FREEDOM OF INFORMATION (FOI) SUMMARY

Ovuplant™ (deslorelin acetate)

Horses (mares)

NADA 141-044

Peptech Animal Health Pty Limited

35-41 Waterloo Road

North Ryde NSW 2113

Australia

Date of Approval June 18, 1998

Ovuplant™

FREEDOM OF INFORMATION (FOI) SUMMARY

TABLE OF CONTENTS

FREEDOM OF INFORMATION (FOI) SUMMARY

Ovuplant™ (deslorelin acetate)

I. GENERAL INFORMATION:

NADA Number: 141-044

Sponsor: Peptech Animal Health Pty Limited
35-41 Waterloo Road
North Ryde NSW 2113
Australia

Generic Name: Deslorelin Acetate

Trade Name: OVUPLANT™

Marketing Status: Rx

II. INDICATIONS FOR USE:

OVUPLANT™ is a gonadotropin-releasing hormone (GnRH) analog and is indicated for inducing ovulation within 48 hours in estrous mares with an ovarian follicle greater than 30 mm in diameter. Follicular size should be determined by rectal palpation and/or ultrasonography prior to treatment.

III. DOSAGE FORM:

Biocompatible, short-term implant

Route of Administration: Subcutaneous Implantation

Recommended Dosage: One implant, containing 2.1 mg deslorelin (as the acetate), per animal

IV. EFFECTIVENESS:

A. DOSE DETERMINATION

1. Two-site Dose Determination Study

a. Investigators:

Location 1:
Edward L. Squires, PhD
Equine Reproduction Laboratory
Colorado State University (CSU)
Fort Collins, CO 80523

Location 2:
John P. Hughes, DVM
Equine Research Center
Department of Reproduction
School of Veterinary Medicine
University of California (UCD)
Davis, CA 95616

b. General Design:

1) Purpose: To determine an effective dose of deslorelin for accelerating and timing ovulation in mares in estrus.

2) Test Animals: A total of 100 cyclic mares of mixed breeds were treated at the two locations (60 at CSU, 40 at UCD). Mares were nonlactating, 3 to 15 years old, and ranged in bodyweight from 250 to 500 kg. All were subjected to physical examination for reproductive soundness and were vaccinated and dewormed.

3) Treatment Groups: Mares were assigned to one of five treatment groups at each location using a randomization chart. Treatments consisted of single subcutaneous implants of the following doses of deslorelin/implant: 0, 1.2, 1.7, 2.1 and 2.7 mg. Investigators received five sets of implants in bottles numbered 1 through 5. All implants were the same size and color; thus, investigators were blinded to the doses being administered.

Each group at CSU contained 12 mares and each group at UCD contained 8 mares. Two mares were removed; one from 2.1 mg group at CSU and one from 2.7 mg group at UCD.

4) Route of Administration: The neck was thoroughly wetted with a suitable disinfectant, but not alcohol. The skin was penetrated with 12 gauge

needle and the implant was deposited subcutaneously using a stainless steel obturator.

5) Test Duration: Approximately four months.

6) Admittance Criteria: Mares were teased with a stallion daily during the acclimatization period and during the entire study to determine signs of estrus. Each mare's reproductive tract was examined by rectal palpation and ultrasonography every 3 days during diestrus and every day during estrus until ovulation occurred. The mares were again examined by ultrasonography every 3 days during a normal diestrous period (≥10 days) and upon spontaneous return to estrus, with a lead follicle ≥30 mm, they were assigned to treatment. During the treatment estrus, mares were examined by rectal palpation and ultrasonography twice daily until ovulation. The day estrous behavior was first observed was called Day 1. On this day, individual mares were admitted to the trial.

7) Pertinent Parameters Measured:

a) Interval to ovulation: After implantation, ovaries were examined by rectal palpation and ultrasonography every 12 hours until ovulation occurred. Data were obtained for the interval from treatment to ovulation. Data were also obtained for days in estrus at time of implantation, largest follicle size at implantation, duration of estrus, number of ovulations and size of follicle prior to ovulation.

b) Pregnancy determination: As mares exhibited estrus, they were inseminated with either fresh or cooled semen. Inseminations were performed every other day during estrus. Pregnancy diagnoses were performed using ultrasonography on Days 12, 18 and 35 after ovulation.

c) Hormones: Jugular blood samples were collected twice daily (four mares per group at CSU and all mares at UCD) beginning on the first day of estrus and continuing until ovulation. After ovulation, samples

were collected at 3-day intervals until Day 18. All samples were assayed for LH, FSH and progesterone.

d) Reaction to injection of implant: Clinical examination of the implantation site was made daily for the first six days after implantation and once weekly thereafter, for a total of three weeks. The following criteria were used for daily/weekly examinations of the implantation site:

Visible signs of swelling: none = 0 (no swelling detectable), slight = 1 (diameter of swelling about 1 cm or 0.4 inch), moderate = 2 (diameter of swelling about 2.5 cm or 1.0 inch), significant = 3 (diameter of swelling about 5.0 cm or 2.0 inches or larger);

Sensitivity to touch: none = 0, slight = 1, moderate = 2, significant = 3;

Skin temperature over implantation site: unchanged = 0, slightly elevated = 1, moderately elevated = 2, significantly elevated = 3.

c. Results and statistical analyses:

Key parameters evaluated for dose determination were interval to ovulation and time to ovulation being less than or equal to 48 hours (Table 1).

1) Interval to ovulation: Although mean size of follicles at treatment and pre-ovulation was slightly smaller at UCD where mares were treated earlier in estrus (35.2 and 41.0 mm vs 37.5 and 41.6 mm at CSU), treatment with all doses shortened the interval to ovulation significantly. Overall, mean time to ovulation decreased with increasing doses and were 77, 56, 52, 47 and 49 hours, respectively (Table 1). Although the trends for both sites were in the same direction, the means for time to ovulation from the UCD site were higher than the means for the CSU site except for the 2.1 mg dose.

The standard deviations were larger for the placebo group than for the treatment groups. The 2.1 mg dose had the smallest standard deviation at both locations (Table 1). Time to ovulation was analyzed using an ANOVA procedure. The treatment effect was significant (p=.0018); the location effect was significant (p=.0181); but the location by treatment interaction was not significant (p=.7049).

2) Ovulation within 48 hours: Using the definition of time to ovulation being less than or equal to 48 hours and using a Fisher's exact test, a significant linear trend was found (one-sided p=.001). When the placebo dose was omitted, the linear trend was significant at p=.0299, one-sided. When both the placebo and the 1.2 mg dose were omitted, the linear trend was not significant at p=0.2230.

A significant linear trend was seen among all the doses for time to ovulation being less than or equal to 48 hours, but the significant trend was not seen among the three highest doses. This together with the fact that the 2.1 mg dose had the smallest standard deviation for the time to ovulation provides evidence that the 2.1 mg dose was the dose to be tested further in clinical field trials.

Results from other parameters are as follows:

3) Pregnancy Rate: Overall, the percent of mares pregnant after the treatment cycle breeding was similar (p>0.05) among treatment groups (55, 65, 60, 68 and 63 for 0, 1.2, 1.7, 2.1, and 2.7 mg, respectively). See Table 2.

4) Hormone Response:

LH: Thirty-six hours prior to ovulation concentrations of LH were higher in deslorelin-treated mares than controls (P<0.05), but values were similar among active treatment groups. When data were arranged in relation to implantation dose, concentrations of LH were similar among mares given deslorelin, but all deslorelin-treated mares had higher (P<0.05) concentrations of LH than controls at 12 and 24 hours after implantation.

FSH: Thirty-six hours prior to ovulation, levels of FSH were significantly higher ($P<0.05$) in all treatment groups, except the 1.7 mg group, compared to controls. At 12 hours after implantation, concentrations of FSH were higher ($P<0.05$) in all treatment groups than controls and continued to remain significantly higher ($P<0.05$) in the 1.7 and 2.7 mg groups than controls 1 day after implantation.

Progesterone: Concentrations of progesterone were similar ($P>0.05$) among groups after ovulation. Peak concentrations of progesterone occurred 9 days after ovulation.

Overall, hormonal blood concentrations of both LH and FSH rose immediately in response to treatment. Progesterone blood levels reached their peak in all groups at about Day 9 after ovulation and were not different between treatment groups.

5) Implant site reactions: Local reactions to implantations, including the placebo implants, were minor and were restricted mainly to local swellings, most of which disappeared between Days 3 and 5 after treatment. Sensitivity to touch and elevated skin temperature of a mild to moderate nature, were seen in the 1.7, 2.1 and 2.7 mg groups in four animals during the first four days after implantation; however, these animals did not require local or systemic therapy.

6) Adverse Reactions: No systemic side effects of any kind were observed after deslorelin implantation.

d. Conclusions: Based on the results of this study, 2.1 mg of deslorelin is an effective dose for the induction of ovulation within 48 hours after implantation.

Table 1. Summary statistics* for the time to ovulation (hours) by location and treatment group.

Center		Treatment Group No. (Deslorelin dose, mg) 1 (0)	2 (1.2)	3 (1.7)	4 (2.1)	5 (2.7)
CSU	x	68.00	49.00	48.00	46.91	44.00
	s	38.74	8.02	11.44	3.62	9.34
	n	12	12	12	11	12
	P	50.0	75.0	83.3	100.0	100.0
UCD	x	91.50	66.00	58.50	46.50	58.29
	s	35.68	37.40	45.10	10.01	32.81
	n	8	8	8	8	7
	P	25.0	75.0	87.50	87.50	85.71
Combined	x	77.40	55.80	52.20	46.74	49.26
	s	38.44	25.01	29.21	6.81	21.50
	n	20	20	20	19	19
	P	40.0	75.0	85.0	94.7	94.74

*Summary statistics include the mean (x) and standard deviation (s) of the time to ovulation, the sample size (n), and the percent of mares ovulating within 48 hours (P).

Table 2. Summary* of pregnancy rate determined at Day 35 post-implantation among study mares by location and treatment group.

Center		Treatment Group No. (Deslorelin dose, mg) 1 (0)	2 (1.2)	3 (1.7)	4 (2.1)	5 (2.7)	Overall
CSU	n	12	12	12	11	12	59
	m	5	8	8	8	8	37
	P	41.7	66.7	66.7	72.7	66.7	62.7
UCD	n	8	8	8	8	7	39
	m	6	5	4	5	4	24
	P	75.0	62.5	50.0	62.5	57.1	61.5
Combined	n	20	20	20	19	19	98
	m	11	13	12	13	12	61
	P	55.0	65.0	60.0	68.4	63.2	62.2

* Summary includes the sample size (n), the number (m) and percent (P) of mares pregnant from breeding during the treatment estrous cycle.

B DOSE CONFIRMATION

1. SIX LOCATION MULTICENTER FIELD TRIAL

a. Investigators:

Location 1:
Steve Conboy, DVM
1335 Harp Innis Road
Lexington, KY 40511

Location 2:
Patrick J. Meyers, DVM
Equine Research Center
University of Guelph
Guelph, Ontario

Location 3:
Beryl C. Taylor, VMD
Rd. #2, Box 266
Cream Ridge, NJ 08514

Location 4:
Thomas Bowman, DVM
10395 Riley's Mill Road
Chestertown, MD 21620

Location 5:
Thomas Gimenez, DVM
Clemson University
Animal, Dairy and Veterinary
Science Department
Clemson, SC 29634

Location 6:
Poag Reid, DVM
2929 6th and 20th Road
Pendelton, SC 29670

b. General Design:

1) Purpose: To confirm, under blinded field conditions, the efficacy of the 2.1 mg dose of deslorelin in accelerating and timing ovulation in cyclic mares, and to evaluate treatment effects on early pregnancy rate, percent of pregnancies carried to term and the characteristics of foalings. The general health of foals was observed during the first 72 hours and at four weeks of age.

2) Test Animals: A total of 158 mares were treated at the six locations. Breeds included Standardbreds and grades (47.5 %), Thoroughbreds (15.2%), Quarterhorses (24.1%), Arabians (6.3%) and others (6.9 %). Mares ranged in age from 3 to 24 years (mean 11.0) and most had body condition scores of moderate to fleshy. Of the 158 mares, 67.8% were lactating and 27.8% were maiden or barren mares, or mares which had aborted or lost their foal at or after delivery. Reproductive history of 4.4% of 158 mares was unknown.

3) Treatment Groups: Animals were randomly assigned to one of two treatment groups. Treatments consisted of a single subcutaneous implant

of either 2.1 mg deslorelin or a placebo implant (0 mg deslorelin). Implants were the same size and color; thus, investigators were unaware of the treatments being administered.

Mare were assigned to treatment and location as follows:

Location	Deslorelin Implant	Placebo Implant	
1	19	16	35
2	20	20	40
3	10	7	17
4	6	6	12
5	13	12	25
6	16	13	29
	84	74	158

4) Route of Administration: The neck was thoroughly wetted with a suitable disinfectant, but not alcohol. The skin was penetrated with a 12 gauge needle and the implant was deposited subcutaneously using a stainless steel obturator.

5) Test Duration: Total duration including all locations was approximately 15 months.

6) Admittance Criteria: At each location, normally cycling mares were teased daily for signs of estrus. Their reproductive tract was examined by rectal palpation and ultrasonography every two to three days until the mares showed clinical and behavioral signs of estrus. The day estrous behavior was first observed was called Day 1. From Day 1 on, ovaries were examined by rectal palpation and ultrasonography at 24 to 48 hour intervals. Growth of all follicles ≥20 mm was recorded. Mares in estrus with a follicle which had reached ≥30 mm were admitted to the study and were assigned randomly to one of the two treatment groups.

7) Pertinent Parameters Measured:

a) Interval from implantation to ovulation: After implantation, ovaries were examined per rectum and with ultrasound at 24 hour intervals until ovulation occurred at locations 1 through 5. At location 6, examination intervals were 48 hours and occasionally 72 hours.

b) Pregnancy Rate: Mares with a pre-ovulatory follicle were bred every other day, or immediately in case ovulation had occurred between the two last examinations. The number and dates of each breeding were recorded. Pregnancy diagnosis was made by ultrasonography 18 and 38 days after breeding, and presence or absence of embryos or fetuses, singles or twins, was recorded. Mares were followed through gestation; abortions, normal or abnormal (dystocia) deliveries were also recorded.

c) Implantation Site Reactions: Clinical examination of the implantation site was made daily for the first six days after implantation and once weekly thereafter, for a total of three weeks. Observations were scored as in the dose titration study.

c. Results and Statistical Analyses:

1) Interval to ovulation: The time interval between treatments and ovulations in hours was significantly different ($P<0.05$) between deslorelin implants and placebo implants at locations 1, 2, and 5; the difference at location 6 was significant at ($P<0.10$); the difference at location 3 was not significant. At location 4, with only 12 mares treated very late in the season (August), intervals were very similar, short and not significantly different (Table 3). Overall, the difference between treatments was significant ($P<0.05$).

2) Percentage of mares ovulating within 48 hours: The percentage of mares ovulating within 48 hours was significantly different between deslorelin

and placebo treated mares at locations 1, 2, 5 and 6 (Table 4), with P values from 0.018 to <0.001, and a P value over all locations of P<0.001.

3) Pregnancy Rates: Percent of mares pregnant at the 18th day of the treatment estrous cycle by treatment group and location are shown in Table 5. Although there was a numerically lower pregnancy rate in the deslorelin group at all but one of the locations, only two of the six sites had rates which fell below the normal range for artificially inseminated mares.

4) Vitality at 4 weeks: Only those pregnancies which resulted from breedings at the treatment estrus are shown in Table 6. There was no significant difference between the treatments groups with respect to foal vitality at 4 weeks of age.

5) Implantation Site Reactions: Reports of mild to moderate swelling were made for equal numbers (approximately 12) of deslorelin and placebo mares. Mild to moderate sensitivity was reported for several mares in the deslorelin group and about six mares in the placebo group. Mild temperature increases were noted for two deslorelin treated mares and three of the placebo treated mares.

For each location and overall, a common observation was that mean ratings for swellings, sensitivity to touch, and the rare impression of elevated local temperature, were "slight" (score 1) or below; and in the majority of cases did not last longer than three or four days, with no significant differences between deslorelin or placebo implants. No treatment was required for any of the implantation site reactions.

6) Adverse Reactions: No adverse reactions or systemic side effects to treatments were seen at any of the six locations.

d. Conclusions: Treating estrual mares having a dominant ovarian follicle of 30 mm or larger with deslorelin short-term implants containing 2.1 mg of the GnRH analog deslorelin resulted in accelerated ovulation(s), occurring within

48 hours in most animals. Pregnancy rates at Day 18 were numerically lower at five out of six locations; however, these differences were not statistically significant. Foaling rates and foal vitality were similar for both groups.

Table 3. Mean (1) time (hours) to ovulation following implantation by treatment group and investigator.

	Treatment Group	
Location	Deslorelin	Placebo
1	49.26* 5.51 19	95.25* 50.05 16
2	45.60* 10.73 20	102.00* 50.39 20
3	50.20 21.13 10	61.71 23.42 7
4	52.00 25.92 6	42.50 18.63 6
5	45.85* 18.38 13	86.17* 50.88 12
6	57.00 31.45 16	84.92 47.61 13
Overall	49.64* 19.14 84	86.34* 48.04 74

(1) Standard deviation and number of mares are shown below the mean; treatment group means followed by an asterisk (*) are significantly different

($p<0.05$) based on an overall F-test for the overall means and individual F-tests for each location.

Table 4. Percent (1) of mares ovulating within 48 hours after treatment by treatment group and location.

Location	Treatment Group		Chi-square Statistic(2)
	Deslorelin	Placebo	
1	94.74 18/19	18.75 3/16	20.90 (<0.001)
2	95.00 19/20	25.00 5/20	20.42 (<0.001)
3	70.00 7/10	71.43 5/7	0.00 (0.949)
4	66.67 4/6	66.67 4/6	0.00 (1.000)
5	92.31 12/13	33.33 4/12	9.42 (0.002)
6	81.25 13/16	38.46 5/13	5.58 (0.018)
Overall	86.90 73/84	35.14 26/74	45.06 (<0.001)

(1)The denominator of each percent was the number of treated mares, as shown.

(2)Significance level (i.e., probability value) of each Chi-square statistic is shown in parentheses.

Table 5. Percent(1) of mares pregnant at the 18th day of the treatment estrus cycle by treatment group and location.

Location	Deslorelin	Placebo
1	42.11 (8/19)	75.00 (12/16)
2	55.00 (11/20)	50.00 (10 /20)
3	40.00 (4/10)	42.86 (3/7)
4	33.33 (2/6)	66.67 (4/6)
5	76.92 (10/13)	91.67 (11/12)
6	43.75 (7/16)	61.54 (8/13)
	50.0 (42/84)	64.86 (48/74)

(1) Numbers in parentheses represent number pregnant/number treated

Table 6: Vitality of Foals 4 Weeks After Birth for Those Mares Pregnant from the Treatment Estrus

	Foal Indicated As Born But No Data	Vitality Weak or Fair or No Foal Born	Vitality Good or Excellent	Total
Deslorelin	1 (2%)	12 (29%)	29(69%)	42
Placebo	2 (4%)	18 (38%)	28 (58%)	48
Total	3	30	57	90

2. Three Location US and Canada Clinical Field Trial
   a. Investigators:

Location 1:
P.J. Meyers, DVM
Seelster Farms, Inc.
RR #3
Lucan, Ontario
Canada, NOM 2J0

Location 2:
Glenn Blodgett, DVM
6666 Ranch
Highway 82 West
P.O. Box 130
Guthrie, TX 79236

Location 3:
Jill Thayer, DVM
Fossil Creek Equine Services, Inc.
7791 S.W. Frontage Road
Fort Collins, CO 80525

   b. General Design:
      1) Purpose: To confirm, under field conditions, the efficacy of 2.1 mg deslorelin in accelerating and timing ovulation in cyclic mares.

      2) Test Animals: A total of 84 mares were enrolled in this study. Mares ranged in age from 3 to 24 years (mean 10.2 years) and had a mean body condition of fleshy. Of the total, 53 (63.1%) were lactating while 31 (36.9%) were non-lactating or were maiden mares, barren mares or mares which had aborted or had lost their foals at or after delivery.

3) Treatment Groups: Mares were randomly assigned to 2.1 mg deslorelin or placebo implants. Placebo implants were of the same size and color, and differed from treatment implants only by the lack of deslorelin. Implants were number coded when provided to investigators, who were thus unaware of the treatments.

Mares were randomly allocated to treatment as follows:

Location	Deslorelin	Placebo	Total
1	15	13	28
2	9	14	23
3	17	16	33
Total	41	43	84

4) Route of Administration: The neck was thoroughly wetted with a suitable disinfectant, but not alcohol. The skin was penetrated using the preloaded implantation device intended for marketing and the implant was deposited subcutaneously.

5) Test Duration: Overall, the study lasted five months.

6) Admittance Criteria: Identical to those used in the preceding clinical study.

7) Pertinent Parameters Measured were identical with those used in the preceding clinical study. Mares were observed for general side effects after treatments, and observations recorded. Specifically, clinical examination of the implantation site was made daily for the first six days after implantation and once weekly thereafter, for a total of three weeks. The criteria used for daily/weekly examinations were identical with those used in the dose determination study.

d. Results and Statistical Analyses:

1) Interval from treatment to ovulation: The mean time interval between treatments and ovulations in hours was significantly different ($P<0.05$) between deslorelin and placebo implants at locations 2 and 3 (Table 7).

Overall, this difference (55.32 hr vs. 91.16 hr) was statistically significant ($P<0.001$).

2) The percentage of mares ovulating within 48 hours was significantly different between deslorelin and placebo treated mares at locations 2 and 3 (Table 8), with P values of 0.008 and 0.001, and a P value over all locations of $P<0.001$ for the difference between deslorelin (78.05% ovulations) and placebo (25.58% ovulations).

3) Pregnancy rates at Day 18 ensuing from breedings at the treatment estrus are shown in Table 9. At location 3, one deslorelin treated mare was euthanized due to colic after treatment but before pregnancy diagnosis could be made. One placebo treated mare was not bred during the treatment estrus. Due to the removal of the above two mares, 82 treated mares were available for pregnancy evaluation. The percentage of mares pregnant from breeding at the treatment estrus was 57.5% in the deslorelin group and 76.2% in the placebo group.

4) Implantation Site Reactions: Observations regarding the implantation site varied significantly between locations ($P<0.001$). Mean ratings for swellings, sensitivity to touch and the impression of elevated local temperature were mostly considered slight (score 1). Only 9, 2 and 1 incidences of swelling were recorded, on Days 1, 2 and 3, respectively, when swelling exceeded score 1 (slight = 1 cm in diameter) and reached score 2 (moderate = 2.5 cm in diameter). On Day 1, the incidence of swellings was higher with deslorelin compared with placebo (77% vs. 52%; $P<0.01$), while on Days 2 to 4 the incidence for swellings was higher with placebos, with 27.1% vs. 32.0%, 12.5% vs. 16.0% and 0.0% vs. 8.0% on Days 2, 3 and 4, respectively (not statistically significant). The incidence of sensitivity of touch and of elevated skin temperature were highest on Day 1 with 13.3% and 2.0%, deslorelin and placebo respectively, and dropped and disappeared rapidly over the next three and two days. All occurrences lasted from two to five days only, with mean duration for swelling, sensitivity of touch and elevated skin temperature of

2.5 days, 1.5 days and 1 day, respectively. Implantation site reactions did not require therapeutic intervention.

5) Adverse Reactions: No adverse reactions or systemic side effects to treatments were seen.

d. Conclusions: Treating estrual mares having a dominant ovarian follicle of 30 mm or larger with deslorelin resulted in accelerated ovulation(s), occurring within 48 hours in most animals. As a consequence, duration of estrus and the number of breedings were often reduced. The percentage of mares pregnant from breeding at the treatment estrus was 57.5% in the deslorelin group and 76.2% in the placebo group.

Table 7. Mean[(1)] time (hours) to ovulation following implantation by treatment group and location

	Treatment Group	
Location	Deslorelin	Placebo
1	56.80[(1)] 31.25 15	83.69[(1)] 50.44 13
2	56.00*[(1)] 16.97 9	99.43*[(1)] 44.01 14
3	53.65*[(1)] 31.21 17	90.00*[(1)] 28.40 16
Overall	55.32*[(1)] 28.13 41	91.16*[(1)] 40.68 43

[(1)]Standard deviation and number of mares are shown below the mean; treatment group means followed by an asterisk (*) are significantly different ($p \leq 0.05$) based on the overall F-test from the analysis of variance for the overall means and individual F-tests for each location.

Table 8. Percent (1) of mares ovulating within 48 hours after treatment by treatment group and location

Location	Treatment Group		Chi-square Statistic(2)
	Deslorelin	Placebo	
1	66.67 10/15	46.15 6/13	1.20 (0.274)
2	77.78 7/9	21.43 3/14	7.08 (0.008)
3	88.24 15/17	12.50 2/16	18.93 (<0.001)
Overall	78.05 32/41	25.58 11/43	23.12 (<0.001)

(1) The denominator of each percent was the number of treated mares.

(2) Significance level (i.e., probability value) of each Chi-square statistic is shown in parentheses.

Table 9. Percent (1) of mares pregnant at the 18th day of the first cycle by treatment group and location.

Location	Treatment Group	
	Deslorelin	Placebo
1	40.00 6/15	69.23 9/13
2	66.67 6/9	92.86 13/14
3	68.75 11/16	66.67 10/15
Overall	57.50 23/40	76.19 32/42

(1) The denominator of each percent was the number of treated mares with data available, as shown.

V. ANIMAL SAFETY

A. Target Animal Safety Studies

1. Drug Tolerance Study

a. Investigators:

E. L. Squires, PhD, Study Director
Equine Science Center
Colorado State University
College of Veterinary Medicine and Biomedical Sciences
Fort Collins, CO 80523

L. Harrison, DVM, Investigator
Taft Hill Farm
1021 North Taft Hill Road
Fort Collins, CO 80524

b. General Study Design:

1) Purpose: To evaluate the safety of deslorelin when administered at 10x the recommended dose (22 mg) under blinded conditions.

2) Test Animals: Ten reproductively sound, mixed-breed mares were used.

3) Treatment Groups: Mares were randomly assigned to two groups of five mares each. One group received 22 mg of deslorelin (ten subcutaneous implants) and the other group received 10 placebo implants, irrespective of the phase of their individual estrous cycle.

4) Route of Administration: Subcutaneous placement in the neck using the preloaded implantation device intended for marketing.

5) Test Duration: This study lasted 14 days.

6) Parameters Measured:

a) Comprehensive physical examination prior to, and on days 3 and 7 after treatment.

b) Behavior, food and water intake twice daily.

c) Heart rate and rhythm, respiratory rate and rhythm, sweating, tremors, defecation patterns and stool consistency, urination patterns and urine color, piloerection, salivation and panting prior to

treatment, and at 15 minute intervals for one hour, then hourly for six hours after treatment.

d) Body temperature and reactions at implantation site (swelling, elevation of skin temperature, sensitivity to touch) prior to treatment, hourly for six hours after treatment, then daily for six days and on day 14.

e) Hematology, serum chemistry and urinalysis at group assignment, prior to treatment, 6-8 hours after treatment, and on day 14.

f) Gross pathology at necropsy on day 14, and histopathologic evaluation.

c. Results and Statistical Analyses: There were no significant differences between groups in heart rate, respiratory rate, body weight (Day 3), implantation site reactions, respiratory abnormalities, hematologic parameters or urinalyses in examinations conducted pretreatment and on Days 3 and 7 post treatment.

Observations made hourly during the six hours after treatment revealed no differences between groups in body temperature.

Implantation site reactions:

Swelling occurred in all animals in both groups within 6 hours after treatment. Swelling resolved in 80% of horses by Day 6. Swelling was no longer apparent on Day 14.

Sensitivity to touch was 100% in both the placebo and deslorelin groups 2 hours after treatment. Sensitivity had subsided in the deslorelin and placebo groups by the sixth hour to 80% and 40%, respectively, and had disappeared in the deslorelin group after 24 hours. Sensitivity to touch was significantly greater ($p<0.05$) in the placebo group on days 1, 2, 4 and 5 than in the 10x group.

Skin temperature was not elevated in any of the horses during the first six hours. Skin temperature was elevated in both groups 24 hours after treatment but had disappeared by 48 hours.

Macropathologic and histopathologic findings revealed no treatment-related effects except for very slight local reactions around the implantation site which were considered to be the result of the implantation procedure. Evaluations of ovarian tissues obtained at necropsy showed marked structural differences between 10x treated mares and placebo treated mares. Of the ten ovaries collected from the 10x mares, only a single follicle was observed. Six of the ten ovaries revealed no visible or palpable structures, two showed a mid-cycle corpus luteum, and one showed a corpus albicans. Conversely, in the ten placebo ovaries, 25 follicles were counted among eight ovaries while one ovary showed a new corpus luteum and one ovary had no structures. These findings indicate that 10x the recommended dose of deslorelin caused shutdown of ovarian activity presumably due to GnRH (gonadotropin-releasing hormone) receptor down regulation in the anterior pituitary gonadotrophs.

d. Conclusions: Administration of ten times the recommended dose of deslorelin implants to reproductively sound mares caused neuroendocrine downregulation of the ovaries. No other clinically significant adverse effects were observed under the conditions of this study.

2. Combined target animal safety study and reproductive safety study
   a. Investigators:

E. L. Squires, PhD, Study Director
Equine Science Center
Colorado State University
College of Veterinary Medicine and Biomedical Sciences
Fort Collins, CO 80523

L. Harrison, DVM, Investigator
Taft Hill Farm
1021 North Taft Hill Road
Fort Collins, CO 80524

   b. General Study Design:
      1) Purpose: To evaluate under blinded conditions the safety to mares of 1x, 3x and 5x the recommended 2.1 mg dose of deslorelin when administered

during each of three consecutive estrous cycles, and to determine treatment effects on estrous cycle length, interval from treatment to ovulation, conception rate, and on early stages of pregnancy.

2) Test Animals: Forty reproductively sound, mixed breed mares.

3) Dosage Form: Subcutaneous implants as intended for marketing.

4) Dosages Used: Implants contained either no deslorelin (placebo) or 2.1 mg deslorelin (as the acetate). Ten mares were assigned to each treatment group. Mares received one placebo implant, one active implant (2.1 mg; 1x), three active implants (6.6 mg; 3x) or five active implants (11 mg; 5x). All treatments were administered three times - once during each of three consecutive estrous cycles. Mares in estrus were treated when the lead follicle had reached >30 mm in diameter.

5) Route of Administration: Subcutaneous implantation in the neck using the preloaded implanter intended for marketing.

6) Test Duration: Approximately five months.

7) Parameters Measured:
   a) Detailed physical examination before first treatment, and on days 3 and 7 after last treatment.
   b) Behavior, food and water intake twice daily between treatments and for one week after final treatment.
   c) Heart rate/rhythm, respiratory rate/rhythm, sweating, tremors, defecation patterns/stool consistency, urination patterns/urine color, piloerection, salivation, panting, behavioral reactions prior to each treatment, at 15 minute intervals for one hour, then hourly for six hours after each treatment.
   d) Implantation site reactions before each treatment, hourly for six hours after each treatment, daily for six days after treatment, then once per week for three weeks.

e) Body temperature before each treatment then hourly for six hours after each treatment.
f) Hematology, serum chemistry and urinalysis 10-14 days before treatment and 6-8 hours after the last treatment in all mares; additionally, on day of first treatment estrus prior to implantation and 6-8 hours thereafter in placebo and 5x treatment groups.
g) Body weights at time of first treatment, 4-8 hours post-treatment and eight days after last treatment.
h) Follicle size and day of estrus at each treatment, day of ovulation after each treatment, duration of estrus.
i) Conception rate, as determined by pregnancy tests 18 and 50 days after last treatment.
j) Blood samples for LH and FSH radioimmunoassay collected in morning and evening daily during behavioral and/or clinical estrus, and in the morning every other day during diestrus.

c. Results and Statistical Analyses: The comprehensive physical examinations conducted before first treatment and on days 3 and 7 after last treatment revealed a slightly higher body temperature ($p<0.05$) in 5x mares compared to placebo mares at day 7; body temperatures were similar among groups at other times. No statistically significant differences were seen among groups in mean heart rate, mean respiratory rate or incidence of implantation site abnormalities at these examinations.

Additional examinations prior to each treatment and during the first six hours after treatment were conducted. No clinically significant difference was seen among treatment groups in body temperature, heart rate, respiratory rate, or respiratory rhythm.

Implantation site reactions:

Swelling occurred in all groups, was generally slight and not evident by day 14 except in some animals in the 5x group following the third set of implantations. The incidence in the 3x group sporadically appeared

greater than in the placebo group; however, in the 1x group swelling was never significantly greater than seen in the placebo group.

All treatment groups exhibited increased sensitivity to touch, which decreased over time. In general, sensitivity was greater in the 3x and 5x groups than in the placebo and 1x groups, where sensitivity was similar.

Elevated skin temperature over the implantation site occurred infrequently, with differences seen only in the 3x and 5x groups, and had generally disappeared by days 3 or 4.

No treatment related differences were seen in behavior, feed and water consumption, hematology, blood, serum chemistries, or urinalyses at any time.

The interval to ovulation following implantation was always shorter by 1.3 to 2.1 days in treated mares compared to control mares. This effect was significant overall ($p<0.05$). In addition, the proportion of mares ovulating within 48 hours was significantly higher for all deslorelin treatment groups compared to controls during each of the three cycles and overall (87.7% vs. 25%; $p<0.05$). However, during the second and third estrus the duration of the estrus period for the 3x and 5x groups increased and the lead follicle took longer to reach the size required for treatment. Consequently, the interovulatory interval increased for these groups between the first and second estrus and the second and third estrus.

A smaller follicle diameter at ovulation was seen in deslorelin-treated mares which had no effect on fertility. Two mares in the 5X group failed to develop a preovulatory follicle following the 2nd treatment and were not treated again, since they did not show a third cycle. The remaining 8 mares in this group were treated, ovulated and were subsequently bred. A total of 24 of 27 deslorelin-treated mares (1x=8/10; 3x=8/9; 5x=8/8) became pregnant after 1 or 2 cycles of breeding, compared to 8 of 10 placebo-treated mares.

In general, levels of luteinizing hormone (LH) peaked 12 hours after deslorelin implantation. In contrast, the preovulatory surge of LH in placebo-treated mares did not occur until 1 to 1.5 days after ovulation.

d. Conclusions: Under the conditions of this study, administration of 1x, 3x, or 5x the recommended dose of 2.1 mg deslorelin for 3 consecutive cycles caused no clinical safety concerns. Administering three or five times the recommended dose caused short term signs of interference with neuroendocrine regulation which did not impair reproductive functions or fertility.

However, during the second and third estrus the duration of the estrus period for the 3x and 5x groups increased and the lead follicle took longer to reach the size required for treatment. Consequently, the interovulatory interval increased for these groups between the first and second estrus and the second and third estrus.

VI. HUMAN SAFETY:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use only in horses that are not to be used for food. The following Warning statement appears on the product label: "Not for use in horses intended for food."

User Safety: Product labeling contains adequate “Precaution” and “Warning” statements to insure human safety relative to possession, handling, and administration of this animal drug product.

VII. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514.111 of the implementing regulations. The data demonstrate that Ovuplant™ (deslorelin acetate), when used under labeled conditions, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the administration of a drug that accelerates ovulation after a 30 mm follicle has been detected. If the product is used without the knowledge necessary for understanding the physiological effects of deslorelin, the efficacy of the drug would be jeopardized.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

Patent Info: U.S. Patent number 5545408. Expiration August 13, 2013.

VIII. LABELING (ATTACHED):

package insert
pouch which holds applicator and implant
folding carton