FREEDOM OF INFORMATION SUMMARY

I. General Information:

NADA Number: 138-903

Sponsor: Syntex Agribusiness, Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

Generic Name: Fenprostalene

Trade Name: Porcilene® (fenprostalene) sterile solution

II. Indications for Use:

Porcilene® (fenprostalene) sterile solution is indicated for use in sows and gilts pregnant at least 112 days for the induction of parturition.

III. Dosage Form(s), Route(s) of Administration, and Recommended Dosages(s):

Form: Sterile PEG 400 solution

Route of Administration: Individually administered subcutaneously (SC)

Dose: Porcilene® sterile solution is supplied at a concentration of 0.25 mg fenprostalene per ml with 0.25 mg fenprostalene (equivalent to 1 ml Porcilene® Sterile Solution) injected subcutaneously once per animal.

IV. Effectiveness:

A. Pivotal Studies:

The new animal drug application on which fenprostalene is based contains adequate and well-controlled studies demonstrating the effectiveness of the new animal drug for the indications for use as given in Part II above.

1. Dose Response Studies:

The following three investigators conducted a total of five dose titration studies to determine the most efficacious dose of fenprostalene for inducing parturition in swine.

Julian H. Edwards, D.V.M.
P.O. Box 10
Scotland Neck, NC 27874

Paul A. Martin, D.V.M.
Vet Med Research Center
Iowa State University
Ames, IA 50011

Thomas A. Miller, D.V.M.
P.O. Box 306
Milford, IN 46542

The studies were conducted under similar protocols except for the dose range of the drug given to the animals.

For each study, pregnant sows and gilts with known breeding dates were selected from existing herds in the area and randomly assigned to either a sham control group or to one of several fenprostalene dose groups. Numbers of animals entered into each study and dose group are given as follows:

	Fenprostalene (mg)								
Study	0	.03125	.0625	.125	.25	.50	.75	1.0	1.25
Miller									
480.1	16				16	16	16	16	16
480.3	20	20	21	20	19				
Edwards									
480.1	16				14	16	15	13	13
480.3	20	20	20	18	20				
Martin									
480.2	16	17	18	17	18	17			

All sows and gilts were injected s.c. on day 112 of gestation (except eight animals in Martin's 480.2 study which were injected on Day 113). Animals were moved into the farrowing house on approximately Day 111 of gestation and housed in accordance with customary practices in use at each test station.

Data recorded for each study included time from treatment to parturition, duration of labor, total number piglets born (alive and dead), birth and weaning weights and post-treatment rebreeding rate. The mean interval between injection of fenprostalene and initiation of parturition for each study is shown as follows:

	Mean Interval Between Injection and Initiation of Parturition (Hrs)								
Study	0	.03125	.0625	.125	.25	.50	.75	1.0	1.25
Miller									
480.1	83.1				28.1	24.3	26.9	24.6	23.6
480.3	58.5	64.4	38.1	33.5	39.0				
Edwards									
480.1	82.3				28.7	28.4	34.7	29.1	24.4
480.3	94.7	49.7	44.3	38.5	29.9				
Martin									
480.2	49.7	61.4	51.2	31.0	29.8	28.8			

Results from each of the above studies show a reduction in mean interval to parturition when .125 mg fenprostalene or more is administered.

The data from the studies were pooled by analysis of variance in three steps as follows:

a. The studies where dose levels 0, .03125, .0625, .125, and .25 were all present were analyzed together, using only those doses. Least square means for time to parturition were determined to be 67.7, 58.5, 44.5, 34.3, and 32.9 for Groups 0, .03125, .0625, .125, and .25 mg, respectively. A significant effect ($P = .04$) was seen for dose. Using linear plateau models, it was concluded that the .125 and .25 mg doses were superior to lower doses and, although not significant, the .25 mg dose was numerically better.

   The pooled data was also evaluated with respect to the variability (variances and ranges) of the response time. The least squares means for variances and ranges of time to parturition for Groups 0, .03125, .0625, .125, and .25 were 1420.5, 1124.7, 912.4, 365.9, and 154.0 for variances and 143.1, 107.9, 100.3, 71.2, and 56.3 for ranges, respectively. The results of these analyses

indicate that the overall variability of the interval to parturition was significantly reduced (P = .11 and P = .05 for variances and ranges, respectively). Again, using linear plateau models, Groups .125 and .25 were seen to provide the optimum dose with Group .25 numerically better.

b. The three studies where dose levels 0, .25 and .50 mg were all present were analyzed, again using only those doses. Least square means for time to parturition were calculated to be 71.7, 28.9, and 27.2 for Groups 0, .25, and .50 mg, respectively. The effect for dose was significant at P = .02 and there were significant differences between the control and .25 mg (P = .01) and .50 mg (P = .01) groups but not between the .25 and .50 mg groups (P = .87).

   The pooled data was also evaluated with respect to the variability (variances and ranges) of the response time. The least squares means for variances and ranges of time to parturition for Groups 0, .25, and .50 mg were 1261.3, 98.1, and 114.6 for variances and 133.0, 40.5, and 37.7 for ranges, respectively. The results of these analyses indicate that the variability of the interval to parturition was significantly reduced (P = .03 for variances and ranges) with either the .25 or .50 mg groups.

c. Lastly, the two trials where dose levels 0, .25, .50, .75, 1.0, and 1.25 were all present were analyzed. Least squares means for time to parturition were calculated to be 82.7, 28.5, 26.4, 30.7, 26.8, and 24.1 for Groups 0, .25, .50, .75, 1.0, and 1.25 mg, respectively. The effect for dose was significant at P = .0001. There were no significant differences between non-zero doses.

   As above, the pooled data was evaluated with respect to the variability (variances and ranges) of the response time. The least squares means for variances and ranges of time to parturition for Groups 0, .25, .50, .75, 1.0, and 1.25 mg were 1529.2, 112.8, 132.7, 165.7, 87.7, and 104.09 for variances and 144.8, 40.1, 39.9, 41.6, 34.0, and 39.0 for ranges, respectively. There were no significant differences between non-zero doses.

The data indicated steady reduction in interval to parturition, variation in the time to parturition, and ranges of time to parturition with increasing dose of fenprostalene through the .25 mg level with a significant positive response through .125 mg. Little or no additional response was seen above the .25 mg level.

It is held that for this type of claim, it is more important that a sufficient quantity of drug be administered to be reasonably certain of inducing parturition within a short time frame than it is to administer the "minimum effective dose." Consequently, it is concluded that the .25 mg dose is superior to the .125 dose on the basis that it provides a margin of assurance that virtually all susceptible animals in the proposed treatment population will be induced to farrow in the minimum amount of time.

No differences were detected between the treated and control groups in duration of labor, percent born alive, birthweight, or weaning weight for the induced farrowing. Also, no differences were detected in rebreeding rate, litter size at birth, percent born alive, and litter size at weaning for the subsequent untreated pregnancy and farrowing. There were no adverse reactions observed among the fenprostalene-treated animals.

2. Clinical Field Trials:

The following five investigators conducted a total of six clinical field trials under various protocols to determine the efficacy of fenprostalene for induction of parturition in swine.

Lee Edgerton, Ph.D.
University of Kentucky
Dept. of Animal Sciences
Ag. Science Bldg., South
Lexington, KY 40546-0215

Julian H. Edwards, D.V.M.
P.O. Box 10
Scotland Neck, NC 27874

Richard N. Goddard, D.V.M.
P.O. Box 384
Sommerville, TN 38068

Thomas A. Miller, D.V.M.
P.O. Box 306
Milford, IN 46542

A total of 415 gestating sows and gilts of breeds common to the area were used. At each location, animals with known breeding dates were injected s.c. on approximately 112 days of gestation with either fenprostalene or carrier.