulse Rate	0.726	128.4	130.0	
Vaginal Erosion Score	0.52	0.00	0.07	Only 1 animal with non-zero score
Vaginal Mucous Score	0.121	1.56	2.12	

** significant at the $\alpha=0.10$ level.

Conclusions:

Results from this study support the safe use of the CIDR-G in meat and dairy goat does for up to 19 days. The mild and transient vaginal irritation noted in this study, support a label statement that describes these observations:

“You May Notice:

Clear, cloudy or yellow mucus on the outside of the CIDR-G when removed from goat does. This is a result of mild irritation to the vaginal lining by the presence of the CIDR-G, and generally clears between the time of removal and breeding.

We will make a final decision on whether we can approve your application after we have reviewed all of the data for all applicable technical sections submitted in support of an Administrative New Animal Drug Application (NADA), NADA, or supplemental NADA, and any other information available to us as a whole, and determined whether the requirements for approval set forth in the Federal Food, Drug, and Cosmetic Act have been met.

If you submit correspondence relating to this letter, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions, please contact me at 240-276-8228 or Dr. Gerald L. Rushin, Acting Leader, Ruminant Drugs Team, at 240-276-8103.

Sincerely yours,

Daniel A. Benz, PhD, PAS
Acting Director, Division of Production Drugs
Office of New Animal Drug Evaluation
Center for Veterinary Medicine