Approval Date: April 25, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-863

PAYLEAN 9 and PAYLEAN 45
(Ractopamine Hydrochloride)

Type A Medicated Article
for Finishing Swine

For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter.

This supplement provides for the replacement of the current indication and dosage with a new indication that allows use in pigs weighing in excess of 240 lb and a new dose range of 4.5 to 9.0 grams per ton. Additionally, this supplement updates the caution statement to reflect new animal safety data.

Sponsored By:

Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

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PAYLEAN 9 and PAYLEAN 45
Type A Medicated Article for Finishing Swine

1. GENERAL INFORMATION:

a. File Number:	NADA 140-863
b. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
c. Established Name:	Ractopamine hydrochloride
d. Proprietary Name:	PAYLEAN 9 and PAYLEAN 45
e. Dosage Form:	Type A Medicated Article
f. How Supplied:	25 lb bag
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	9 g per lb (20 g per kg) or 45.4 g per lb (100 g per kg)
i. Route of Administration:	Oral, in feed
j. Species/Class:	Finishing Swine
k. Recommended Dosage:	Feed ractopamine hydrochloride (PAYLEAN) continuously as the sole ration to finishing swine weighing not less than 150 lbs for the last 45 to 90 lbs (group average) of weight gain prior to slaughter at a dietary concentration of 4.5 to 9.0 g of ractopamine hydrochloride per ton of feed. No increased benefit has been shown when ractopamine concentrations in the diet are greater than 4.5 g/ton.
l. Pharmacological Category:	Beta adrenergic agonist
m. Indications:	For increased rate of weight gain, improved

	feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter.
n. Effect of Supplement:	This supplement provides for the replacement of the current indication and dosage with a new indication that allows use in pigs weighing in excess of 240 lb and a new dose range of 4.5 to 9.0 grams per ton. Additionally, this supplement updates the caution statement to reflect new animal safety data.

2. EFFECTIVENESS:

a. Dosage Characterization

The effective dose range for ractopamine was previously demonstrated in the original approval of NADA 140-863. The original approval allowed use in the dose range of 4.5 to 18.0 g/ton (5 to 20 ppm). For the current approval, the sponsor chose to demonstrate effectiveness only in the 4.5 to 9.0 g/ton dose range.

b. Substantial Evidence

A. Summary of Pooled Effectiveness Studies

A single clinical effectiveness study was conducted at five Live Phase sites. Carcass evaluations were conducted at four Carcass Phase sites. In addition, samples were collected and shipped from all Carcass Phase sites to a single site for sensory evaluation. Live Phase sites were located at different geographic locations in the United States.

The effectiveness study design was a randomized complete block design with location within a facility as a blocking factor and the pen as the experimental unit. Each block consisted of 18 pens. Within a block, there were three weight gain groups [Weight gain group 1 (WGG 1): last 20.4 kg gain with an ending weight of 111.1 kg; Weight gain group 2 (WGG 2): last 20.4 kg of gain with an ending weight of 131.5 kg; Weight gain group 3 (WGG 3): last 40.8 kg gain with an ending weight of 131.5 kg] composed of 6 contiguous pens. Within each weight gain group, the 6 contiguous pens were divided into 2 subgroups of 3 contiguous pens, to which gender (barrow or gilt) was randomly assigned. Finally, within each subgroup of 3 contiguous pens, ractopamine concentration (0, 5 or 10 ppm) via color code was randomly assigned to each of the 3 pens.

In addition to the pens allotted in the effectiveness study design above, a baseline pen for each gender subgroup at each Live Phase site was allotted. Animals (n=2) closest to the predefined target start weights (90.7 kg or 111.1 kg) from each baseline pen were selected for determination of baseline carcass composition. These baseline pens of animals were allotted in conjunction with gender subgroups, but were not housed contiguously in the effectiveness

study design, and were not administered any test article. The animals were used to calculate lean gain and efficiency of lean gain.

For the treatment animals, there were 2 blocks per Live Phase site, each block consisting of 18 pens. Each pen contained 5 animals, resulting in a total of 180 animals per site. In total, 900 animals were evaluated across 5 Live Phase sites. Animals used in the effectiveness studies were the progeny of genetic lines commonly used within the swine industry.

Animals were fed diets containing 0, 5 or 10 ppm ractopamine from an average initial pen weight of 90.7 ± 2.7 kg, 111.1 ± 3.2 kg, or 90.7 ± 2.7 kg for WGG 1, WGG 2, and WGG 3, respectively until the termination of the Ractopamine Treatment Phase. Ractopamine Treatment Phase termination was designated as when the average weight of the heaviest pen within each gender subgroup (3 pens) reached an average final weight of 111.1 ± 3.2 kg, 131.5 ± 4.0 kg, or 131.5 ± 4.0 kg, for WGG 1, WGG 2, and WGG 3, respectively. Animals were weighed at ractopamine treatment initiation (Day 0), and at the end of the Ractopamine Treatment Phase (final weight). Feed offered during the study and remaining in the feeders at the end of the live phase were recorded.

Animals completing the Ractopamine Treatment Phase of the study were tattooed, removed from their test pens, and transported to a site specific USDA or state inspected slaughter facility for harvest. The marketing process was defined as the period beginning with the departure of the animals from the test pens through stunning. Load-out distances from study pens to trailers ranged from an average of 15.7 to 105.2 m across all five live sites. Transport distances from live sites to carcass sites ranged from 4.3 km to 619.3 km.

Upon arrival at the slaughter facility, all animals within a gender subgroup were slaughtered for the collection of standard carcass and meat quality measurements. To determine the actual carcass composition (protein % of carcass soft tissue), the two animals within each pen that were closest to the target final weight of 111.1 ± 3.2 kg, 131.5 ± 4.0 kg, or 131.5 ± 4.0 kg, for WGG 1, WGG 2, and WGG 3, respectively were selected for carcass dissection. A side of each carcass was separated into soft tissue, bone, and skin and each component was weighed. A representative subsample of the soft tissue was sent to a contract laboratory for determination of chemical fat, protein, ash and moisture using the appropriate AOAC procedure. Carcasses were evaluated for differences in Warner-Bratzler shear force, pH, water holding capacity and color. Animals selected for dissection had a *longissimus dorsi* section harvested for sensory evaluation. *Longissimus dorsi* roasts were evaluated for differences in subjective sensory panel scores.

The claim variables of Average Daily Gain (Rate of Weight Gain), Gain:Feed (Gain Efficiency), and Chemical Lean were analyzed using the GLM procedure of SAS. Chemical Lean was determined as follows:

Weight of Lean = Weight of Chemical Lean = (weight of soft tissue) minus (weight of fat + weight of ash+ weight of moisture). Since there was no significant gender x treatment interaction, gender was pooled across treatment.

Data Analyses Summary

Fixed effects for the mixed model analysis on data collected during the performance part of the study were Dosage, Gender, Dosage x Gender interaction, Weight Gain Category, and Dosage x Weight Gain Category interaction while the random effect was Site, Location within Site, Treatment x Site interaction, Gender x Site interaction, and Weight Gain Category x Site interaction. The Dosage x Gender interaction was tested and if significant, individual gender analyses were conducted. In all cases, linear contrasts were used to compare the non-zero concentrations of ractopamine to controls and to each other within each Weight Gain Group Category.

In addition to effectiveness data, data on occurrence of adverse events (AE) including lameness and death or removal due to adverse events were collected. The information was converted into binary data and analyzed using linear-by-linear association test in StatXact.

Pooled Effectiveness Results

For average daily gain (ADG), the contrasts for WGG2 and WGG3 showed that the non-zero doses of ractopamine had higher weight gain ($P \leq 0.031$) than the controls (Table 2.1). For WGG1, the non-zero doses tended to have higher ($P = 0.073$) ADG compared to controls. There were no differences in ADG between the two non-zero doses ($P \geq 0.284$). It should be noted that WGG1 represents the previous approval weight gain group and therefore data from the original approval of ractopamine was considered in the decision to justify ADG effectiveness for this weight range.

For efficiency of gain (G/F) or feed efficiency, both non-zero doses of ractopamine resulted in improved G/F compared to controls ($P < 0.001$). For WGG1 and WGG2, G/F was improved for pigs fed the 10 ppm dose compared to pigs fed the 5 ppm dose ($P \leq 0.041$). For WGG3, G/F was not improved in the 10 ppm dose pigs compared to the 5 ppm dose pigs ($P = 0.684$).

For Chemical Lean %, the contrasts within each weight gain group showed that the non-zero concentrations had higher ($P < 0.031$) lean percent than controls but showed no differences ($P > 0.104$) when compared to each other.

Carcass fat was decreased for the non-zero doses of ractopamine compared to the controls for WGG1 and WGG3 ($P < 0.049$), but not for WGG2 ($P > 0.104$) (Table 2.2). Tenth rib backfat was not affected by ractopamine with the exception of the 10 ppm dose significantly reducing 10th rib backfat in WGG3 ($P< 0.001$). Last rib backfat was not affected by treatments. Loin eye area was increased in the 10 ppm and 5 ppm ractopamine treated pigs compared to controls ($P < 0.033$), except the 5 ppm treated pigs in WGG2 were not different than controls ($P = 0.093$). The 10 ppm ractopamine treated pigs also had increased loin eye areas compared to the 5 ppm treated pigs ($P < 0.033$). Rate of lean gain and efficiency of lean gain were both improved with the non-zero doses of ractopamine ($P < 0.033$). However, for rate of lean gain and efficiency of lean gain, only efficiency of lean gain for WGG2 was improved in the 10 ppm treatment compared to the 5 ppm treatment ($P = 0.049$). Dressing percentage was increased with the 10 ppm ractopamine dose compared to controls ($P < 0.024$). The 5 ppm ractopamine treatment increased dressing percentage over the controls only in WGG3 ($P = 0.002$).

Differences in Warner-Bratzler Shear Force values were detected ($P \leq 0.057$) when the 10 ppm dose was compared to the control or the 5 ppm dose across weight gain groups and in WGG3 (Table 2.3). However, no differences were detected in tenderness when evaluated by trained sensory panelists across all weight groups and ractopamine levels. Therefore, no caution about differences in tenderness with ractopamine treatment was deemed necessary. Further, no differences were detected between treatments for pH, color, or water holding capacity as measured by drip loss percent, thereby indicating no reduction in meat quality with ractopamine treatment.

Pooled Effectiveness Conclusions

The pooled effectiveness studies demonstrated that ractopamine improves ADG, efficiency of gain and carcass leanness for the last 20.4 to 40.8 kg (45-90 lbs) of gain when fed in a complete ration containing at least 16% crude protein. The 10 ppm dose was not found to significantly improve ADG, G/F (feed efficiency) or carcass leanness above the response of the 5 ppm dose. Lastly, use of ractopamine up to 10 ppm did not adversely affect meat quality.

Table 2.1: Pooled Analysis - Performance of Finishing Swine Fed Diets Containing Ractopamine

Primary Claim Variables

Variables	Weight Gain Group[b]	Ractopamine (ppm)[a]				P-value		
		0	5	10	SE	0 vs 5	0 vs 10	5 vs 10
Average Daily Weight Gain, kg/d	1	1.04	1.12	1.16	0.077	0.073	0.005	0.284
	2	0.91	1.09	1.11	0.077	<0.001	<0.001	0.626
	3	0.96	1.06	1.05	0.077	0.021	0.031	0.856
Gain Efficiency, G/F	1	0.34	0.37	0.38	0.013	<0.001	<0.001	0.041
	2	0.28	0.32	0.34	0.013	<0.001	<0.001	0.019
	3	0.30	0.33	0.34	0.013	<0.001	<0.001	0.684
Chemical Lean, %	1	13.49	14.15	13.96	0.208[c]	0.002	0.031	0.376
	2	12.96	13.52	13.86	0.208	0.010	<0.001	0.104
	3	13.12	14.01	14.10	0.208[c]	<0.001	<0.001	0.673

[a] All values are least squares means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

[c] Standard Error was 0.211 for 10 ppm dose

Table 2.2: Pooled Analysis - Performance of Finishing Swine Fed Diets Containing Ractopamine

Label Panel Variables

Variables	Weight Gain Group[b]	Ractopamine (ppm)[a]				P-value		
		0	5	10	SE	0 vs 5	0 vs 10	5 vs 10
Carcass Fat, kg	1	7.58	6.75	6.89	0.460[c]	0.017	0.049	0.691
	2	10.48	10.17	9.91	0.460	0.371	0.104	0.460
	3	10.52	9.49	9.25	0.460[c]	0.003	<0.001	0.495
Tenth Rib Back Fat (3/4 location), cm	1	1.75	1.69	1.65	0.090	0.343	0.118	0.536
	2	2.11	2.12	2.05	0.090	0.852	0.323	0.240
	3	2.08	1.95	1.80	0.090	0.053	<0.001	0.023
Last Rib Back Fat (midline), cm	1	2.07	1.98	1.98	0.143	0.127	0.120	0.976
	2	2.48	2.57	2.51	0.143	0.171	0.593	0.402
	3	2.38	2.37	2.34	0.143	0.899	0.480	0.561
Tenth Rib Loin Eye Area, sq cm	1	42.47	44.25	46.02	0.879	0.033	<0.001	0.033
	2	48.02	49.42	51.71	0.879	0.093	<0.001	0.006
	3	48.52	51.79	55.06	0.879	<0.001	<0.001	<0.001
Rate of Lean Gain, g/d	1	98.69	130.35	130.20	13.219[d]	0.004	0.004	0.989
	2	77.97	111.73	129.46	13.219	0.002	<0.001	0.099
	3	105.61	128.91	132.90	13.219[e]	0.033	0.013	0.716
Efficiency of Lean Gain	1	0.03	0.04	0.04	0.004	0.001	<0.001	0.714
	2	0.02	0.03	0.04	0.004	0.002	<0.001	0.049
	3	0.03	0.04	0.04	0.004	0.019	0.001	0.384
Dressing Percentage	1	76.66	77.03	77.12	0.518	0.068	0.024	0.655
	2	77.21	77.58	77.84	0.518	0.064	0.002	0.200
	3	77.23	77.88	78.26	0.518	0.002	<0.001	0.059

[a] All values are least squares means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

[c] Standard Error was 0.463 for 10 ppm dose

[d] Standard Error was 13.337 for 10 ppm dose

[e] Standard Error was 13.337 for 5 and 10 ppm dose

Table 2.3: Pooled Analysis - Performance of Finishing Swine Fed Diets Containing Ractopamine

Shear Force Variable

Variables	Weight Gain Group[b]	Ractopamine (ppm)[a] 0	5	10	SE	P-value 0 vs 5	0 vs 10	5 vs 10
Warner-Bratzler Shear Force, kg	1	4.24	4.54	4.53	0.165	0.134	0.149	0.956
	2	4.28	4.22	4.44	0.165	0.761	0.410	0.260
	3	4.20	4.03	4.58	0.165[c]	0.400	0.054	0.006

[a] All values are least squares means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

[c] Standard Error was 0.166 for 10 g/ton dose

B. Summary of Individual Effectiveness Studies

1. Study T4V310309

One hundred eighty progeny of the Danbred 771 sireline were evaluated in this study. Arithmetic means for claim variables and feed intake are presented in Table 2.4. The live phase of this study was conducted at the University of Nebraska Swine Unit, Ithaca, NE (Phillip Miller, Ph.D., Investigator). The live phase facility had 2 buildings with a total of 50 pens. The research facility consisted of a modified open front barn with curtains and had 2/3 solid concrete floors and 1/3 slatted floor. The pen size was 1.22 m x 4.72 m (5 ft x 15.5 ft), which calculated to a pen density of 1.44 m^2/pig (15.5 ft^2) and was uniform across all pens based on 5 pigs/pen.

Animals were evaluated to the targeted end weights, moved an average distance of 105.2 m from treatment pens to the trailer, transported an average of 419.6 km to the slaughter facility and harvested using standard commercial techniques. During the Marketing Phase, study animals were commingled during transport and in lairage prior to harvest.

The Carcass Phase of the study was conducted at South Dakota State University Meat Science Laboratory, Brookings, SD (Robert Maddock, Ph.D., Investigator). *Longissimus dorsi* roasts posterior to the 10^{th} rib were collected and shipped to Iowa State University, Ames, IA for sensory evaluation (Ken Prusa, Ph.D., Investigator).

Table 2.4: Performance of Finishing Swine Fed Diets Containing Ractopamine - T4V310309 – Genders Combined[a]

		Ractopamine (ppm)		
Variables	**Weight Gain Group[b]**	**0 (SD)**	**5 (SD)**	**10 (SD)**
Average Daily Weight Gain, kg/d	1	0.92 (0.057)	1.09 (0.087)	1.05 (0.114)
	2	0.98 (0.084)	1.14 (0.102)	1.19 (0.054)
	3	0.94 (0.048)	1.01 (0.042)	0.98 (0.164)
Gain Efficiency, G/F	1	0.32 (0.019)	0.36 (0.021)	0.36 (0.026)
	2	0.30 (0.015)	0.33 (0.019)	0.36 (0.012)
	3	0.28 (0.015)	0.33 (0.021)	0.33 (0.028)
Average Daily Feed Intake (kg/d)	1	2.88 (0.163)	3.04 (0.072)	2.90 (0.236)
	2	3.30 (0.177)	3.43 (0.208)	3.33 (0.178)
	3	3.31 (0.164)	3.08 (0.091)	2.98 (0.359)
Chemical Lean, %	1	13.22 (0.767)	13.91 (0.752)	13.65 (0.305)
	2	12.25 (0.379)	13.26 (0.587)	13.89 (1.064)
	3	12.46 (1.037)	14.17 (0.855)	13.40 (0.795)

[a] All values are arithmetic means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

2. Study T4V170310

One hundred eighty progeny of the PIC 337 sireline were evaluated in this study. Arithmetic means for claim variables and feed intake are presented in Table 2.5. The live phase of this study was conducted at the University of Illinois Swine Unit, Champaign, IL (Mike Ellis, Ph.D., Investigator). The live phase facility had 2 identical rooms with 48 pens per room. One room was used for this study. The research facility was a totally enclosed mechanically ventilated unit. The barn was 50% solid concrete and 50% slotted concrete for flooring. The pen size was 2.62 m x 1.80 m (8.58 ft x 5.92 ft), which calculated to a pen density of 0.94 m^2/pig (10.16 ft^2) and was uniform across all pens based on 5 pigs/pen.

Animals were evaluated to the targeted end weights, moved an average distance of 15.7 m from treatment pens to the trailer, transported an average of 4.3 km to the slaughter facility and harvested using standard commercial techniques. During the Marketing Phase, study animals were commingled during transport and in lairage prior to harvest.

The Carcass Phase of the study was conducted at University of Illinois Meat Science Laboratory, Urbana, IL (Floyd McKeith, Ph.D., Investigator). *Longissimus dorsi* roasts posterior to the 10th rib were collected and shipped to Iowa State University, Ames, IA for sensory evaluation (Ken Prusa, Ph.D., Investigator).

Table 2.5: Performance of Finishing Swine Fed Diets Containing Ractopamine - T4V170310 – Genders Combined[a]

		Ractopamine (ppm)		
Variables	**Weight Gain Group[b]**	**0 (SD)**	**5 (SD)**	**10 (SD)**
Average Daily Weight Gain, kg/d	1	1.17 (0.203)	1.38 (0.099)	1.50 (0.182)
	2	1.00 (0.109)	1.17 (0.155)	1.14 (0.203)
	3	1.08 (0.059)	1.27 (0.141)	1.28 (0.135)
Gain Efficiency, G/F	1	0.33 (0.047)	0.38 (0.028)	0.42 (0.045)
	2	0.28 (0.047)	0.32 (0.075)	0.32 (0.061)
	3	0.31 (0.025)	0.35 (0.014)	0.37 (0.028)
Average Daily Feed Intake (kg/d)	1	3.57 (0.274)	3.62 (0.278)	3.61 (0.199)
	2	3.61 (0.416)	3.68 (0.409)	3.58 (0.200)
	3	3.51 (0.330)	3.59 (0.254)	3.48 (0.240)
Chemical Lean, %	1	13.17 (0.642)	14.01 (0.543)	13.59 (0.474)
	2	12.69 (0.596)	13.56 (0.377)	13.24 (0.673)
	3	13.35 (0.890)	14.10 (0.658)	14.11 (0.748)

[a] All values are arithmetic means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

3. Study T4V060311

One hundred eighty progeny of the Genetiporc V300 sireline were evaluated in this study. Arithmetic means for claim variables and feed intake are presented in Table 2.6. The live phase of this study was conducted at HMS Veterinary Development Inc., Tulare, CA (Terry TerHune, D.V.M., Ph.D, Investigator). Animals were housed in barn number 5, which contained 80 pens. The research facility was an open-sided, naturally ventilated barn. The barn had 100% concrete floors. The pen size was 2.59 m x 1.83 m (8.5 ft x 6.0 ft). Pens were modified to mimic industry standards and provide the following space allowances based on five pigs per pen:

> Pigs in the 0-20 kg and 20-41 kg weight gain groups were reared in pens allowing 0.770 m^2 / pig (8.25 ft^2 / pig) and 0.863 m^2 / pig (9.25 ft^2 / pig), respectively. Space allowances for the 0-41 kg weight gain group were 0.770 m^2 / pig (8.25 ft^2 / pig) from Study Day 0 to Study Day 17. On Study Day 17, study site personnel adjusted pen size to allow for a space allowance of 0.863 m^2 / pig (9.25 ft^2 / pig) for the remainder of the study.

Animals were evaluated to the targeted end weights, moved an average distance of 44.5 m from treatment pens to the trailer, transported an average of 90.0 km to the slaughter facility and harvested using standard commercial techniques. During the Marketing Phase, study animals were commingled during transport and in lairage prior to harvest.

The Carcass Phase of the study was conducted at California State University, Fresno - Meat Science Laboratory, Fresno, CA (John Henson, Ph.D., Investigator). *Longissimus dorsi* roasts posterior to the 10^{th} rib were collected and shipped to Iowa State University, Ames, IA for sensory evaluation (Ken Prusa, Ph.D., Investigator).

Table 2.6: Performance of Finishing Swine Fed Diets Containing Ractopamine - T4V060311 – Genders Combined[a]

		Ractopamine HCl (ppm)		
Variables	**Weight Gain Group[b]**	**0 (SD)**	**5 (SD)**	**10 (SD)**
Average Daily Weight Gain, kg/d	1	1.32 (0.163)	1.27 (0.320)	1.25 (0.333)
	2	0.84 (0.036)	1.04 (0.182)	1.09 (0.102)
	3	1.04 (0.077)	1.09 (0.072)	1.08 (0.068)
Gain Efficiency, G/F	1	0.40 (0.032)	0.41 (0.064)	0.42 (0.066)
	2	0.23 (0.012)	0.27 (0.038)	0.31 (0.025)
	3	0.31 (0.018)	0.33 (0.032)	0.34 (0.007)
Average Daily Feed Intake (kg/d)	1	3.32 (0.211)	3.04 (0.387)	2.92 (0.405)
	2	3.63 (0.132)	3.81 (0.204)	3.53 (0.303)
	3	3.42 (0.319)	3.31 (0.244)	3.19 (0.238)
Chemical Lean, %	1	14.21 (0.977)	14.56 (0.966)	14.53 (0.774)
	2	13.42 (0.851)	13.94 (0.821)	14.36 (1.12)
	3	13.74 (0.870)	14.47 (0.314)	14.95 (0.611)

[a] All values are arithmetic means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

4. Study T4V370312

One hundred eighty progeny of the Monsanto Choice Genetics EB sireline were evaluated in this study. Arithmetic means for claim variables are presented in Table 2.7. The live phase of this study was conducted at the North Carolina State University – Swine Evaluation Station, Clayton, NC (Todd See, Ph.D., Investigator). The live phase facility contained 99 pens. The research facility was open-sided and naturally ventilated with 100% solid concrete floors. The pen size was 1.52 m x 3.66 m (5.0 ft x 12.0 ft), which calculated to a pen density of 1.11 m^2/pig (12.0 ft^2) and was uniform across all pens based on 5 pigs/pen.

Animals were evaluated to the targeted end weights, moved an average distance of 36.9 m from treatment pens to the trailer, transported an average of 619.3 km to the slaughter facility and harvested using standard commercial techniques. During the Marketing Phase, study animals were commingled during transport and in lairage prior to harvest.

The Carcass Phase of the study was conducted at University of Georgia - Meat Science and Technology Center, Athens, GA (Dean Pringle, Ph.D., Investigator). *Longissimus dorsi* roasts posterior to the 10th rib were collected and shipped to Iowa State University, Ames, IA for sensory evaluation (Ken Prusa, Ph.D., Investigator).

Table 2.7: Performance of Finishing Swine Fed Diets Containing Ractopamine - T4V370312 – Genders Combined[a]

		Ractopamine HCl (ppm)		
Variables	**Weight Gain Group[b]**	**0 (SD)**	**5 (SD)**	**10 (SD)**
Average Daily Weight Gain, kg/d	1	0.80 (0.023)	0.86 (0.133)	0.87 (0.077)
	2	0.77 (0.184)	0.84 (0.177)	0.86 (0.073)
	3	0.81 (0.099)	0.88 (0.078)	0.80 (0.106)
Gain Efficiency, G/F	1	0.33 (0.019)	0.34 (0.012)	0.36 (0.014)
	2	0.26 (0.033)	0.31 (0.026)	0.32 (0.007)
	3	0.29 (0.005)	0.31 (0.011)	0.32 (0.035)
Average Daily Feed Intake (kg/d)	1	2.42 (0.107)	2.48 (0.295)	2.40 (0.135)
	2	2.90 (0.346)	2.72 (0.367)	2.68 (0.168)
	3	2.76 (0.352)	2.80 (0.229)	2.53 (0.130)
Chemical Lean %	1	13.89 (1.30)	14.39 (0.453)	14.08 (0.479)
	2	13.46 (0.517)	13.33 (0.807)	13.69 (0.508)
	3	13.22 (0.636)	13.78 (0.836)	14.00 (0.935)

[a] All values are arithmetic means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

5. Study T4V370313

One hundred eighty progeny of the Newsham XL sireline were evaluated in this study. Arithmetic means for claim variables are presented in Table 2.8. The live phase of this study was conducted at Diamond K Research, Marshville NC (Ken Krueger, Ph.D., Investigator). The live phase facility had 2 rooms each containing 36 pens. The research facility was an open-sided and mechanically ventilated barn. The barn had 100% solid concrete floors. The pen size was 1.68 m x 3.66 m (5.5 ft x 12.0 ft), which calculated to a pen density of 1.23 m^2/pig (13.2 ft^2) and was uniform across all pens based on 5 pigs/pen.

Animals were evaluated to the targeted end weights, moved an average distance of 47.1 m from treatment pens to the trailer, transported an average of 379.8 km to the slaughter

facility and harvested using standard commercial techniques. During the Marketing Phase, study animals were commingled during transport and in lairage prior to harvest.

The Carcass Phase of the study was conducted at University of Georgia - Meat Science and Technology Center, Athens, GA (Dean Pringle, Ph.D., Investigator). *Longissimus dorsi* roasts posterior to the 10th rib were collected and shipped to Iowa State University, Ames, IA for sensory evaluation (Ken Prusa, Ph.D., Investigator).

Table 2.8: Performance of Finishing Swine Fed Diets Containing Ractopamine - T4V370313 – Genders Combined[a]

		Ractopamine HCl (ppm)		
Variables	**Weight Gain Group[b]**	**0 (SD)**	**5 (SD)**	**10 (SD)**
Average Daily Weight Gain, kg/d	1	1.01 (0.168)	1.00 (0.209)	1.13 (0.222)
	2	0.97 (0.045)	1.25 (0.199)	1.26 (0.111)
	3	0.95 (0.063)	1.02 (0.061)	1.12 (0.045)
Gain Efficiency, G/F	1	0.32 (0.024)	0.34 (0.060)	0.37 (0.047)
	2	0.30 (0.004)	0.37 (0.034)	0.39 (0.018)
	3	0.30 (0.017)	0.33 (0.015)	0.33 (0.016)
Average Daily Feed Intake (kg/d)	1	3.16 (0.335)	2.93 (0.245)	3.08 (0.201)
	2	3.21 (0.119)	3.31 (0.291)	3.22 (0.162)
	3	3.16 (0.090)	3.11 (0.149)	3.35 (0.114)
Chemical Lean, %	1	12.97 (0.898)	13.88 (0.191)	13.86 (0.541)
	2	12.98 (0.420)	13.49 (0.168)	14.14 (0.706)
	3	12.81 (0.492)	13.54 (0.843)	14.04 (0.716)

[a] All values are arithmetic means

[b] Weight gain groups1, 2 and 3 were 90.7-111.1 kg, 111.1-131.5 kg and 90.7-131.5 kg respectively

3. TARGET ANIMAL SAFETY:

Target animal safety was determined using data from three studies, a non-clinical laboratory study, the clinical field study and a post-approval surveillance study. Observations with a significance level of $P < 0.10$ were further examined to determine any potential animal safety concerns.

A. Pivotal Study T4V060408

Non-Clinical Laboratory Study: The Effects of PAYLEAN and Marketing Conditions on Non-Ambulatory Incidence in Heavyweight Finishing Swine: Determined within a Controlled Environment. Study (T4V060408).

a. Type of Study: The study was conducted in finishing swine which were fed a complete diet containing 0, 5, or 10 ppm of ractopamine hydrochloride for up to 35 days and observed for adverse effects during the finishing period and through a simulated marketing process.

b. Study Director: T. N. TerHune, D.V.M., Ph.D., HMS Veterinary Services, Inc., Tulare, CA

c. General Design:

1) Purpose: This study was designed to clinically evaluate the safety of feeding ractopamine hydrochloride to heavyweight (i.e., heavier than 240 pounds; with a target weight of approximately 290 pounds) finishing barrows and gilts during a simulated marketing process using two different handling/marketing conditions. Potential target organs and tissues were identified through clinical observations, gross necropsy, and histological examination. Other variables of interest included: hematological variables, body weight, and feed consumption.

2) Experimental Design: Randomized Complete Block.

3) Animals: Swine (a total of 288 animals; 144 barrows and 144 gilts).

4) Experimental Unit: Each pen of 12 same-sex animals was an experimental unit (2 pens per dose x gender x marketing condition combination).

5) Experimental Blocks: Two blocks with a 7-day staggered start day were used to accommodate for the simulated marketing procedures (1 pen per block x dose x gender x marketing condition combination).

6) Control: Swine (24 animals per gender x handling condition combination) received the same basal diet as the treated swine, but without ractopamine hydrochloride.

7) Dosage Form: PAYLEAN 9, a Type A Medicated Article containing 9 grams of ractopamine hydrochloride per pound was used to make a Type C medicated feed containing 5 or 10 ppm ractopamine hydrochloride.

8) Dosages: The 16% crude protein diets, which were fed for *ad libitum* intake during the finishing period, contained 0, 5 or 10 ppm ractopamine hydrochloride.

9) Route of Administration:
Oral, in the diet, provided for *ad libitum* intake during the finishing period.

10) Marketing Conditions: Two different marketing conditions, Non-Progressive Condition (NC) and Progressive Condition (PC), were tested. For the NC, compared to the PC, the animals were moved at a faster pace with more noise during the loading, unloading, and final drive; moved a greater distance with more turns in the course during loading, unloading, and final drive; had a larger group size during loading; were transported in the front trailer compartment with smaller dimensions; were held on the trailer for a longer duration (i.e., loaded before the PC groups and unloaded after the PC group); and had a shorter lairage duration. Within a block, each pen was represented by three or four different animals on each of the three consecutive marketing simulations, phase days.

11) Study Duration: PAYLEAN was fed for up to 35 days. Performance variables were determined on study day 33. The Marketing Simulation Phase within each block occurred on study days 34, 35, and 36.

12) Pertinent Measurements/ Observations: Clinical Observations, adverse events, body weight, feed consumption, rectal temperature, hematological measurements, and gross necropsy/histopathology.

During the marketing simulation phase of the study, the Number of Dead Animals (*An animal that dies during the marketing process),* the Number of Non-Ambulatory Non-Injured (NANI) Animals (*An animal that becomes unwilling or unable to move for no apparent reason - no obvious injury),* the Number of Non-Ambulatory Injured (NAI) Animals (*An animal that is recumbent and is unwilling or unable to move due to obvious injury i.e.: broken leg, other trauma, etc.),* and the Number of Ambulatory Injured (AI) Animals (*An animal that is able to move, but is obviously injured or lame; i.e., foot, leg or shoulder injury)* were recorded.

d. Data Analyses Summary:

A mixed model analysis was conducted on the data. The analysis was conducted on either the actual data or a transformation of the data. If a transformation of the data was necessary, the transformation was an arcsine square root.

Fixed effects for the mixed model analysis on data collected during the performance part of the study were Dosage, Gender, and Dosage x Gender interaction while the random effect was Block. The Dosage x Gender interaction was tested and if significant, individual gender analyses were conducted. In all cases, linear contrasts

were used to compare the non-zero concentrations of ractopamine hydrochloride to controls and to each other.

Fixed effects for the mixed model analysis on data collected during the marketing simulation phase of the study were Dosage, Gender, Dosage x Gender, Handling, Dosage x Handling, Gender x Handling, and Dosage x Gender x Handling and a random effect of Block. Interactions involving Dosage that were significant resulted in analyses for each gender or each handling condition. Linear contrasts were used to compare the non-zero concentrations of ractopamine hydrochloride to controls and to each other.

d. Results Summary:

The feeding of ractopamine hydrochloride at 5 or 10 ppm up to 35 days was not associated with an increased incidence of abnormal health observations prior to the animals being exposed to a simulated marketing process.

During a simulated marketing process, the feeding of ractopamine hydrochloride to heavyweight finishing swine was associated with an increase in the incidence of animals classified as ambulatory injured (i.e., obvious limp or injury) none of which required animals to be removed from the study ($P \leq 0.10$; Table 3.1). The significant ($P \leq 0.10$) health observations are presented in Table 3.1.

Table 3.1: Significant Observations During a Simulated Marketing Process

			Ractopamine Hydrochloride Concentration (ppm)			Significance ($P \leq 0.10$)[1]			
Variable	**Time Period**	**Unit of Measure**	**0**	**5**	**10**	**Overall Dose Effect**	**0 vs 5**	**0 vs 10**	**5 vs 10**
Ambulatory injured	During Final Drive	Number of animals (total)	1 (95)	10 (94)	6 (95)	0.005	0.002	0.027	NS
Ambulatory injured	Following Final Drive	Number of animals (total)	1(95)	10(94)	5(95)	<0.001	<0.001	0.031	0.020
Ambulatory injured observed (Progressive Handling)	Following Final Drive	Number of animals (total)	0 (48)	6 (48)	0 (48)	<0.001	<0.001	NS	<0.001
Ambulatory injured observed (Non-Progressive Handling)	Following Final Drive	Number of animals (total)	1 (47)	4 (46)	5 (47)	0.079	0.091	0.035	NS

[1]Significance determined by arcsine square root transformed proportion of each variable by pen.

Feeding of ractopamine hydrochloride was associated with increased blood creatinine, decreased blood glucose, and decreased absolute and relative (i.e., as a percent of body weight) weights of the kidneys, heart, and liver after successful completion of the simulated marketing process ($P \leq 0.10$; Table 3.2). However, none of these findings manifested themselves into clinical observations that could be attributed to ractopamine hydrochloride treatment.

Table 3.2: Significant Observations Following a Simulated Marketing Process

			Ractopamine Hydrochloride Concentration (ppm)			Significance (P ≤ 0.10)			
Variable	**Time Period**	**Unit of Measure**	**0**	**5**	**10**	**Overall Dose Effect**	**0 vs 5**	**0 vs 10**	**5 vs 10**
Blood Glucose	Following Final Drive	mg/dl	83.01	76.94	75.10	<0.001	<0.001	<0.001	NS
Blood Creatinine	Following Final Drive	mg/dl	1.57	1.77	1.80	<0.001	<.001	<.001	0.335
Heart Weight	Following Final Drive	kg	0.47	0.44	0.44	0.025	0.016	0.019	NS
Relative Heart Weight	Following Final Drive	Percent of Body weight	0.36	0.34	0.34	0.021	0.016	0.013	NS
Kidney Weight*	Following Final Drive	kg	0.43	0.39	0.38	0.023	0.028	0.011	NS
Relative Kidney Weight*	Following Final Drive	Percent of Body weight	0.33	0.30	0.29	0.013	0.019	0.005	NS
Liver Weight	Following Final Drive	kg	1.84	1.73	1.72	0.053	0.045	0.027	NS
Relative Liver Weight	Following Final Drive	Percent of Body weight	1.40	1.32	1.30	0.043	0.048	0.019	NS

*both kidneys

The feeding of ractopamine hydrochloride to heavyweight finishing swine was not associated with an increased incidence of animals displaying abnormal health observations during the loading and unloading processes and was not associated with an increased incidence of animals that were unable to complete the study. However, there was an increase in the number of ractopamine hydrochloride-treated animals exhibiting signs of injury during the final drive to slaughter.

e. Conclusion:

Based on the results of this study, ractopamine hydrochloride is safe for finishing pigs heavier than 240 pounds when administered in the diet at concentrations up to 10 ppm and fed for up to 35 days. However, users should be cautioned that ractopamine hydrochloride has been associated with an increased number of injured and lame pigs during marketing.

B. Multiple-Location Field Effectiveness Study

a. Design:

The design of the multiple-location field effectiveness study can be found in section 2 B above.

b. Health observations:

Daily health observations were recorded for each pen of animals. Additionally, hearts were weighed and observed by a pathologist at slaughter. During the marketing phase of the study, the numbers of dead, NANI, NAI, and AI animals were recorded.

c. Results Summary:

Across weight gain groups, heart weights relative to body weights were smaller in pigs fed the 10 ppm dose compared to controls ($P = 0.04$). For weight gain group 2 (245-290 lbs), pigs fed the ractopamine hydrochloride treatments had smaller relative heart weights compared to controls ($P \leq 0.086$).

A review of the pooled data indicated a significant increase in treatment-related (10 ppm vs. 0 ppm and 10 ppm vs. 5 ppm) removals from the ractopamine hydrochloride treatment phase of the study ($P \leq 0.028$). The reasons for removal included lameness, anorexia, labored breathing and hernia. Additionally, the number of removals was significantly different between the 5 ppm and 10 ppm treatments ($P = 0.033$) for weight gain group 3 (200-290 lbs).

During the loading, transport, unloading/holding, and final drive of animals to stunning, no dead, NANI, or NAI animals were observed. An increased incidence of AI animals treated with ractopamine hydrochloride was observed within the loading, unloading, and final drive components of the Marketing Phase. Linear by linear association tests detected a treatment related increase in AI incidence within the final drive for gilts fed PAYLEAN (0 ppm - 1 of 148 observations; 5 ppm – 0 of 148 observations; 10 ppm – 5 of 143 observations).

d. Conclusion:

During the marketing phase, ractopamine hydrochloride treatment was associated with an increased incidence of AI animals.

C. Post Approval Surveillance Study (PASS)

a. Study Purpose:

The purpose of the PASS was to determine the incidence of non-ambulatory animals in pigs fed the approved ractopamine hydrochloride product (NADA 140-863, PAYLEAN 9 and PAYLEAN 45) and non-ractopamine hydrochloride-fed pigs under commercial conditions. The study evaluated the feeding of 0, 5 or 10 ppm doses on the incidence of non-ambulatory pigs (animals that are unable or unwilling to move or are dead).

b. Study Design:

The study was designed to obtain non-ambulatory information for approximately one year from two packing plants, one in the Midwest and another in the Southeast. For each of the two packing plants, there were four farms that supplied the pigs for the study. Each farm was assigned a study number. Consequently, there were eight study numbers. Studies T4V910301, T4V910302, T4V910303, and T4V910304 (conducted in the Midwest region of the U.S.), and studies T4V910305, T4V910306, T4V910307, and T4V910308 (conducted in the Southeast region of the U.S.) were the eight studies involved in the PASS.

Each quarter (total of 4 quarters), the farm assigned to each study number selected a site, consisting of at least 3 barns, from which pigs were shipped. The same site may have been used for more than one quarter, or a unique site may have been used for each quarter. Each site was assigned a unique site ID.

For each site selected, 3 barns were identified with each barn being randomly assigned a treatment (0, 5 or 10 ppm) for that quarter. Each barn was assigned a unique barn ID. After 21 to 35 days of pigs being on treatment, two loads of pigs (approximately 160 to 190 pigs per load) from each barn were shipped to the designated slaughter plant during each quarter. Each load was assigned a unique load ID to maintain the identity of the treatment.

Animals were observed at loading, unloading and during the final drive and the number of NANI, NAI, and dead animals were recorded. Pigs recorded as NANI, NAI or dead during loading remained at the site and were not loaded onto the truck. Normal farm procedures were followed when caring for these animals.

c. Results Summary:

The numbers of pigs at loading across both regions were 11,372, 11,358, and 11,334 for the 0, 5, and 10 ppm ractopamine hydrochloride concentrations respectively. There was a total of 612 non-ambulatory pigs that were identified, of which, 22 occurred in the loading phase, 425 occurred in the unloading phase, and 165 in the final drive phase. The overall incidence of NAI observations was significantly different between treatments across all phases ($P = 0.072$) with treated pigs having a higher incidence than controls. Furthermore, the NAI incidence was higher ($P = 0.03$) for pigs fed the 10 ppm treatment compared to pigs fed the 0 ppm treatment. The NANI incidence

during the loading phase was a linear response of ractopamine hydrochloride ($P < 0.001$). The numbers of pigs at loading that were observed to be NANI were 1, 3, and 7 for the 0, 5, and 10 ppm treatments, respectively. The NAI incidence during the loading phase was also a linear response of ractopamine hydrochloride ($P < 0.03$). The numbers of pigs at loading that were observed to be NAI were 3, 2, and 6 for the 0, 5, and 10 ppm treatments respectively. During the unloading phase, the incidence of combined non-ambulatory (NAI, NANI, and dead) pigs was a linear response to ractopamine hydrochloride level ($P < 0.039$) with 110, 143, and 172 observations for the 0, 5, and 10 ppm treatments, respectively.

d. Conclusion:

Feeding of ractopamine hydrochloride for 21 to 35 days at concentrations of 5 or 10 ppm to pigs weighing up to 240 lb. can increase the number of non-ambulatory pigs often referred to as fatigued pigs. Users should be cautioned that ractopamine hydrochloride has been associated with an increased number of non-ambulatory pigs (due to fatigue and/or injury) during marketing.

4. HUMAN SAFETY:

No new human food safety data are required for the approval of this supplement. The product's human food safety in finishing swine has been established in the Freedom of Information (FOI) Summary for the new animal drug application for PAYLEAN (NADA 140-863) in finishing swine dated December 22, 1999.

A. Toxicity:

Summaries of pivotal toxicology studies of ractopamine hydrochloride can be found in the FOI Summary for the original December 22, 1999, approval for NADA 140-863. These studies support the establishment of an Acceptable Daily Intake (ADI) and Safe Concentration for ractopamine hydrochloride in swine.

B. Safety Concentration of Total Residues – Calculation of the Acceptable Daily Intake (ADI) and the Safe Concentration (SC):

The safe concentrations for total residues of ractopamine hydrochloride are: 0.25 ppm in muscle, 0.75 ppm in liver, and 1.5 ppm in kidney and fat. The acceptable daily intake for total residues of ractopamine is 1.25 micrograms ractopamine hydrochloride per kilogram of body weight per day as codified under 21 CFR 556.570 (see the FOI Summary for the original December 22, 1999, approval for NADA 140-863).

C. Total Residue Depletion and Metabolism Studies:

Summaries of pivotal residue studies of ractopamine hydrochloride can be found in the FOI summary for the original December 22, 1999, approval for NADA 140-863.

D. Tolerance and Withdrawal Time:

Tolerances are established for residues of ractopamine hydrochloride parent (marker residue) in edible swine tissues of 0.05 ppm in muscle and 0.15 ppm in liver (target tissue) as codified under 21 CFR 556.570. The changes in conditions of use under the current supplement do not alter the original decision that a withdrawal time is not required for ractopamine hydrochloride in swine as codified under 21 CFR 558.500. (see the FOI Summary for the original December 22, 1999 approval for NADA 140-863).

E. Microbial Food Safety:

Does not apply.

F. Regulatory Method:

The regulatory method for residues of ractopamine in swine is described in the FOI summary for the original December 22, 1999, approval for NADA 140-863. The validated regulatory analytical methods for detection and confirmation of residues of ractopamine in liver and muscle are on file at Center for Veterinary Medicine's Document Control Unit (HFV-199), FDA, 7500 Standish Place, Rockville, MD 20855.

G. User Safety Concerns:

See the FOI Summary for the original December 22, 1999, approval for NADA 140-863.

5. 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 of the implementing regulations. The data demonstrate that ractopamine hydrochloride under the outlined conditions of use is safe and effective for the claims indicated in section 1 of this FOI Summary. The Agency has concluded that the toxicological and residue decisions made for the original approval in swine also apply to changes described in the current supplement.

The Center for Veterinary Medicine has concluded that, for this product, PAYLEAN, adequate directions for use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

The drug is to be fed in Type C medicated feeds in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the use of the product PAYLEAN for increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter for which this supplement is approved.

Pursuant to 21 CFR 514.106 (b)(2)(vi), this supplemental NADA approval is regarded as a Category II supplemental change which required a reevaluation of safety and effectiveness data in the parent NADA.

PAYLEAN is under the following US patent number:

U.S. Patent Number	Date of Expiration
4,690,951	September 1, 2007

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

PAYLEAN 9 Type A Medicated Article
PAYLEAN 45 Type A Medicated Article
Ractopamine Finishing Swine Feed Concentrate Type B Medicated Feed
Ractopamine Finishing Swine Feed Type C Medicated Feed