Date of Approval:

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-319

SUCROMATE Equine

deslorelin acetate
injectable
Horses/Estrous mares

For inducing ovulation within 48 hours of treatment in cyclic estrous mares with an ovarian follicle between 30 and 40 mm in diameter.

Sponsored by:

Thorn BioScience LLC

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-319
B. Sponsor:	Thorn BioScience LLC 1044 E. Chestnut St. Louisville, KY 40204 Drug Labeler Code: 051330
C. Proprietary Name:	SUCROMATE Equine
D. Established Name:	Deslorelin acetate
E. Pharmacological Category:	Gonadotropin-releasing hormone (GnRH) analog
F. Dosage Form:	Injectable
G. Amount of Active Ingredient:	Each mL contains 1.8 mg deslorelin acetate (1.7 mg deslorelin)
H. How Supplied:	10 mL vial
I. How Dispensed:	Rx
J. Dosage:	Shake well before use. Administer 1 mL (one dose) per estrus cycle, 48 hours prior to desired ovulation. Verify that the mare is in estrus and has at least one ovarian follicle between 30 and 40 mm in diameter. SUCROMATE Equine is a suspension of deslorelin and settling will occur over time. Warm the product for 2 minutes by rolling the vial between the palms (to reach room temperature), or allow the vial to sit for 30 minutes at room temperature prior to administration. Shake the vial vigorously for 1 minute before use. Administer a 1 mL intramuscular injection into the thick musculature of the neck.
K. Route of Administration:	Intramuscular (neck)

L. Species/Class: Horses/Estrous mares

M. Indication: For inducing ovulation within 48 hours of treatment in cyclic estrous mares with an ovarian follicle between 30 and 40 mm in diameter.

II. EFFECTIVENESS:

A. Dosage Characterization:

The dosage characterization is based on the two pilot studies described below. These two studies were conducted to establish the effective dose of deslorelin acetate to be used for further evaluation in the pivotal field study described in the Substantial Evidence section (See page 4).

One controlled study compared the effectiveness of a single intramuscular injection of preliminary deslorelin acetate/ethanol formulations at doses of 0, 0.45 mg (per horse), 0.9 mg, 1.35 mg and 1.8 mg deslorelin acetate. The first part of the study compared the effectiveness of the four doses of deslorelin acetate/ethanol to placebo (10 mares per treatment arm). The results of Part 1 of the study indicated that the 1.8 mg deslorelin acetate/ethanol dose was the most effective dose for advancing ovulation to within 48 hours following treatment (90% of actual treated mares). Similar results were seen with the 0.9 mg dose of deslorelin acetate/ethanol. In Part 2, the 0.9 mg and 1.8 mg doses found to be most effective in Part 1 were studied to determine which dose would be optimal. Twenty mares were randomly assigned to each deslorelin acetate/ethanol dose group and 38 mares were assigned to an untreated control group. The results of Part 2 further supported a single dose of 1.8 mg deslorelin acetate/ethanol as being the most effective in advancing ovulation (90% of mares ovulated within 48 hours compared to 70% in the 0.9 mg group). These results are presented in Table 1.

Table 1. Mean Hours to Ovulation

Part 1: Mare Ovulation Data		
Treatment Group	**Mean Hours to Ovulation***	**Percent Ovulation by 48 Hours**
Placebo	112.8	20%
Deslorelin acetate/ethanol		
0.45 mg	88.8	30%
0.9 mg	50.4	90%
1.35 mg	55.2	80%
1.8 mg	50.4	90%

Part 2: Mare Follicle Size					
Treatment Group	**Mean Follicular Size (mm) at Treatment and at Ovulation (SE):**		**Mean Hours to Ovulation* (SE)**	**Percent Ovulation by 48 hours**	**Multiple Ovulations**
	Treatment	**Ovulation**			
Placebo	36.8 (0.5)	48.0 (1.0)	109.5 (6.4)	6.3% (2/32)	13% (5/38)
Deslorelin acetate/ethanol					
0.9 mg	35.4 (0.5)	40.8 (1.4)	67.2 (10.3)	70% (14/20)	25% (5/20)
1.8 mg	35.9 (0.5)	39.3 (1.1)	56.4 (7.4)	90% (18/20)	20% (4/20)

*ovulation determined via transrectal ultrasound

A second study compared SUCROMATE Equine (70:30 w/w deslorelin acetate/propylene carbonate suspension) at single, intramuscular doses of 0, 0.9 mg, 1.35 mg, and 1.8 mg. This study included 48 adult cyclic mares (12 mares per treatment group). The results of this study confirmed that the 1.8 mg dose of SUCROMATE Equine was more effective in advancing ovulation (82% of treated mares ovulated within 48 hours of treatment) compared to the 0.9 mg dose (50% of the treated mares) and the 1.35 mg dose (75% of the treated mares). These results are presented in Table 2.

Table 2. Mean Hours to Ovulation

Treatment Group	Mean Hours to Ovulation Mean (SE)	Percent Ovulating Within 48 Hours
Placebo	148 (54.0)	0%
SUCROMATE Equine 0.9 mg	88.8 (59.92)	50%
SUCROMATE Equine 1.35 mg	64 (47.3)	75%
SUCROMATE Equine 1.8 mg	65.5 (48.11)	82%

Based on the results of these two studies a SUCROMATE Equine dose of 1.8 mg was selected as the recommended dose.

B. Substantial Evidence:

SUCROMATE Equine, comprised of deslorelin acetate in a sucrose acetate isobutyrate/propylene carbonate suspension, is indicated for inducing ovulation within 48 hours of administration to cyclic estrous mares with an ovarian follicle between 30 and 40 mm in diameter. SUCROMATE Equine is a sustained release formulation of the GnRH analog, deslorelin acetate, capable of inducing endogenous secretion of a lutenizing hormone (LH) in concentrations sufficient to result in ovulation.

Effectiveness Field Study

1. Study Title: Evaluation of SUCROMATE Equine for the Controlled Release of Deslorelin Acetate for Advancing Ovulation in the Mare: In a Controlled Multi-center Clinical Study

2. Type of Study: Multi-center, GCP clinical effectiveness study

3. Study Dates: October 1998 – November 2000

4. Location(s) and Investigator(s):

Dr. John Hyland Avenel, Victoria 3664 Australia	Dr. William Coleman Killenaule, Co. Tipperary Ireland
Dr. Wendel L. Cooper Middleburg, VA 20117	Dr. William J. Solomon New Freedom, PA 17349-0129
Dr. Joe Landers Weathordford, Texas 76086	Dr. Jody Anderson Billings, MT 59107

5. General Design:

a. Purpose of Study: To evaluate, under masked conditions and field management conditions, the effectiveness and field safety of single,1.0 mL intramuscular injections of SUCROMATE Equine, a suspension containing 1.8 mg/mL deslorelin acetate in sucrose acetate isobutyrate/propylene carbonate (70:30 wt:wt). Specifically, this multi-center study evaluated the effectiveness of deslorelin acetate in accelerating the timing of ovulation in cyclic mares and its effects on the inter-ovulatory interval, and pregnancy rate.

b. Description of Test Animals: A total of 283 mares (143 in the placebo group and 140 in the SUCROMATE Equine group) were treated.

Table 3. Treatment Groups

Group #	Treatment (IM)	Number and Sex
1	1.0 mL Placebo (0.9% saline)	143 Mares
2	1.0 mL SUCROMATE Equine (1.8 mg deslorelin acetate)	140 Mares

A total of 191 mares (97 placebo and 94 mares in the SUCROMATE Equine group) were used in the effectiveness analysis. Breeds included 23 (8%) Standardbreds, 159 (56%) Thoroughbreds, 98 (35%) Quarter Horses and 3 (1%) Paints. Mares treated with SUCROMATE Equine ranged from 3 to 20 years of age (mean was 10.6 years of age), and most had "good" body condition scores. The available reproductive history at the beginning of the study showed that 67% of the study mares were lactating, 10% were maiden, and 19% had been barren for either one, two, or three years prior to enrollment.

c. Dosage and Administration: Mares were randomly assigned to one of two treatment groups. Treatments consisted of a single intramuscular injection of 1.0 mL of SUCROMATE Equine (1.8 mg/mL deslorelin acetate, final market formulation) or placebo (0.9% saline solution). A dosing technician, independent from the other study activities, administered the treatments to keep investigators masked. A single injection was administered once the mare was observed to have an ovarian follicle of 30 to 40 mm. Dosing was repeated in each subsequent estrus cycle until the mare demonstrated no estrus behavior or was pregnant.

d. Route of Administration: Injections were administered intramuscularly into the thick, fleshy part of the neck using an 18 to 21 gauge needle.

e. Study Duration: Approximately 25 months

f. Inclusion/Exclusion Criteria: The overall study period comprised a pre-admission screening physical, a pre-treatment assessment of estrus, and a teasing period of at least two days. Mares that passed the health and reproductive soundness examinations were teased by a stallion at least every other day. Teasing continued through the first ovulatory period. Beginning the first day of estrus, ovaries were examined by rectal palpation and ultrasonography at 24 to 48 hour intervals. The growth of all follicles was recorded. Mares in estrus with a follicle that had reached ≥ 30 mm and ≤ 40 mm were admitted to the study and were randomly assigned to one of the two treatment groups.

g. Parameters Measured:

- The percentage of mares ovulating within 48 hours after treatment was assessed. Ovaries were examined by rectal palpation and via ultrasound every day following treatment until ovulation occurred.
- The time to ovulation was calculated from the day of SUCROMATE Equine (or placebo) administration to the day of ovulation in 24 hour increments. Ovulation following treatment was determined by the presence of a bright echogenic structure at the location of the previously observed largest follicle.
- The percentage of mares that became pregnant following treatment and breeding in any ovulatory period was also assessed. Fertility was determined by ultrasound on Days 18 and 50 after breeding. Mares were followed through gestation (abortions), and normal or abnormal (dystocia) deliveries were recorded.
- The number of estrus cycles required to become pregnant was recorded.
- Injection sites were examined for signs of swelling, sensitivity to touch, and skin temperature elevation daily for the first 7 days and then at 14 and 21 days post-treatment.

h. Statistical Analysis: Effectiveness was based on the number of mares ovulating within 48 hours of treatment, and the mean hours to ovulation following treatment. Mares that did not conceive during their first cycle were treated again during their second cycle after achieving an ovarian follicle size of 30 to 40 mm. Likewise, mares that did not conceive during their second cycle were again treated during their third cycle. Other variables included follicle size at ovulation, number of multiple ovulations and length of estrus prior to ovulation.

Continuous data were analyzed according to a linear mixed model with terms for treatment, site, and the treatment by site interaction. Count and ordinal data were analyzed by the Cochran-Mantel-Haenszel test with clinical sites as strata.

6. Results:

a. Ovulation within 48 hours: The proportion of mares ovulating within 48 hours of treatment during Cycle 1 was 68 of 94 mares (72%) in the SUCROMATE Equine group and 23 out of 97 mares (24%) in the placebo group. During Cycle 2, 29 out of 35 mares (83%) in the SUCROMATE Equine group and 9 out of 25 mares (36%) in the placebo group ovulated within 48 hours of treatment. During Cycle 3, 12 out of 13 mares (92%) in the SUCROMATE Equine group and 3 out of 9 mares (33%) in the placebo group ovulated within 48 hours of treatment. The proportion of mares ovulating within 48 hours of treatment was significantly higher in the SUCROMATE Equine group as compared to the placebo group (Cycle 1, $p = 0.000$, Cycle 2, $p = 0.000$, and Cycle 3, $p = 0.006$) in the Cochran-Mantel-Haenszel test with sites as strata. See Table 4.

Table 4. Percentage of Mares Ovulating Within 48 Hours of Treatment
(Yes = ovulated / No = did not ovulate)

	Placebo (1.0 mL)	**SUCROMATE Equine (1.0 mL)**	**P value**
1st cycle			
Number of mares treated	97	94	
Yes	23 (24%)	68 (72%)	p = 0.000*
No	73 (75%)	25 (27%)	
Not determined	1 (1%)	1 (1%)	
2nd cycle			
Number of mares treated	25	35	
Yes	9 (36%)	29 (83%)	p = 0.000*
No	16 (64%)	6 (17%)	
3rd cycle			
Number of mares treated	9	13	
Yes	3 (33%)	12 (92%)	p = 0.006*
No	6 (67%)	0 (0%)	
Not determined	0 (0%)	1 (8%)	
Percent of mares ovulating within 48 hours after treatment in any cycle	**27%**	**77%**	

* statistically significant

b. Mean Hours to Ovulation: Starting on the first day of estrus, mares were examined every other day until a 30 mm pre-ovulatory follicle was detected, at which time the mare was administered SUCROMATE Equine. After treatment, the mares were examined daily until the pre-ovulatory follicle disappeared. The presence of a bright echogenic structure at the location of the previously observed pre-ovulatory follicle, and the presence of a corpus luteum was considered indicative of ovulation. Following treatment in each of three estrus cycles, the mean hours to ovulation were reduced in the SUCROMATE Equine group (65.1, 56.2, and 41.0 hours, respectively) compared to the placebo group (91.8, 83.0, and 85.3 hours, respectively). The mean hours to ovulation in Cycle 1 were significantly lower in the treated group compared to the placebo group (p = 0.019) in the mixed linear model. There were no statistically significant differences between the treated and the placebo group for Cycle 2 and Cycle 3 in the mixed linear model. The mean hours to ovulation per cycle per group is represented in Table 5.

Table 5. Mean Hours to Ovulation*

	Placebo (1.0 mL)	SUCROMATE Equine (1.0 mL)	P value
1st Cycle	91.8 (n = 96)	65.1 (n = 90)	p = 0.019**
2nd Cycle	83.0 (n = 24)	56.2 (n = 35)	p = 0.099
3rd Cycle	85.3 (n = 9)	41.0 (n = 12)	p = 0.155

* data could not be obtained on all mares

** statistically significant

c. Reproductive Safety: The following reproductive parameters were evaluated and compared between the SUCROMATE Equine group and the placebo group: length of estrus, follicle size, inter-ovulatory interval, number of mares to get pregnant, number of cycles to become pregnant, foaling rates and foal viability.

The inter-ovulatory interval was statistically analyzed between cycles for all mares that did not become pregnant in the previous cycle. There was no significant difference in the length of inter-ovulatory intervals between the SUCROMATE Equine treated group and the placebo treated mares as represented in Table 6.

Table 6. Mean Inter-ovulatory Interval in Days*

	Placebo (1.0 mL)	SUCROMATE Equine (1.0 mL)	P value
Cycles 1-2	26.1 (n = 27)	22.3 (n = 32)	p = 0.182
Cycles 2-3	21.3 (n = 9)	18.5 (n = 11)	p = 0.336
Cycles 3-4	13.0 (n = 1)	18.0 (n = 1)	

* data could not be obtained on all mares

The twinning occurrence rate is presented in the table below. Although the placebo group had more twins than the treated group, the incidence rate was relatively low and the data for a large portion of the animals was not available (see Table 7).

Table 7. Incidence of Detected Twinning (No = did not twin / Yes = did twin)

	Placebo (N = 97)	**SUCROMATE Equine (N = 94)**	**Overall (N = 191)**
No	45 (47%)	52 (55%)	97 (51%)
Yes	8 (8%)	2 (2%)	10 (5%)
Not Available	44 (45%)	40 (43%)	84 (44%)

Foaling Information: Efforts were made to ascertain the outcome of all pregnancies in the SUCROMATE Equine and placebo mares; however, data could not be obtained on all mares. Of the 140 SUCROMATE Equine mares in the study, 114 were known to be pregnant during the 1999 breeding season with 96 mares confirmed to have given birth to a live foal, and 3 mares confirmed to have had a stillbirth. Of the 143 placebo mares in the study, 118 were known to be pregnant during the 1999 breeding season with 111 confirmed to have given birth to a live foal and no confirmed stillbirths.

The nursing behavior, mobility and general health of the live foals at 72 hours and 4 weeks after foaling were similar for foals from mares in the SUCROMATE Equine and placebo groups. See Table 8 for a summary of the foaling and foal assessment data.

Table 8. Foaling and Foal Assessment Data*

	Treatment Group	
Assessment	**Placebo**	**SUCROMATE Equine**
Mares confirmed pregnant in 1999 breeding season out of total # of mares per group % (n/N)	83% (118/143)	81% (114/140)
Mares confirmed to have a live foal out of # of pregnant mares % (n/N)	94% (111/118)	84% (96/114)
Mares confirmed to have a stillbirth out of # of pregnant mares % (n/N)	0% (0/118)	3.0% (3/114)
72 Hour-General Health Foal Assessment % (n/N)		
Good	80% (89/111)	79% (76/96)
Satisfactory	16% (18/111)	20% (19/96)
Not Satisfactory	2% (2/111)	2% (2/96)
4 Week-General Health Foal Assessment % (n/N)		
Good	34% (38/111)	36% (35/96)
Not Assessed	66% (73/111)	67% (64/96)

*data could not be obtained on all mares

7. Adverse Events:

   Injection sites were observed once each day for the first 7 days after injection and then again at 14 and 21 days after injection for swelling, sensitivity to touch, and skin temperature. There was no sensitivity to touch or increase in skin temperature observed at any injection site in either the SUCROMATE Equine or placebo-treated mares following treatment in any cycle.

   Following treatment in Cycle 1, slight swelling was observed at the injection site in 3 mares in the placebo group and in 2 mares in the treated group soon after injection. The swelling resolved in all mares by Day 5. Slight swelling was seen in one SUCROMATE Equine mare on Days 0 and 3, in Cycle 2.

   With the exception of the injection site reactions and one case of colic in a placebo-treated mare, there were no adverse effects reported during the study treatment period. The placebo-treated mare with colic subsequently died; this death was not considered treatment-related. In addition, one SUCROMATE Equine mare died of colic 4 months after the last treatment. Two mares, one in the placebo group and one in the SUCROMATE Equine group, died either during or after foaling. None of these deaths were considered to be treatment related.

8. Conclusion: A single 1.0 mL injection of SUCROMATE Equine (1.8 mg deslorelin acetate/mL) administered to cyclic estrous mares with a pre-ovulatory follicle between 30 mm and 40 mm in diameter resulted in ovulation within 48 hours after treatment in 77% of treated mares. The length of the inter-ovulatory interval between cycles was not altered. The pregnancy rate of the treated mares was similar to the placebo mares.

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety Study

1. Study Title: Tolerance Study

2. Type of Study: GLP safety study

3. Study Director: E. L. Squires, PhD
   Fort Collins, CO

4. General Design:

   a. Purpose: To evaluate the safety of SUCROMATE Equine (final market formulation), when administered at 10X the recommended dose of 1.8 mg in a masked fashion.

b. Test Animals: Sixteen reproductively sound, mixed-breed mares were used. Mares ranged from 3 to 11 years of age.

c. Test Animal Management: Mares were group housed in dry lots. Due to the time of year in which the study was conducted, all mares were under artificial lighting from August through December to counteract the natural decrease in daylight hours.

d. Treatment Groups: Mares were randomly assigned to two groups of eight mares each. One group received 18 mg of SUCROMATE Equine and the other group received a 10 mL saline intramuscular injection. Mares had follicle diameters from 30 to 40 mm and were in estrus.

e. Route of Administration: Intramuscular injections of SUCROMATE Equine or saline were given into the thick musculature of the neck with an 18 gauge needle. The total volume of 10 mL of SUCROMATE Equine or saline was equally divided into two 5 mL intramuscular injections on the same side of the neck.

f. Study Duration: 21 days

g. Variables Measured:
   (1) Comprehensive physical examination prior to, and on Days 3 and 7 post-treatment.
   (2) Behavior, food and water intake twice daily.
   (3) 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 then at 1, 3, and 6 hours after treatment.
   (4) Skin temperature and reactions at injection site (swelling, elevation of skin temperature, sensitivity to touch) prior to treatment, and at 1, 3, and 6 hours after treatment, and then daily for seven days, and on Days 14 and 21.
   (5) Hematology and serum chemistry 1 day prior to treatment, and 6-8 hours after treatment. Urinalysis prior to treatment, and at 6 and 24 hours after treatment.
   (6) LH and FSH levels prior to treatment, 6 and 12 hours after treatment and then AM and PM during estrus and every third day following ovulation to next estrus or Day 18 of pregnancy.

5. Results and Statistical Analyses: Statistical comparisons between treatment groups for safety study variables were considered significant if their p-values were 0.10 or less.

   a. Physical Examinations: There were no clinically significant differences between treatment groups in the results of the physical examinations including body temperature, cardiovascular, respiratory, gastrointestinal and urinary tract,

muscular and equilibrium, behavioral, skin and integument, and ocular assessments.

b. Adverse Reactions: One 10X mare exhibited moderate tremors and hives at 6 hours post-treatment. The physical exams at 1, 3, and 6 hours post-treatment for this mare showed that she had an elevated heart rate and elevated respiratory rate.

c. Injection Site Reactions: Assessments of the injection sites showed statistically significant increases in the number of mares experiencing swelling at 1, 3, and 6 hours after injection in the SUCROMATE Equine group compared to placebo ($p \leq 0.046$). Sensitivity to touch and elevations in skin temperature were significantly more frequent in the SUCROMATE Equine treated group compared to placebo at 1 hour, and at 1, 3, and 6 hours respectively, after injection ($p \leq 0.072$). These changes were mild to moderate and in all cases resolved without intervention. Results from the injection site assessments at Days 3 and 7 were not statistically significantly different between the SUCROMATE Equine treated group and the placebo group. However, there was some residual injection site swelling, hardness, and inflammation in several SUCROMATE Equine treated mares, which resolved by Day 14.

d. LH/FSH: The profile of LH levels in both groups exhibited a typical pattern of surge prior to ovulation followed by a gradual return to baseline levels. The LH concentrations in the SUCROMATE Equine group reached a mean Cmax of 462.5 ng/mL at 8.3 hours post-dosing, compared to a mean Cmax of 93.8 ng/mL at 40.5 hours post-dosing in the placebo group. Mares treated with SUCROMATE Equine reached a mean Cmax FSH concentration of 125.7 ng/mL by 7.5 hours following treatment compared to a mean Cmax FSH concentration of 34.9 ng/mL at 20.3 hours following treatment in the placebo group. The LH concentrations during Days 3-18 post ovulation ranged from 14.0 to 64.2 ng/mL and 14.7 to 161.0 ng/mL for the SUCROMATE Equine and placebo groups, respectively. The FSH concentrations during Days 3 to 18 post-ovulation ranged from 31.3 to 45.4 ng/mL and 34.6 to 47.6 ng/mL for the SUCROMATE Equine and placebo groups, respectively. LH concentrations were evaluated by repeated measures analysis and were found to be lower than those of the placebo group during Days 3-18 post-ovulation ($p \leq 0.0544$). FSH concentrations were evaluated by repeated measures analysis and were not statistically significantly different between the groups from Days 3 to 18 post-ovulation. The dose of SUCROMATE Equine did not appear to adversely suppress FSH concentrations.

e. Estrus and Ovulation Measures: Time to ovulation and length of estrus were statistically significantly reduced ($p \leq 0.005$) in the SUCROMATE Equine group compared to placebo. Mares treated with SUCROMATE Equine had statistically significantly ($p \leq 0.002$) smaller ovulatory follicles as compared to the placebo group (37.13 mm vs. 46.63 mm). The proportion of mares ovulating within 48

hours was statistically significantly higher in the SUCROMATE Equine group ($p \leq 0.001$).

f. Fertility Measures: The 18.0 mg dose of SUCROMATE Equine (10X the proposed dose) had no adverse effects on pregnancy rates. The number or proportion of mares becoming pregnant 50 days after the first ovulation period was equivalent for both treatment groups. Six of eight (75%) mares were pregnant both in the placebo and SUCROMATE Equine groups after the first cycle and after 50 days. The total number of mares pregnant 50 days after the 3rd cycle was seven out of eight (87.5%) in the placebo group and eight out of eight (100%) in the SUCROMATE Equine group.

6. Conclusions: Administration of ten times the recommended dose of SUCROMATE Equine to reproductively sound mares resulted in transient swelling, increased sensitivity to touch and increased temperature at the injection sites. Ten times the recommended dose of SUCROMATE Equine did not have any adverse effects on fertility.

B. Target Animal Safety Study

1. Study Title: Combined target animal safety and reproductive safety study

2. Type of Study: GLP safety study

3. Study Director: E. L. Squires, PhD
Fort Collins, CO

4. General Design:

a. Purpose: To evaluate under masked conditions, the safety of 1X, 3X and 5X the recommended 1.8 mg dose of SUCROMATE Equine when administered to mares during each of three consecutive estrous cycles; and to determine treatment effects on conception rate, and on early pregnancy.

b. Test Animals: Thirty-two reproductively sound, mixed breed mares. Mares ranged from 3-15 years of age.

c. Test Animal Management: Mares were group housed in dry lots. Due to the time of year in which the study was conducted, all mares were under artificial lighting from August through December to counteract the natural decrease in daylight hours.

d. Dosage Form: Injectable

e. Dosages Used: Placebo (saline) or SUCROMATE Equine (1.8 mg/mL deslorelin acetate in suspension). Eight mares were assigned to each treatment group. Mares received either 1.0 mL of placebo, 1.0 mL SUCROMATE Equine (1.8 mg = 1X), 3.0 mL SUCROMATE Equine (5.4 mg = 3X), or 5.0 mL SUCROMATE Equine (9.0 mg = 5X). Each treatment was administered once during each of three consecutive estrus cycles. Mares in estrus were treated when the largest follicle reached a diameter of 30 to 40 mm.

f. Route of Administration: Intramuscular injection of SUCROMATE Equine or saline was administered into the thick musculature of neck with an 18 gauge needle.

g. Study Duration: July 1998 – December 1998

h. Variables Measured:
   (1) Comprehensive physical examination prior to treatment in each estrous cycle and on Days 3 and 7 post-treatment in the last cycle.
   (2) Body weight, food and water intake were assessed prior to treatment in each of the three treatment cycles.
   (3) Heart rate and rhythm, respiratory rate and rhythm, sweating, tremors, defecation patterns and stool consistency, urination patterns and urine color, piloerection, and salivation prior to each treatment and then at 1, 3, and 6 hours after each treatment.
   (4) Skin temperature and reaction at the injection site (swelling, elevation of skin temperature and sensitivity to touch) prior to each treatment and at 1, 3, and 6 hours after treatment, and then daily for 7 days, and on Days 14 and 21, or until next treatment.
   (5) Hematology, serum chemistry and urinalysis one day prior to treatment, prior to treatment on treatment day and 6-8 hours after treatment for the first and third treatments.
   (6) LH and FSH levels prior to treatment, 6 and 12 hours post-treatment, twice daily during estrus and every third day following ovulation until the next estrus or Day 18 of pregnancy (Days 3, 6, 9, 12, 15 and 18).
   (7) Time from treatment to ovulation, follicle size at ovulation, duration of estrus, number of cycles to pregnancy, pregnancy rate after the third treatment were also recorded.

5. Results and Statistical Analyses: Statistical comparisons between treatment groups for safety study variables were considered significant if their p-values were 0.10 or less.

   a. Physical Examination and Laboratory Assessments: Results of the physical examinations including body temperature, cardiovascular, respiratory, gastrointestinal, urinary tract, muscular and neurological, behavioral, skin and

integument, and ocular assessments were generally comparable across all treatment groups including placebo at the pre-treatment assessments in each of the three treatment cycles. There were no statistically significant differences between the SUCROMATE Equine groups and placebo group with respect to physical examination results or laboratory assessments (hematology, chemistry, and urinalysis) during any of the three treatment cycles. There were no statistically significant differences between treatment groups with respect to body weight, food intake, and water intake.

b. Injection Sites: In the six hours following injection in all treatment cycles, some mares in all treatment groups exhibited mild to moderate swelling at the injection site. At certain assessment times, the number of mares experiencing swelling, sensitivity to touch, and elevations in skin temperature in the SUCROMATE Equine groups was statistically significantly higher than the placebo group. Assessments of injection sites showed the number of SUCROMATE Equine treated mares experiencing swelling at Day 1 of Cycle 1, and 6 hours after injection in Cycle 2 were statistically significantly higher than the placebo group ($p \leq 0.081$). Sensitivity to touch was significantly more frequent in the 5X group than in the placebo group at Day 1 post-treatment in Cycle 1, and at Days 2 and 4 post-treatment in Cycle 2 ($p \leq 0.052$), and in the 3X group at Day 1 post-treatment in Cycle 1 ($p \leq 0.091$). All injection site reactions in the 1X treated horses had resolved by 3 days post-treatment. Two mares, one 3X mare and one 5X mare, had swelling and hardness noted at injection sites at Day 7 post-treatment.

   The incidence of the injection site adverse reactions was higher in the 5X SUCROMATE Equine groups, although not statistically significant. The incidence of injection site reactions for the placebo, 1X, 3X and 5X groups was 37%, 75%, 50%, and 87%, respectively.

c. Adverse Reactions: One 3X mare repeatedly reacted violently after injection of SUCROMATE Equine and was extremely difficult to treat. This was most likely a behavioral reaction as there was no injection site swelling or long term sequela.

d. Luteinizing Hormone (LH): The profiles of LH in the SUCROMATE Equine treated groups in all three cycles exhibited an expected surge following treatment and prior to ovulation, followed by lower concentrations during the midluteal phase, with a gradual return to pretreatment levels. The following figures display LH concentrations for Hours 0 to 48 and Days 3 to 18 for SUCROMATE Equine or placebo for each cycle and each dose group. In the Hours 0 to 12, LH concentrations in all dose groups were significantly elevated from placebo ($p \leq 0.042$) in Cycles 1 and 2. There was a dose response relationship with the 5X dose resulting in the highest levels of LH over all three cycles. For Days 3 to 18 post-ovulation, the values of LH in the SUCROMATE Equine groups were similar to those in the placebo group. Analysis of variance was used to check the

group differences for LH for each time point for 3, 6, 9, 12, 15 and 18 days post-ovulation. Statistically significant findings were noted in the 3X group LH concentrations in Cycle 3 for Days 9 and 12 post-ovulation which were significantly lower than that of the placebo group ($p \leq 0.0697$).

Figure 1. Cycle 1 LH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

Figure 2. Cycle 2 LH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

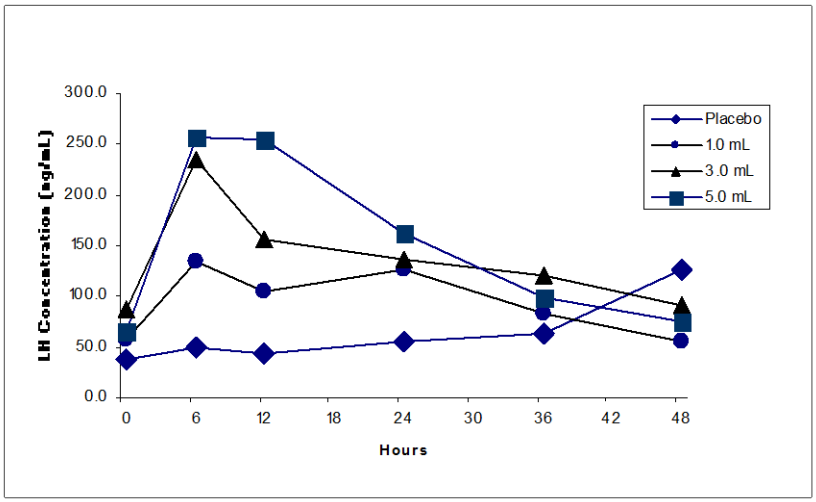


Figure 3. Cycle 3 LH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

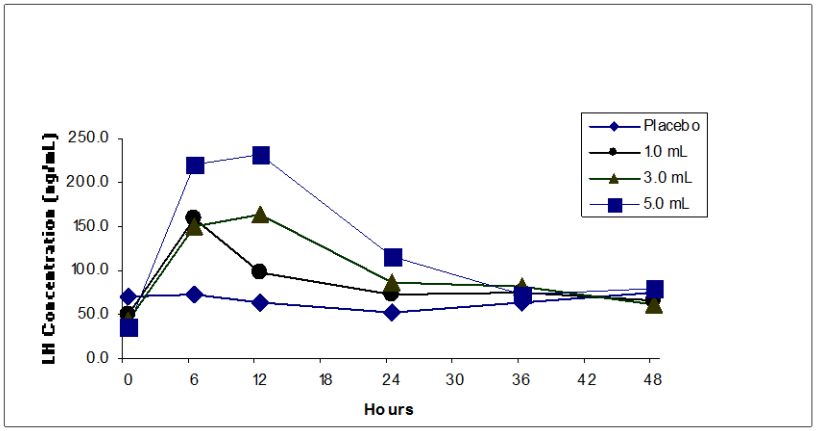


Figure 4. Cycle 1 LH Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)

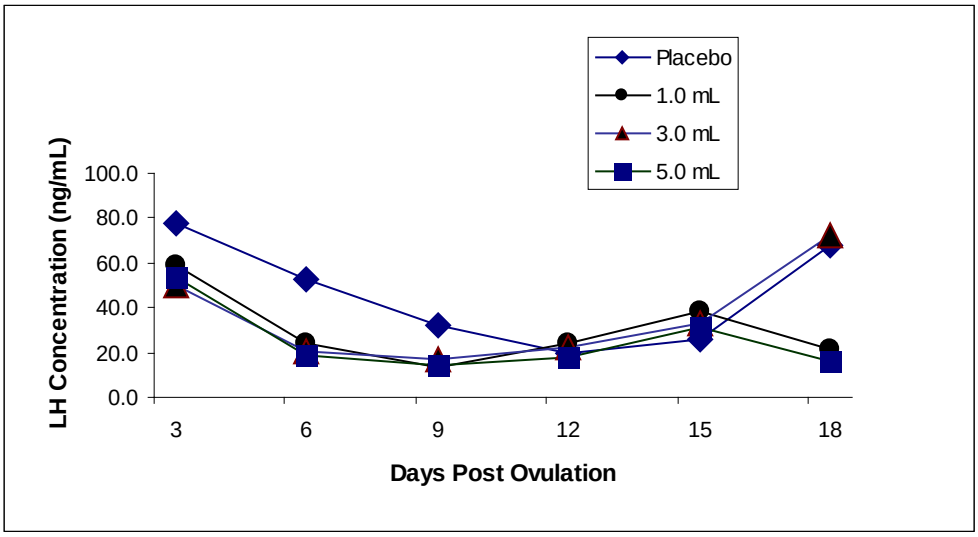


Figure 5. Cycle 2 LH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)

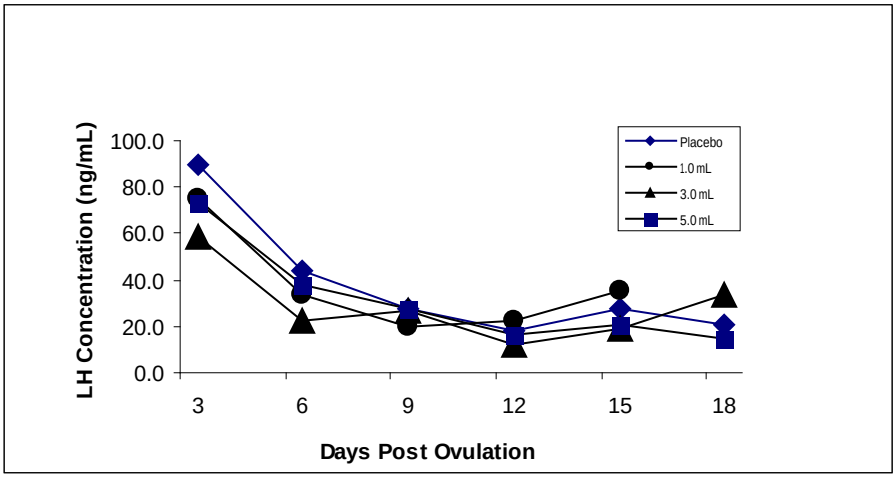
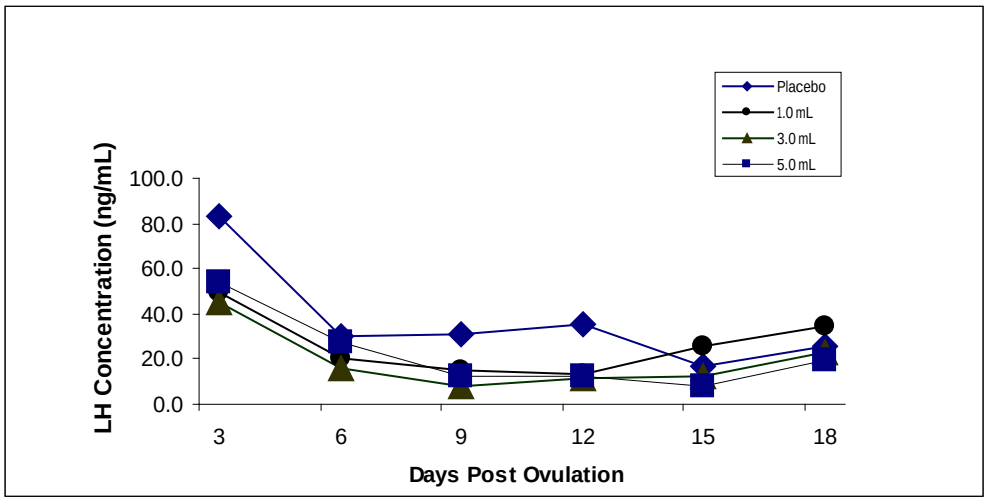


Figure 6. Cycle 3 LH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)



e. Follicle Stimulating Hormone (FSH): The profiles of FSH in the SUCROMATE Equine treated groups in all three cycles exhibited an expected surge following treatment, followed by lower concentrations during the midluteal phase, with a gradual return to pretreatment levels. The following figures display FSH concentrations for Hours 0 to 48, and Days 3 to 18 for SUCROMATE Equine or placebo for each cycle and each dose group. In the Hours 0 to 48, mares in the 1X group had higher serum concentrations of FSH compared to all other groups in all cycles at 6 and 12 hours following treatment ($p \leq 0.053$). For Days 3 to 18 post-ovulation, the range of values of FSH in the SUCROMATE Equine groups was similar to that in the placebo group, ranging from 20 to 70 ng/mL; however, there was an overall trend for the values in the 5X group to be less variable and the lowest in each of the cycles. When FSH levels from Days 3 to 15 post-ovulation were analyzed using a repeated measures linear model for each cycle, there was a statistically significant difference among the dose groups ($p \leq 0.0111$) in Cycle 1. The FSH level of the 5X group was significantly decreased compared to that of the placebo group ($p \leq 0.0528$). There were no statistically significant differences among dose groups in the FSH level from Days 3 to 15 post-ovulation for Cycles 2 and 3.

Analysis of variance was used to check for group differences for FSH for each time point for Days 3, 6, 9, 12, 15 and 18. The analysis of variance results showed that FSH concentration at Day 15 post-ovulation in Cycle 1 was significantly different among 4 dose groups ($p \leq 0.0048$). The FSH concentrations of 3X and 5X groups for Day 15 post-ovulation in Cycle 1 were significantly lower than that of the placebo group ($p \leq 0.10$) and no other pair wise comparisons were statistically significant. During Cycle 2, FSH concentrations for Day 6 and Day 18 post-ovulation were significantly different among 4 dose groups ($p \leq 0.0962$ and 0.0682, respectively). Only the 5X group FSH concentration on Day 18 post-ovulation of Cycle 2 was significantly lower than that of the placebo group ($p \leq 0.10$). There were no statistically significant differences for FSH in Cycle 3.

The repeated measures findings included that FSH levels from Days 3 to 15 post-ovulation in the 5X group were statistically significantly decreased in Cycles 1 and 2, but not in Cycle 3. Additionally, there were no statistically significant findings in Cycles 2 or 3 for the individual days, which may be due to the fact that three 5X mares with the lowest levels of FSH entered anestrus early. After a mare entered anestrus, her hormone data was no longer analyzed, and therefore, was not included in the mean values. In Cycle 2, two 1X mares and one 5X mare entered anestrus and, therefore, did not receive treatment in that cycle or in subsequent cycles. These mares did not have LH and FSH values for Cycles 2 or 3. In Cycle 3, one placebo mare, and one 5X mare entered anestrus and therefore, did not receive treatment in that cycle or in subsequent cycles. These mares did not have LH and FSH values for Cycle 3. After treatment in Cycle 3, one

additional 5X mare never ovulated, and therefore, did not have LH and FSH values for Days 3 to 18 post-ovulation in Cycle 3.

Figure 7. Cycle 1 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

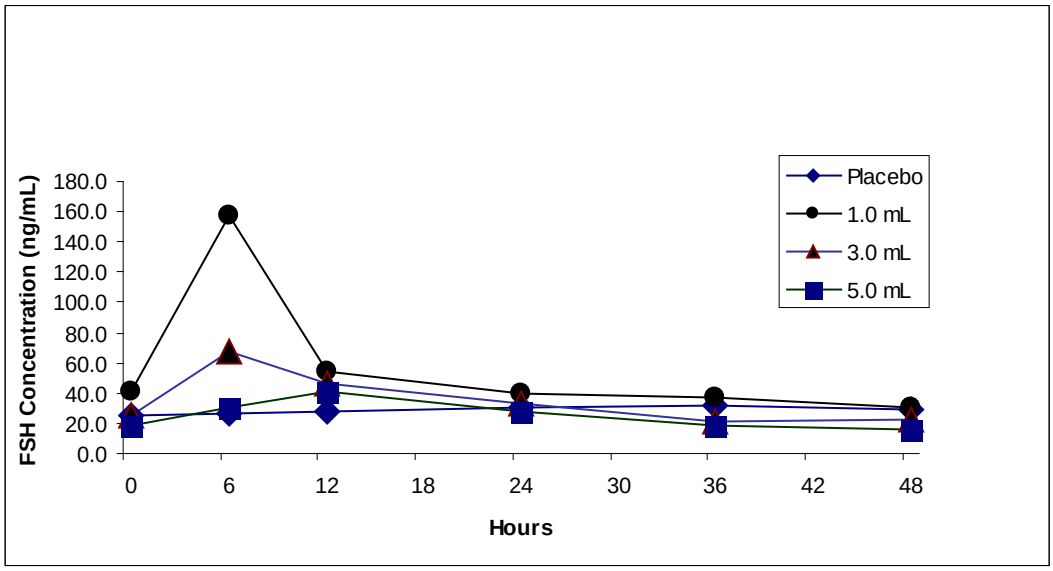


Figure 8. Cycle 2 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

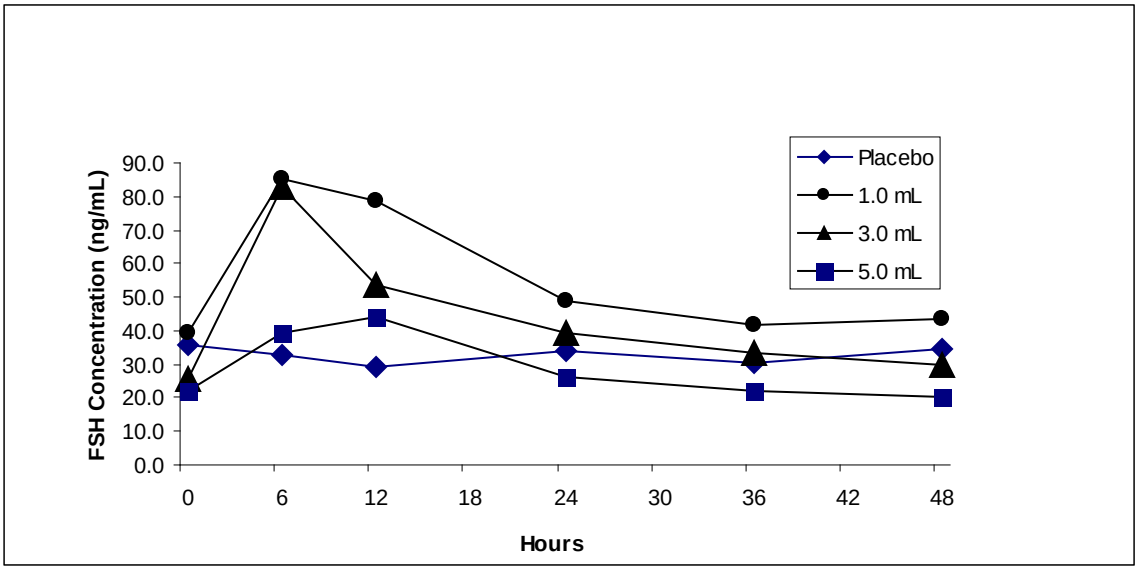


Figure 9. Cycle 3 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (0-48 Hours)

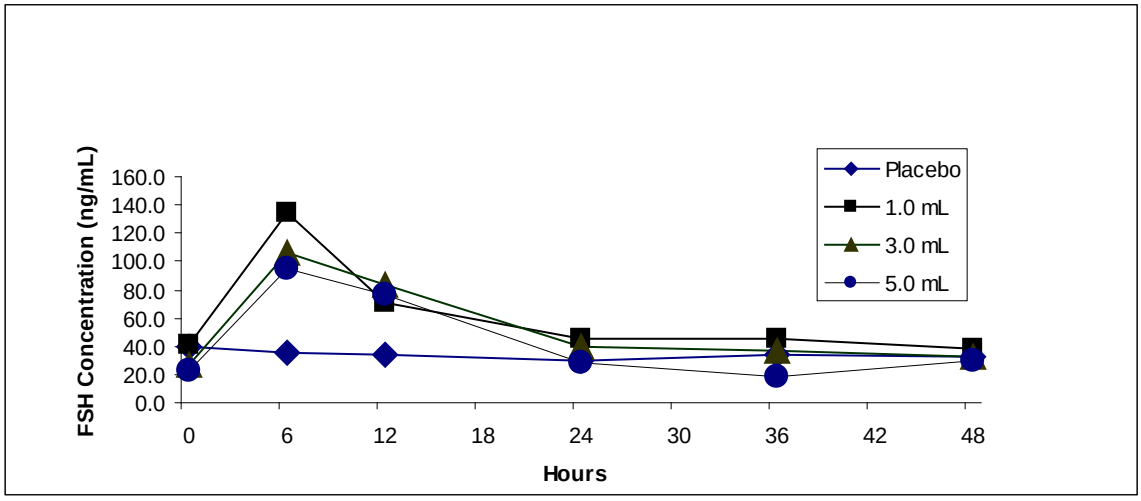


Figure 10. Cycle 1 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)

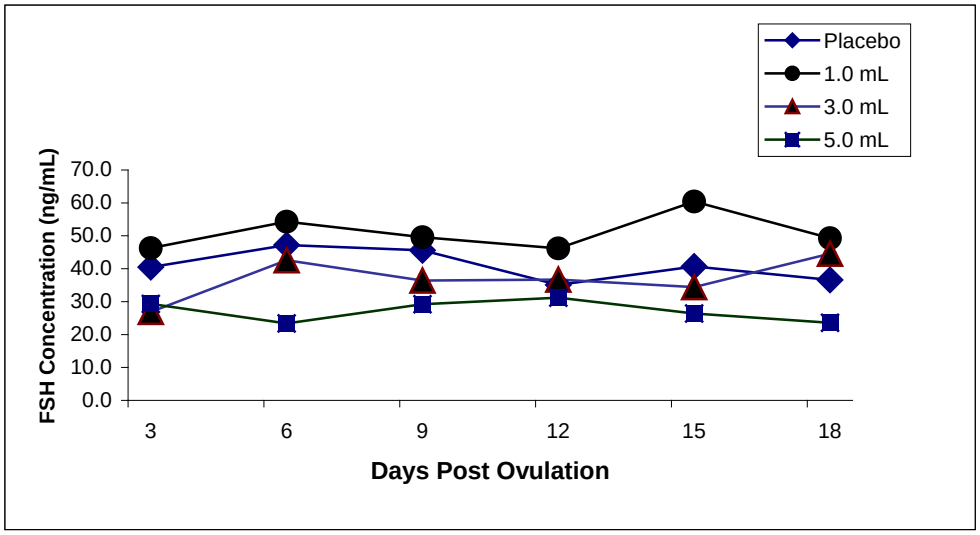


Figure 11. Cycle 2 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)

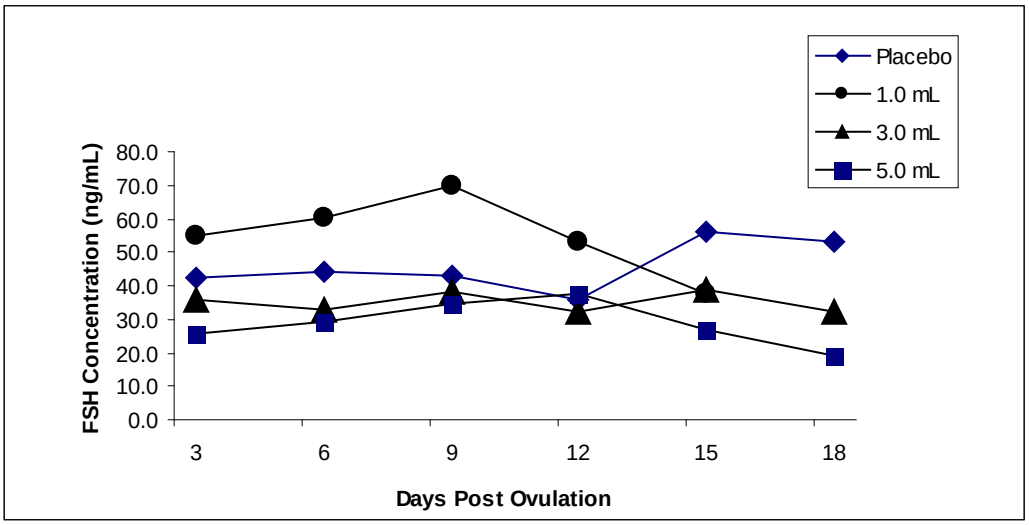
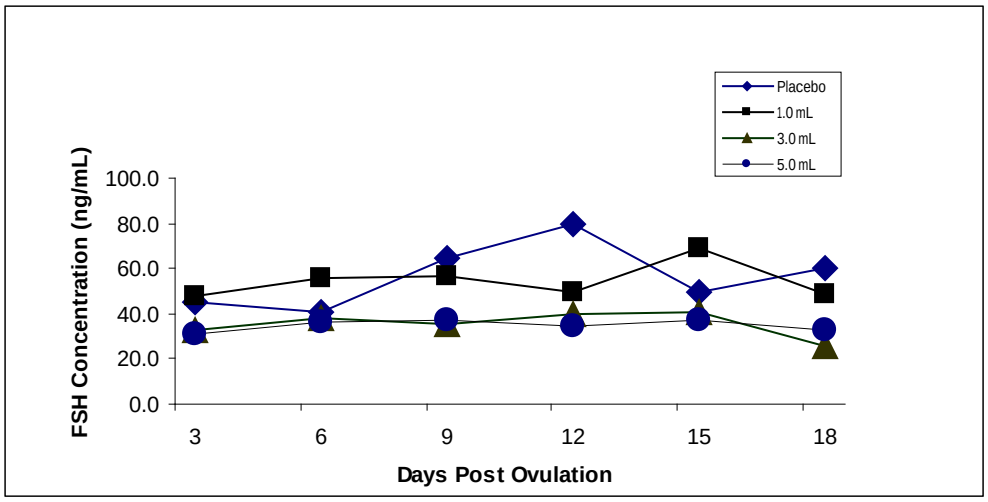


Figure 12. Cycle 3 FSH Mean Concentrations Following Treatment with Placebo or SUCROMATE Equine at 1.0, 3.0, and 5.0 mL (Days 3-18)



f. Time to Ovulation/Ovulation within 48 hours/Length of Estrus: Treatment with SUCROMATE Equine at all doses reduced the mean hours to ovulation during all three treatment cycles compared to placebo group. These reductions in time to ovulation were significant for all three cycles in the 3X and 5X treatment groups ($p \leq 0.024$ and $p \leq 0.048$). The mean time to follicle disappearance in the 1X group reached statistical significance in Cycle 2 ($p \leq 0.003$). Of the sixty-five treatment experiences for the SUCROMATE Equine treated mares across the three cycles, fifty-five (84.6%) were followed by ovulation within 48 hours

compared to five of twenty-three (21.7%) for the placebo mares. There was no statistically significant effect on the length of estrus at any dose level.

g. Inter-ovulatory Interval (IOI): The mean IOI in the SUCROMATE Equine treated groups ranged from 17.8 to 23.0 days compared to 21.0 to 23.5 days in the placebo group. SUCROMATE Equine treatment at 1, 3, and 5X the dose did not have a significant effect on inter-ovulatory intervals.

h. Early Entrance into Anestrus: In Cycle 2, two 1X mares and one 5X mare entered anestrus, and therefore, did not receive treatment in that cycle or in subsequent cycles. The study was conducted at the end of the breeding season, thus it was expected that some mares would enter anestrus. The three 5X mares that entered anestrus also had decreased FSH concentrations in the days post ovulation for all three cycles, thus it was impossible to determine if the anestrus was due to the time of year, the decreased FSH levels as a result of SUCROMATE Equine, or both.

i. Pregnancy: All mares that ovulated after the third treatment with SUCROMATE Equine or placebo were bred. These mares were bred until they became pregnant (not to exceed three cycles). In the placebo group, seven mares ovulated after the third treatment and were bred. Six of the seven mares became pregnant (85.7%). In the 1X group, six mares ovulated after the third treatment and were bred. All six became pregnant (100%). In the 3X group, eight mares ovulated after the third treatment and were bred. Six of the eight mares became pregnant (75%). In the 5X group, five mares ovulated after the third treatment and all became pregnant (100%).

   There were no statistically significant differences across the treatment groups in terms of time to pregnancy or the number and proportion of mares that became pregnant after exposure to three consecutive treatments.

6. Conclusions: Under the conditions of this study, administration of 1X, 3X, or 5X the recommended dose of 1.0 mL (1.8 mg) of SUCROMATE Equine for three consecutive cycles caused some transient injection site swelling. Administration of the 5X dose appeared to suppress FSH levels in the days post-ovulation and may have been responsible for three 5X mares entering anestrus.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in horses (estrous mares), which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

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

> Not for use in humans. Keep this and all drugs out of reach of children. Pregnant women and women of childbearing age should exercise caution when handling this product. Accidental administration may lead to a disruption of the menstrual cycle. Direct contact with the skin should be avoided. If exposure occurs, contact areas should be washed immediately with alcohol followed by soap and water, as this product is insoluble in water. In case of accidental human injection, consult a physician immediately.

The data submitted in support of this NADA were examined to ensure human user safety.

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 SUCROMATE Equine, when used according to the label, is safe and effective for inducing ovulation within 48 hours of treatment in cyclic estrous mares with an ovarian follicle between 30 and 40 mm in diameter.

A. Marketing Status:

This drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to determine stage of estrus and follicle size in cyclic mares, and monitor for possible adverse reactions to the drug.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval.

C. Patent Information:

SUCROMATE Equine is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,051,558	May 28, 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 insert
- Bottle label
- Carton

cc: Document Control Unit, for the administrative file of:
N-141319-A-0000-OT, M-0001, M-0002
Courtesy copy for the sponsor
HFV-12, FOI Staff
HFV-104, Green Book
HFA-305, Division of Dockets Management

Other administrative information: not applicable

template version April 1, 2010

SIGNATURE PAGE FOR THE FREEDOM OF INFORMATION SUMMARY

NADA: 141-319
SUBMISSION NUMBER: A-0000
SPONSOR: Thorn BioScience LLC
NAME OF DRUG: SUCROMATE Equine

	CONCURRENCE (DRAFT):		CONCURRENCE (FINAL):	
1.	Primary Reviewer Team 2, HFV-114	Date	INITIAL	Date
2.	Team Leader Team 2, HFV-114	Date	INITIAL	Date
3.	Acting Director Division of Therapeutic Drugs for Non-Food Animals, HFV-110	Date	INITIAL	Date
4.	NA Director Division of Human Food Safety, HFV-150	Date	NA INITIAL	Date
5.	Quality Assurance Team, HFV-107	Date	INITIAL	Date
6.	Director ONADE, HFV-100	Date	INITIAL	Date
7.	Director CVM, HFV-1	Date	INITIAL	Date