Approval Date: August 30, 1993

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-856

B. Sponsor

Intervet, Inc.
405 State Street, P.O. Box 318
Millsboro, DE 19966

C. Proprietary Name

P.G. 600 ®

D. Established Name

serum gonadotropin and chorionic gonadotropin for injection

E. Dispensing Status

OTC

F. Dosage Forms, Route of Administration and Dosage

P.G. 600® is available in two package sizes:

- SINGLE DOSE VIALS - Five vials containing white freeze dried powder, plus five vials containing sterile diluent. When reconstituted, each single dose vial (5 mL) contains 400 IU serum gonadotropin and 200 IU chorionic gonadotropin (equivalent to 200 USP Units chorionic gonadotropin).

- FIVE DOSE VIALS - One vial containing white freeze dried powder, and one vial containing sterile diluent. When reconstituted, the five dose vial (25 mL) contains 2000 IU serum gonadotropin and 1000 IU chorionic gonadotropin (equivalent to 1000 USP Units chorionic gonadotropin).

One dose (5 mL) of reconstituted P.G. 600® , containing 400 IU serum gonadotropin and 200 IU chorionic gonadotropin, should be injected into the gilt or sow's neck behind the ear with a 20G X 1.5 inch hypodermic needle. Prepuberal gilts should be injected when they are selected for addition to the breeding herd. Sows should be injected at weaning during periods of delayed return to post-weaning estrus.

G. Indication

- PREPUBERAL GILTS: P.G. 600® is indicated for induction of fertile estrus (heat) in healthy prepuberal (non-cycling) gilts over five and one-half months of age and weighing at least 85 kg (187 lb.). CAUTION: Treatment will not induce estrus in gilts that have already reached puberty (begun to cycle). Gilts that are less than five and one-half months of age or that weigh

less than 85 kg (187 lb.) may not be mature enough to continue normal estrus cycles or maintain a normal pregnancy to full term after treatment.

- SOWS AT WEANING: P.G. 600® is indicated for induction of estrus in healthy weaned sows experiencing delayed return to estrus. CAUTION: Treatment will not induce estrus in sows that are returning to estrus normally three to seven days after weaning. Delayed return to estrus is most prevalent after the first litter; the effectiveness of P.G. 600® has not been established after later litters. Delayed return to estrus often occurs during periods of adverse environmental conditions and sows mated under such conditions may farrow smaller than normal litters.

H. Effect of Supplement

The original application provides for use of P.G.600 ® in prepuberal gilts. The supplement extends the conditions of use to include sows at weaning.

II. EFFECTIVENESS

The original application contains data establishing that P.G. 600® is effective for induction of fertile estrus in healthy prepuberal gilts and that the recommended dose of P.G. 600® contains the optimal amount of each gonadotropin for that indication.

Pivotal Studies in Sows

A two-phase clinical study was conducted to establish that P.G. 600® is also effective for induction of estrus in healthy weaned sows experiencing delayed return to estrus, and to confirm that the dose of P.G. 600® recommended for induction of estrus in prepuberal gilts is also the optimal dose for this indication. Phase I was conducted from September, 1985 to August, 1986, and included 473 sows on 4 farms in Missouri and North Carolina. Phase II was conducted from July to December, 1987, and included 822 sows on 8 farms in Indiana, Missouri and North Carolina.

The trials in Indiana were conducted by L. Kirk Clark, D.V.M., Ph.D., Associate Professor of Veterinary Medicine at Purdue University; the trials in Missouri were conducted by Billy N. Day, Ph.D., Professor of Animal Science, and Ronald O. Bates, Ph.D., State Swine Breeding Specialist, at the University of Missouri - Columbia; and the trials in North Carolina were conducted by Jack H. Britt, Ph.D., Professor of Animal Science at North Carolina State University.

Sows at weaning on each farm either served as controls or received a single full dose of P.G. 600® (the "Field Trials"), and additional sows on one farm in each state also received either one-half dose of P.G. 600® or a double dose of P.G. 600®, and the control sows on these farms received a placebo (the "Dose Confirmations").

The sows were observed for estrus, and those in estrus were mated and allowed to farrow. Estrus response during Days 3-7 post-weaning was studied, and among sows in estrus during Days 3-7, percent of sows rebred after first mating, percent of sows farrowed after any mating, number of live pigs per litter, and number of dead pigs per litter were analyzed.

Estrus response was studied with linear modeling and logistic regression, using a backward elimination procedure. Data for sows that exhibited estrus before Day 3 were deleted, and data for the remaining sows were coded as either "0" (anestrus during Days 3-7) or "1" (in estrus during Days 3-7). The parity of each sow was also coded as

either "1" (Parity 1) or "2+" (Parity 2 or greater). The full model included: Treatment (Dose), Parity, and Treatment x Parity interaction.

Parity was considered as both an effect modifier and a confounder: Effect modification was defined as a significant interaction term (P is less than 0.05) and if the interaction term was not significant, it was removed from the model. Confounding was defined as a two-fold change, or a change in sign, in the odds ratio for Treatment if Parity was removed from the model. If confounding was not present, Parity was also removed from the model. The 95 percent confidence intervals on the odds ratios for the comparisons of interest were then examined, and if the confidence interval for a given ratio excluded 1.0, it was considered statistically significant.

Percents of sows rebred and farrowed, and numbers of live and dead pigs per litter, were analyzed in ordinary least-squares analyses of variance for the randomized complete-block design, with farms as blocks. Percents were transformed with the arcsine transformation and numbers were transformed as the natural logarithm of the number plus 1. The model included: Farm, Month and Year of treatment nested within Farm, Treatment, Farm by Treatment interaction, Parity, Farm by Parity interaction, and Treatment by Parity interaction.

Least-squares means and their 95 percent confidence intervals were generated, and differences between the means were tested for significance (P is less than 0.05) with the Protected Least Significant Difference (Protected LSD) Test: If Treatment by Parity interaction was significant (P is less than 0.10), differences between means for Treatments within Parities were tested; if Treatment by Parity interaction was not significant, but Treatment was significant (P is less than 0.05), differences between main effect means for Treatment were tested; and if neither Treatment by Parity interaction or Treatment was significant, differences were not tested.

In Phase I, treatment with P.G. 600® did not affect estrus response during Days 3-7. Nor did treatment with P.G. 600® affect percent of sows rebred, percent of sows farrowed, or number of dead pigs per litter among sows in estrus Days 3- 7. In the Dose Confirmation, however, sows that received the full dose of P.G. 600® farrowed larger live litters than sows that received the other dose levels of P.G. 600® (Table 1).

Table 1: Live litter size of sows in estrus during Days 3-7 in the Dose Confirmation in Phase I.

Dose	**Number of Litters**	**Mean Number of Live Pigs (95% C.I.)**	**Difference from Full Dose**	**Pr>t**
Placebo	57	9.83 (9.57-10.09)	-0.69	0.0295
Half	60	9.78 (9.54-10.03)	-0.74	0.0238
Full	61	10.52 (10.28-10.77)	------	-------
Double	60	9.65 (9.41-9.89)	-0.87	0.0141

In Phase II, sows that received P.G. 600® in the Field Trial were nearly twice as likely to exhibit estrus during Days 3-7 than control sows (Table 2).

Table 2: Estrus response of sows during Days 3-7 in the Field Trial in Phase II.

Treatment	**Number of Sows- Anestrus**	**Number of Sows- Estrus**	**Number of Sows- Totals**	**Odds Ratio: P.G. 600® vs Control (95% C.I.)**
Control	36	245	281	-
P.G. 600	22	272	289	1.82 (1.04-3.17)
Total	58	517	575	

Similarly, Parity 1 sows that received the single full dose of P.G. 600® in the Dose Confirmation in Phase II were 4-7 times more likely to exhibit estrus during Days 3-7 than Parity 1 sows that received the other dose levels of P.G. 600® (Table 3).

Table 3: Estrus response of Parity 1 sows during Days 3-7 in the Dose Confirmation in Phase II.

Treatment	**Number of Sows- Anestrus**	**Number of Sows- Estrus**	**Number of Sows- Totals**	**Odds Ratio: Full Dose vs Other Doses 95% C.I.)**
Placebo	14	25	39	4.04 (1.28-12.75)
Half	14	14	28	4.33 (1.36-13.77)
Full	6	26	32	----------
Double	11	21	32	7.20 (1.85-28.08)
Total	45	76	121	

There were no differences in estrus response among Parity 2+ sows, but in the absence of treatment (i.e., among sows that received the placebo), Parity 2+ sows were more than 6 times more likely to exhibit estrus during Days 3-7 than Parity 1 sows (Table 4).

Table 4: Estrus response of sows that received the placebo during Days 3-7 in the Dose Confirmation in Phase II (from analyses in Table 3 above).

Parity	**Number of Sows - Anestrus**	**Number of Sows - Estrus**	**Number of Sows - Total**	**Odds Ratio: Parity 2+ vs Parity 1 (95% C.I)**
1	14	15	29	-
2+	9	62	71	6.43 (2.34-17.65)
Total	23	77	100	

As In Phase I, treatment with P.G. 600® did not affect percent of sows rebred, percent of sows farrowed, or number of dead pigs per litter among sows in estrus Days 3-7. In contrast to Phase I, however, sows that received P.G. 600® in the Field Trial farrowed smaller live litters than control sows (Table 5).

Table 5: Live litter size of sows in estrus during Days 3-7 in the Field Trial in Phase II.

Dose	**Number of Litters**	**Mean Number of Live Pigs (95% C.I.)**	**Difference from Control**	**Pr>t**
Control	211	10.04 (9.64-10.45)	-	-
P.G. 600®	215	9.13 (8.76-9.51)	-0.91	0.0089

Sows that received the double dose of P.G. 600® in the Dose Confirmation farrowed smaller live litters than sows that received the single full dose of P.G. 600®, but there were no differences among sows that received the Full Dose and sows that received either the Half Dose or the Placebo (Table 6).

Table 6: Live litter size of sows in estrus during Days 3-7 in the Dose Confirmation in Phase II.

Dose	**Number of Litters**	**Mean Number of Live Pigs (95% C.I.)**	**Difference from Full Dose**	**Pr > t**
Placebo	62	10.48 (9.71-11.31)	0.90	0.1322
Half	69	10.20 (9.52-10.92)	0.62	0.2536
Full	67	9.58 (8.89-10.31)	---------	---------
Double	51	7.82 (7.16-8.54)	- 1.76	0.0097

The study confirmed published reports cited in the supplemental application that sows must be experiencing delayed return to estrus if they are to respond to exogenous gonadotropins such as those in P.G. 600®, and that delayed return to estrus is more prevalent after the first litter than after later litters. Therefore, the results of the study establish that P.G. 600® is effective for induction of estrus in those weaned sows that are experiencing delayed return to estrus, and that the dose of P.G. 600® recommended for induction of estrus in prepuberal gilts is also the optimal dose for this indication. Published reports were also cited in the supplemental application that delayed return to estrus often results from adverse environmental conditions, such as high ambient temperatures, which may also reduce live litter size.

III. TARGET ANIMAL SAFETY

The original application contains data confirming the safety of the new animal drug in both gilts and sows. Those conclusions may be found in the original application's F.O.I. summary. Therefore, no additional animal safety studies were required to support the supplemental application.

IV. HUMAN FOOD SAFETY

Toxicity Tests and Residue Studies

The original application contains data showing the human food safety of P.G. 600®. No additional human food safety studies were required to support the supplemental application.

The original application contains data showing the human food safety of P.G. 600®. No additional human food safety studies were required to support the supplemental application.

V. AGENCY CONCLUSIONS

This supplemental NADA satisfies the requirements of section 512(b) of the Federal Food, Drug, and Cosmetic Act, and demonstrates that P.G. 600® (Serum gonadotropin and chorionic gonadotropin), when used under the proposed conditions of use is safe and effective for the labeled indications.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. The approval of this change is not expected to have an adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

P.G. 600® is categorized for over-the-counter use marketing status. Adequate directions for use are provided on the label such that the layman can safely and effectively administer the product. The conditions for use, prescribed on the label, are likely to be followed in practice by producers. The product is for production purposes (induction of estrus) with no special training required for proper use.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.