I. GENERAL INFORMATION

A. File Number

NADA 131-310

B. Sponsor

Hoechst-Roussel Agri-Vet Co.
Route 202-206; P.O. Box 2500
Somerville, N.J. 08876-1258

C. Trade Name

Regu-Mate® for Horses

D. Generic Name

altrenogest

E. Marketing Status

Prescription

F. Effect of Supplement

This supplement provides for label and package insert changes. This supplement does not affect the status of the original approval and Regu-Mate; (altrenogest) remains a "by prescription only" product.

II. INDICATIONS FOR USE

REGU-MATE® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares.

Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal and to facilitate the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

III. DOSAGE

A. Dosage Form- oil solution
B. Route of Administration- oral
C. Recommended Dosage- Administer orally at the rate of 1 ml/110 pounds body weight (0.044 mg/kg). To be given one dose daily for 15 consecutive days.

IV. EFFECTIVENESS

The new animal drug application upon which this supplement is based was the subject of approved NADA 131-310 dated 9/12/83. See FR Vol. 48, No. 177, p. 40887.

V. ANIMAL SAFETY

Adequate animal safety data was established in the NADA 131-310 as approved 9/12/83. See FR Vol. 48, No. 177, p. 40887.

This supplement provides for reproductive safety studies in pregnant mares which were conducted at two different sites (Colorado State University and University of California at Davis). Summary findings are listed below:

PIVOTAL SAFETY STUDY

SAFETY OF ALTRENOGEST IN PREGNANT MARES AND EFFECT ON REPRODUCTIVE PERFORMANCE OF THE OFFSPRING

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STUDY DESIGN

Animals Used:

- Treated (Receptal): 27 pregnant mares
- Untreated (controls): 24 pregnant mares

Stallion(s): One (1) stallion sired all foals

Treatment:

2 ml Altrenogest/110 lbs body weight orally (2 x amount recommended for estrus suppression) from day 20-325 of gestation. Control mares were given 2 ml neobee oil/100 lbs body weight orally for same time period and duration.

Parameters measured are summarized in data tables below:

SUMMARY DATA TABLES

Presented in Table 1 are the data in days from February 1st to the first ovulation and days from February 1st to the first ovulation accompanied by behavioral estrus. Treated fillies experienced their first ovulation sooner than controls. Treated mares also experienced their first ovulation with behavioral estrus sooner than controls, but this was not a significant difference.

TABLE 1. INTERVAL FROM FEBRUARY 1, 1987 TO OVULATION (DAYS)

Group	No. Mares	First Ovulation	First Ovulation with Estrus
Control	4	73	73
Treated	11	46	56

Presented in Table 2 are data on the average length of estrus, diestrus and estrous cycle for the first two estrous cycles of treated and control mares during 1987. There were no significant differences between treated and control mares.

TABLE 2. ESTROUS CYCLE CHARACTERISTICS OF ALTRENOGEST-TREATED MARES AND CONTROL MARES

Group	No. Mares	Estrus (days)		Diestrus (days		Estrous (days)	
		Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Control	4	8.0	4.5	15.3	14.8	18.3	19.3
Treated	11	8.5	4.7	16.1	21.6	24.5	26.4

The mean interovulatory interval from the first to second cycle (19.0, 23.8) and second to third cycle (19.0, 26.4) was not different between control and treated mares respectively.

Mares in the altrenogest-treated group ovulated follicles similar in size to those in the control group during all 3 cycles (Table 3).

TABLE 3. DIAMETER OF PREOVULATORY FOLLICLE (mm)

Group	No.	Cycle 1	Cycle 2	Cycle 3
Control	4	43.8	40.0	41.3
Treated	11	44.5	43.2	44.7

Pregnancy rates (day 15) for treated controls in each of the three cycles are shown in Table 4. The cycle 1 pregnancy rate for control animals was 100% while that for treated was 81.8%. These pregnancy rates are considered to be extremely high. Due to the 100% pregnancy rate experienced by control animals, no statistical comparison could be made with the treated group for cycles 2 and 3. Two treated mares from the first cycle did not become pregnant and one mare (913) experienced early embryonic death between 25 and 30 days and was inseminated on a second cycle. Two of the three mares became pregnant on cycle 2 (66.7%). One treated mare was bred on cycle 3 but failed to become pregnant. Over 3 cycles, 11 of 12 treated mares and 4 of 4 control mares became pregnant (mare 913 counted twice). In addition to one treated mare not becoming pregnant, one mare (911) experienced early embryonic death between 45 and 50 days. Thus, at 50 days of gestation, 9 of 11 altrenogest-treated mares were pregnant (81.8%) as compared to 4 of 4 controls.

TABLE 4. PREGNANCY RATE (day 15)

Group	Cycle 1			Cycle 2			Cycle 3			Total		
	No. Bred	No. Preg	%	No. Bred	No. Preg	%	No. Bred	No. Preg	%	No. Bred	No. Preg	%
Control	4	4	100	0	0		0	0		4	4	100
Treated	11	9	81.8	3*	2	66.7	1	0	0	12	11	91.7

*Mare 913 experienced embryonic loss between days 25-30, was rebred and became pregnant therefore, mare 913 was counted twice in the data.

There was no early embryonic loss in the control group, but 2 treated mares lost pregnancies between days 15 and 50. Mare #911 experienced embryonic loss between days 45 and 50. Mare #913 lost a pregnancy between days 25 and 30, but was rebred and carried the pregnancy to day 50. The incidence of early embryonic death was 18.2% versus 0% for treated versus control and was not different.

Average clitoral size from birth to 21 months is presented in table 5. Treated animals had larger clitori at all ages measured. The differences were significant at all ages except 1 and 4 months.

TABLE 5. CLITORAL SIZE (sq. mm.) FROM BIRTH TO 21 MONTHS

Age	Control		Treated	
	No. Horses	Avg sq. mm.	No Horses	Avg sq. mm.
Birth	2	1.1	5	1.8
1 mo	4	1.9	6	2.5
4 mo	4	3.0	6	4.1
7 mo	4	3.9	13	5.7
10 mo	4	4.2	13	6.0
12 mo	4	5.2	13	6.7
15 mo	4	4.4	12	5.9
18 mo	4	4.3	12	6.0
21 mo	4	4.3	11	5.9

Age at puberty was similar for treated (82 wk) as compared to control stallions (84 wk). Seminal characteristics of the last 9 ejaculates for treated and control stallions are presented in Table 6. There were no differences between treated and control stallions in seminal volume, spermatozoal concentration and motility and total sperm per ejaculate. Sexual behavior was also not affected by treatment (Table 7). Both treated and control stallions readily obtained an erection and ejaculated after only one to two mounts. Testicular data obtained at castration are presented in Table 8. Total scrotal width, testis weight, parenchymal weight, epididymal weight and height, width and length of testes were similar for treated and control stallions.

TABLE 6. SEMINAL CHARACTERISTICS*

Group	No.	Volume (ml)	Concentration (10^{E6}/mL)	Mortality (%)	Total Sperm per ejaculate
Control	9	22.0	145.4	26.4	3.3
Treated	6	19.2	173.5	27.8	3.1

* Based on data for 9 ejaculates/stallion.

TABLE 7. BEHAVIORAL CHARACTERISTICS

Group	No.	Parameter		
		Time to Erection (min)	No. Mounts	Time to Ejaculation
Control	9	2.20	1.6	4.12
Treated	6	2.01	1.6	3.47

TABLE 8. TESTICULAR CHARACTERISTICS

Group	No.	Parameter						
		Total Scrotal Width (mm)	Combined Epididymal Wt. (g)	Combined Testes Wt. (g)	Combined Parenchymal Wt. (g)	Testis Size (mm)		
						Height	Length	Width
Control	9	83.2	41.9	207.04	184.6	49.3	77.6	46.6
Treated	6	82.9	44.7	204.52	185.1	48.1	79.0	45.9

TABLE 9. SPERMATOZOAL PRODUCTION AND EPIDIDYMAL RESERVES

Group	No.	Spermatazoal Production		
		Epididymal Sperm Reserves (10^{E9})	Spermatids per gram (10^{E6})	Spermatids per testis (10^{E9})
Control	9	9.89 ± 6.64	49.1 ± 11.3	5.30 ± 2.63
Treated	6	9.10 ± 6.65	64.1 ± 21.7	6.02 ± 3.27

Presented in Table 9 is the number of spermatozoa stored in the epididymis at the time of castration. There was similar number in treated stallions. In addition, the number of elongated spermatids per gram of testis did not differ between control and treated stallions (Table 9). Thus, the efficiency of spermatozoal production was similar in treated and control stallions. Based on examination of codes-histologic sections, it was evident that spermatogenesis was not affected by prior treatment of the dams during gestation with Altrenogest (Table 10). The number of spermatids, old spermatocytes, young spermatocytes and spermatogonia were similar between treated and control stallions.

TABLE 10. NUMBER OF GERM CELLS PER STAGE 1 TUBULAR CROSS SECTION OF STALLION SEMINIFEROUS TUBULE

Group	No.	Type Germ Cell			
			Spermatocyte		
		Spermatid	Old	Young	Spermatagonia
Control	9	51.7 ± 24.9	15.86 ± 6.91	15.50 ± 6.93	2.2 ±60
Treated	6	47.8 ± 20.3	14.02 ±5.32	14.12 ±5.62	2.6 ± 31

CONCLUSIONS

There appears to be little difference in reproductive performance between offspring of mares that were administered Altrenogest throughout pregnancy and the offspring of mares who received no progesterone supplementation. The only parameters where there was a significant difference between control and treated groups was the interval from February 1st to the first ovulation and the clitoral size of the fillies. Filly offspring from treated mares experienced their first ovulation approximately one month sooner than their counterparts from untreated mares. Filly offspring from treated mares (at all ages) also had slightly larger clitori than their counterparts from untreated mares. There were no parameters measured in the stallions that were different between to pregnant mares does not appear to be a detriment to the functional reproductive performance of the offspring.

CORROBORATIVE STUDY

EFFECT OF *SALMONELLA TYPHIMURIUM* ENDOTOXIN OF PGF-2 ALPHA RELEASE AND FETAL DEATH IN THE MARE

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Summary

Seven mares (21 d. to 32 d. pregnant) were treated with 44 mg. altrenogest daily from 12 hours after administration of *S. typhimurium* endotoxin until day 40 of gestation. A Second group of 5 mares (27 d. to 33 d. pregnant) were treated identically, except altrenogest administration was continued for 70 days. Results were as follows:

Group	Number	Treatment	Aborted
1	7	Altrenogest @ 44mg/day x 40 d.	6/7 @ day 44
2	5	Altrenogest @ 44mg/day x 70 d.	0/5 to term

These uncontrolled data demonstrate that altrenogest is safe to use in pregnant mares and may be therapeutically useful in the face of a prostaglandin induced repression of the corpus luteum and subsequent progesterone deficiency at an appropriate dosage.

CORROBORATIVE STUDY

URINARY ESTROGEN CONJUGATE CONCENTRATIONS BETWEEN DAY 20 AND 70 OF GESTATION IN PREGNANT AND OVARIECTOMIZED PREGNANT MARES MAINTAINED ON ALTRENOGEST

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and G.H. Stabenfeldt
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This study was conducted primarily to measure estrogen levels in pregnant mares as method to clarify the main source of estrogen in the pregnant mare. However, a major component of experimental design was the use of altrenogest on both intact pregnant mares and ovariectomized pregnant mares. All mares were bred by one of two proven sire stallions on site at the Equine Reproductive Laboratory at UCD.

In this study, it would be expected that ovariectomized mares would abort due to inability to produce sufficient progesterone (P4) to maintain pregnancy. Conversely, such mares should (hypothetically) be able to maintain pregnancy if supplemented with an exogenous progesterone/progestin source in sufficient quantity and duration of administration.

Groups, treatment, and pregnancy results are tabulated below:

Group	No.	Ovaries Intact	Altenogest Rx	Pregnancy Data	
				70 Days	Term
1	9	Yes	No (control)	9/9	9/9
2	5	Yes	Yes (44 mg/d- d. 20-70)	4/5	4/5* (to 5th month)
3	5	No	Yes (44 mg/d- d. 20-70)	4/5	4/5

* These mares were all aborted at 5 months gestation to be used in another upcoming study. All mares had healthy and thriving pregnancies at the time of termination.

This study supports the demonstration of the safety of altrenogest when it is administered to pregnant mares.

VI. HUMAN SAFETY

A. Human Food Safety

Data on human safety pertaining to consumption of drug residues in food were not required for approval of this supplemental NDA. The drug is approved for use in

horses that are not to be used for food and is labeled: **"Do not use in horses intended for food"**

B. Human Safety relative to handling, possessing and administration.

"WARNING: Pregnant women and others of childbearing age should exercise extreme caution when handling this product. Accidental absorption could lead to disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water."

INFORMATION FOR HANDLERS:

Effects of overexposure:

There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmacological class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest.
Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed.

In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

People who should not handle this product:

1. Women who are or suspect they are pregnant.
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events.
3. Anyone with cerebral-vascular or coronary-artery disease.
4. Women with known or suspected carcinoma of the breast.
5. Women with known or suspected estrogen-dependent neoplasia.
6. Women with undiagnosed vaginal bleeding.
7. People with a benign or malignant tumor which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

Accidental Exposure

Altrenogest can be absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Absorption can be increased from areas covered by occlusive materials, such as latex or rubber gloves. The following measures are recommended in case of accidental exposure:

Skin Exposure: Wash immediately with soap and water.

Eye Exposure: Immediately flush with plenty of water for 15 minutes. Get medical attention.

If Swallowed: Do not induce vomiting. Regu-mate® (altrenogest) is an oil solution. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage via aspiration of the oil base. If possible, bring container and labeling to the physician.

CAUTION: For oral use in horses only.
Keep this and all medication out of the reach of children.

VII. AGENCY CONCLUSIONS

The data in support of this supplemental NADA complies with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Regu-mate(TM) (altrenogest) Solution when used under the labeled conditions of use is safe and effective.

According to the Center's supplemental approval policy (42 FR 6436) this is a Category II change. This supplement provides for the deletion of the label contraindication statement for use in pregnant mares and replaces it with the contraindication for use in mares having previous or current uterine inflammation. The approval of the supplemental application has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

For the safe and effective use of Regu-Mate(TM) (altrenogest) Solution, it is necessary to provide a differential diagnosis between winter anestrus and the physiological breeding season. To make this diagnosis, it is necessary to know the reproductive status of the ovary per rectal palpation which only a trained professional who can differentiate between acute, subacute or chronic endometritis and be in a position to know the current history of uterine infections. Therefore, the drug is classified as a prescription drug.

Under Section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this supplemental New Animal Drug Application does not qualify for marketing exclusivity, because deletion of the contraindication for use in pregnant mare does not expand the conditions of use of the product. Addition of the contraindication against use in pregnant mares with a history of uterine inflammation does not qualify for exclusivity because the agency has determined that public policy requires that such warnings should appear on all generic copies, and because in this case the sponsor did not submit new clinical or field investigations.

References:

1. Squires, E.L., W.B. Stevens, D.E. McGlothlen and B.W. Pickett. 1979. Effect of an Oral Progestin on the Estrus Cycle and Fertility of Mares. *J. Anim. Sci.* 49:729.
2. Turner, D.D., M.C. Garcia, S.K. Webel, and O.J. Ginther. 1981. Influence of Follicular Size on the Response of Mares to Allyl Trenbolone Given before the Onset of the Ovulatory Season. *Theriogenology*, 16: 73-84.

3. Webel, S.K. 1975. Estrus Control in Horses with a Progestin. *J. Anim. Sci.* 41:385.
4. Shoemaker, C.F., E.L. Squires, and R.K. Shideler. 1989. Safety of Altrenogest in Pregnant mares and on Health and Development of Offspring. *Eq. Vet. Sci.* (9); No. 2: 69-72.
5. Squires, E.L., R.K. Shideler, and A.O. McKinnon. 1989. Reproductive Performance of Offspring from Mares Administered Altrenogest During Gestation. *Eq. Vet. Sci.* (9); No. 2: 73-76.
6. Daels, P.F., M. Starr, M. Kindahl, G. Fredericksson, J.P. Huges, and G.H. Stabenfeldt. Effect of *Salmonella typhimurium* endotoxin of PGF-2a Release and Fetal Death in the Mare. *J. Reprod. Fert. Suppl. 35* (1987); 485-492.
7. Daels, P.F., G.H. Stabenfeld, J.P. Hughes, H. Kindahl and K. Odensvik. The Role of PGF-2a in Embryonic Loss Following Systemic Infusion of *Salmonella typhimurium* Endotoxin in the Mare and the Protective Action of Altrenogest and Flunixin Meglumine. 11th International Congress on Animal Reproduction and Artificial Insemination. Dublin, Ireland, 1988.

VIII. ATTACHMENTS

1. Principal display panel
2. Package insert

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place Rockville, MD 20855