Date of Approval: November 12, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-290

TOPMAX 9

(Ractopamine Hydrochloride)
Type A Medicated Article
Finishing Turkeys

For increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed for the last 14 days prior to slaughter.

For increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed for the last 7 to 14 days prior to slaughter.

Sponsored by:

Elanco Animal Health

A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-290
B. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Name:	TOPMAX 9
D. Established Name:	Ractopamine hydrochloride
E. Pharmacological Category:	Beta adrenergic agonist
F. Dosage Form:	Type A Medicated Article
G. Amount of Active Ingredient:	9 g/lb
H. How Supplied:	25 lb bag
I. How Dispensed:	OTC
J. Dosages:	4.6 to 11.8 g/ton (5 to 13 ppm)
K. Route of Administration:	Oral, in feed
L. Species/Classes:	Finishing Tom and Hen Turkeys
M. Indications:	For increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed for the last 14 days prior to slaughter. For increased rate of weight gain and improved feed efficiency in finishing hen turkeys fed for the last 7 to 14 days prior to slaughter.

II. EFFECTIVENESS:

A. Dosage Characterization:

Three non-pivotal studies using Hybrid and Nicholas turkeys were conducted in 2005–2006 to evaluate ractopamine dose, dietary lysine fortification, and duration of ractopamine treatment in heavy finishing turkeys. Average daily gain (ADG) and gain:feed (G/F) results from these studies indicated the following for dietary lysine fortification, ractopamine dose, and feeding duration:

Lysine fortification

Two studies were conducted in California (T4V060508 using Nicholas line 85 toms and T4V060523 using Nicholas line 85 hens and toms) to evaluate ractopamine dose and dietary lysine fortification levels. In both studies, birds were fed ractopamine for the last 28 days prior to slaughter. Dietary lysine varied from 0.85 to 1.25 % with a constant metabolizable energy (ME) of 1565 (Kcal/lb). For study T4V060508 in which 0, 5, or 13 ppm ractopamine was fed, ADG and G/F improved with ractopamine regardless of lysine fortification. For study T4V060523, in which 0 or 13 ppm ractopamine was fed, there were no effects of dietary lysine and no ractopamine x lysine interactions, although ADG and G/F of hens and toms were improved with ractopamine.

Dose and Duration

A two-site study (California, T4V060509 and North Carolina, T4V370510) was conducted with Hybrid Converter and Nicholas line 85 or 700 strains of heavy toms to evaluate ractopamine dose (0, 5, or 13 ppm), feeding duration, and genetic strain in finishing toms fed ractopamine for the last 7 to 28 days prior to slaughter. Toms fed 5 or 13 ppm ractopamine for the last 7, 14, 21 or 28 days prior to slaughter showed improved ADG and G/F, compared to controls when results were combined across strain and ractopamine feeding duration. The 7 and 14 day ractopamine feeding durations showed the greatest contrasts in ADG and G/F between the controls and the birds treated with 5 or 13 ppm ractopamine, although the two non-zero doses were not different from each other. The 7 day duration responses in ADG and G/F were similar in both Nicholas and Hybrid toms, and the longer durations showed variable responses to ractopamine treatment in ADG and G/F. Additionally, in study T4V060523, in which birds were fed 0 or 13 ppm ractopamine for a 28 day duration, ADG was improved by ractopamine in toms and hens, but was not significantly different among treatment groups by dietary lysine level, and there was no ractopamine x lysine interaction. The G/F was also significantly improved by ractopamine treatment in toms and hens, but was not significantly different among treatment groups by dietary lysine level, and there was no ractopamine x lysine interaction.

Summary

These studies support the selection of lysine levels commonly used for finishing diets in the turkey industry (0.96 to 0.99% lysine, hens and toms, respectively), a dose of 5 to 13 ppm of ractopamine, and a feeding duration of the last 7 to 14 days prior to slaughter as appropriate to use in conducting the clinical effectiveness study.

B. Substantial Evidence:

1. Summary of Pooled Tom Effectiveness Study Sites

Toms

A single clinical effectiveness study was conducted at six sites. The study sites were located in five different geographic locations representing the major turkey producing regions in the United States and one in Canada. In addition, breast meat samples were collected and shipped from all study sites to a single laboratory for Kramer Shear Force evaluation. Three study sites used the Hybrid Converter finishing tom turkeys and three sites used either Nicholas 88 or Nicholas 700 finishing tom turkeys.

The effectiveness study design employed at each study site was a randomized complete block design with pen location as the blocking factor. The treatment structure was factorial in nature with two factors (2 x 4 complete factorial in each block): RAC concentration and Duration. There were four ractopamine concentrations and two durations. Animals were fed ractopamine concentrations of 0, 5, 9 or 13 ppm for either 7 or 14 days using an industry standard diet (0.99% lysine). Birds were either 20 weeks ($\pm$ 3 days) of age or 21 weeks ($\pm$ 3 days) of age at the initiation of the treatment phase for the 14 day or 7 day duration, respectively. Initial weights were measured at treatment initiation and final weights were measured at the end of the treatment period. Feed offered and remaining in the feeders at the end of the medicated treatment period was recorded. Pens at each site contained 9 to 17 animals to achieve an animal density of approximately 0.372 m^2 per tom.

At five of the six study sites, all animals were loaded and transported for a minimum of 4 hours. At the sixth study site, only animals selected for necropsy and breast meat quality evaluation were transported. Forty-eight birds at each site were pre-selected for breast meat quality evaluation which included Minolta L* Color score and ultimate pH measurements taken from turkey breast meat that had been chilled overnight. Breast meat samples were also sent to Iowa State University for Kramer shear force evaluation. Sixteen birds were randomly pre-selected at each site for necropsy and appropriate tissues were collected by a board-certified veterinary pathologist for histological evaluation.

Data Analysis Summary

Data from the six study sites were pooled and analyzed. Results were calculated for each variable on a pen basis. The claim variables of Average Daily Gain and Gain Efficiency were analyzed using a linear mixed model, Proc Mixed SAS®, version 9.1. Fixed effects for the mixed model analysis were RAC, Duration, and RAC x Duration, and random effects of Site, Block (Site), Site x RAC and Site x Duration. Linear contrasts were used to compare the non-zero concentrations of RAC to controls and to each other within Duration.

Initial animal body weights were not different, so no covariate adjustment was made for the claim variables. A test of heterogeneity of variance among sites and among blocks within sites was conducted. Residual but no random study heterogeneity was detected ($P<0.05$) for both Average Daily Gain and Gain Efficiency (claim variables).

Pooled Tom Effectiveness Results

For the 7 day duration, linear contrasts showed that Average Daily Gain was not improved ($P \geq 0.086$) with feeding RAC (Table 1). For the 14 day duration, Average Daily Gain was improved ($P \leq 0.037$) for animals fed a diet containing a non-zero concentration of RAC when compared to controls. Since RAC fed at the 5 ppm concentration was the smallest non-zero dose different from control, it was identified as the minimum effective dose. In addition to the contrasts comparing each non-zero dose of RAC to control, contrasts were conducted to determine differences between the non-zero doses. The additional contrasts indicated no differences between the non-zero doses.

For the 7 day duration, linear contrasts showed that Gain Efficiency was not improved ($P \geq 0.096$) with feeding RAC (Table 1). For the 14 day duration, Gain Efficiency was improved ($P \leq 0.041$) for animals fed a diet containing a non-zero concentration of RAC when compared to controls. Since RAC fed at the 5 ppm concentration was the smallest non-zero dose different from control, it was identified as the minimum effective dose. In addition to the contrasts comparing non-zero doses of RAC to controls, contrasts were also conducted to determine differences between the non-zero doses. The additional contrasts indicated no differences between the non-zero doses.

An unweighted mixed model analysis was conducted for Ultimate pH and linear contrasts and showed no RAC differences ($P \geq 0.236$; Table 2) for animals assigned to either the 7 or 14 day duration.

An unweighted mixed model analysis was conducted for Minolta L* Color measurements and linear contrasts showed no differences ($P \geq 0.187$; Table 2) in Minolta L* Color for animals fed a diet containing 5 ppm or 9 ppm RAC for 7 days or any non-zero concentration of RAC for 14 days when compared to controls. However, animals fed a diet containing 13 ppm RAC for 7 days had lower ($P = 0.018$) Minolta L* Color measures when compared to controls. However, for the range of Minolta L* values, all scores demonstrate acceptable color.

An unweighted mixed model analysis was conducted for Kramer Shear Force (Table 2) and linear contrasts showed no RAC differences in Kramer Shear Force ($P \geq 0.182$) for animals assigned to either the 7 or 14 day duration.

Table 1. Pooled Analysis – Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine: Claim Variables

		Ractopamine (ppm)				SE	P-value		
Variables	Duration	0	5	9	13		0 vs. 5	0 vs. 9	0 vs. 13
Average Daily Gain (kg/d)	7	0.113	0.115	0.115	0.123	0.014	0.772	0.707	0.086
	14	0.115	0.127	0.131	0.132	0.014	0.037	0.006	0.004
Gain Efficiency	7	0.217	0.214	0.216	0.233	0.016	0.716	0.905	0.096
	14	0.213	0.233	0.249	0.247	0.016	0.041	<0.001	<0.001

Table 2. Pooled Analysis – Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine: Breast Meat Quality Evaluation

		Ractopamine (ppm)				SE	P-value		
Variable	Duration	0	5	9	13		0 vs 5	0 vs 9	0 vs 13
Ultimate pH[a]	7	5.75	5.78	5.76	5.78	0.058	0.269	0.563	0.236
	14	5.79	5.78	5.78	5.76	0.058	0.746	0.890	0.289
Minolta L*	7	57.67	57.18	56.94	56.35	1.207	0.378	0.187	0.018
	14	57.38	57.47	57.77	56.80	1.207	0.862	0.472	0.300
Kramer Shear Force (kg/g)	7	6.42	6.55	6.88	7.00	0.355	0.770	0.287	0.182
	14	6.86	7.36	6.68	7.09	0.355	0.241	0.686	0.583

[a] Only 5 of the 6 sites are represented in the ultimate pH values presented.

2. Summary of Tom Individual Effectiveness Study Sites

Toms – Study Site T4V060621

Seven hundred four (704) Hybrid Converter finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 3, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V060621. The live phase for this study site was HMS Veterinary Development, Tulare, CA (Dr. Terry TerHune, Investigator). The facility was an open-sided naturally ventilated barn with solid concrete floors and supplemental mechanical ventilation (as needed). A single barn was used with 72 available pens; animals were allotted to 64 pens. There were 11 animals/pen and the usable pen space was 3.97 m^2 (0.36 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 85.2 to 91.7º F (29.58 to 33.14º C) and mean daily low temperatures ranged from 67.0 to 67.5º F (19.47 to 19.73º C). Relative daily high humidity ranged from 67.69 to 83.63 % and relative daily low humidity ranged from 33.62 to 41.52%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, all animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 3. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V060621

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.074 (0.020)	0.086 (0.018)	0.079 (0.037)	0.096 (0.028)
	14	0.096 (0.024)	0.111 (0.015)	0.116 (0.016)	0.115 (0.017)
Gain Efficiency (G/F)	7	0.158 (0.037)	0.180 (0.036)	0.173 (0.075)	0.211 (0.048)
	14	0.192 (0.040)	0.229 (0.026)	0.233 (0.042)	0.235 (0.027)
Average Daily Feed Intake (kg/d)	7	0.469 (0.027)	0.478 (0.036)	0.442 (0.035)	0.451 (0.033)
	14	0.497 (0.038)	0.486 (0.020)	0.503 (0.049)	0.489 (0.033)

[1]Means are arithmetic means

Toms – Study Site T4V080625

Five hundred seventy-six (576) Hybrid Converter finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 4, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V080625. The live phase for this study site was Colorado Quality Research, Wellington, CO (Dr. Stephen Davis, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of two rooms with 48 available pens in each room.

Animals were allotted to 32 pens per room (64 pens total). There were 9 animals/pen and the usable pen space was 3.41 m^2 (0.38 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 68.4 to 70º F (20.20 to 20.87º C) and mean daily low temperatures ranged from 62.4 to 64.5º F (16.99 to 18.08º C). Relative daily high humidity ranged from 53.50 to 55.45 % and relative daily low humidity ranged from 29.26 to 30.04%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, all animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 4. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V080625

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.097 (0.017)	0.085 (0.022)	0.077 (0.014)	0.102 (0.015)
	14	0.086 (0.020)	0.095 (0.015)	0.086 (0.011)	0.103 (0.014)
Gain Efficiency (G/F)	7	0.212 (0.031)	0.183 (0.040)	0.175 (0.028)	0.216 (0.025)
	14	0.189 (0.030)	0.204 (0.029)	0.194 (0.027)	0.219 (0.022)
Average Daily Feed Intake (kg/d)	7	0.460 (0.024)	0.460 (0.037)	0.438 (0.034)	0.471 (0.033)
	14	0.452 (0.037)	0.464 (0.030)	0.444 (0.012)	0.471 (0.025)

[1]Means are arithmetic means

Toms – Study Site T4V180623

Five hundred seventy-six (576) Nicholas 88 finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 5, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V180623. The live phase for this study site was Purdue

University, West Lafayette, IN (Dr. Todd Applegate, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of four rooms with 24 available pens in each room. Animals were allotted to 16 pens per room (64 pens total). There were 9 animals/pen and the usable pen space was 3.36 m^2 (0.37 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 64.4 to 68º F (18.02 to 20.00º C) and mean daily low temperatures ranged from 60.7 to 65º F (15.93 to 18.32º C). Relative daily high humidity ranged from 64.81 to 72.53 % and relative daily low humidity ranged from 49.13 to 55.01%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, all animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 5. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V180623

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.183 (0.026)	0.184 (0.034)	0.195 (0.023)	0.165 (0.078)
	14	0.156 (0.023)	0.161 (0.019)	0.207 (0.066)	0.164 (0.032)
Gain Efficiency (G/F)	7	0.263 (0.030)	0.267 (0.035)	0.281 (0.029)	0.239 (0.112)
	14	0.226 (0.027)	0.234 (0.029)	0.297 (0.084)	0.239 (0.037)
Average Daily Feed Intake (kg/d)	7	0.695 (0.040)	0.685 (0.051)	0.693 (0.056)	0.693 (0.041)
	14	0.689 (0.051)	0.691 (0.027)	0.691 (0.038)	0.683 (0.053)

[1]Means are arithmetic means

Toms – Study Site T4V270624

Five hundred twenty-eight (528) Hybrid Converter finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 6, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V270624. The live phase for this study site was University of Minnesota, St. Paul, MN (Dr. Sally Noll, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of two rooms with 50 available pens in each room. Animals were allotted to 24 pens per room (48 pens total). There were 11 animals/pen and the usable pen space was 4.18 m^2 (0.38 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 87.2 to 88º F (30.68 to 31.11º C) and mean daily low temperatures ranged from 71.5 to 72.4º F (21.95 to 22.45º C). Relative daily high humidity ranged from 75.22 to 76.35 % and relative daily low humidity ranged from 45.40 to 48.55%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, the preselected animals for the breast quality evaluation (n= 48) and those for the scheduled necropsies (n=16) were manually loaded and transported in a livestock trailer for at least 4 hours.

After transport, the animals were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 6. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V270624

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.105 (0.024)	0.123 (0.029)	0.132 (0.034)	0.107 (0.043)
	14	0.146 (0.082)	0.132 (0.020)	0.125 (0.019)	0.139 (0.023)
Gain Efficiency (G/F)	7	0.229 (0.049)	0.268 (0.057)	0.282 (0.065)	0.236 (0.086)
	14	0.308 (0.174)	0.275 (0.029)	0.266 (0.029)	0.291 (0.030)
Average Daily Feed Intake (kg/d)	7	0.456 (0.016)	0.455 (0.025)	0.464 (0.026)	0.447 (0.031)
	14	0.474 (0.031)	0.478 (0.029)	0.466 (0.021)	0.477 (0.031)

[1]Means are arithmetic means

Toms – Study Site T4V370620

Seven hundred four (704) Nicholas 700 finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 7, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V370620. The live phase for this study site was Diamond K Research, Marshville, NC, (Dr. Kenneth Krueger, Investigator). The facility was a curtain-sided, naturally ventilated barn with solid concrete floors, and supplemental mechanical ventilation (as needed). The barn consisted of two rooms with 32 available pens in each room. Animals were allotted to 32 pens per room (64 pens total). There were 11 animals/pen and the usable pen space was 4.23 m^2 (0.38 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 80.6 to 80.7º F (26.99 to 27.05^o C) and mean daily low temperatures ranged from 59.6 to 61.3º F (15.35 to 16.29^o C). Relative daily high humidity ranged from 78.43 to 81.67 % and relative daily low humidity ranged from 39.72 to 40.22%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, animals were commingled and loaded by block using a tractor that with a loader and box and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 7. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4V370620

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.094 (0.043)	0.108 (0.056)	0.100 (0.014)	0.106 (0.006)
	14	0.091 (0.036)	0.110 (0.013)	0.112 (0.014)	0.116 (0.011)
Gain Efficiency (G/F)	7	0.174 (0.085)	0.190 (0.095)	0.177 (0.025)	0.195 (0.022)
	14	0.170 (0.059)	0.189 (0.019)	0.209 (0.023)	0.215 (0.016)
Average Daily Feed Intake (kg/d)	7	0.547 (0.020)	0.569 (0.029)	0.566 (0.037)	0.549 (0.049)
	14	0.531 (0.036)	0.583 (0.029)	0.538 (0.024)	0.540 (0.022)

[1]Means are arithmetic means

Toms – Study Site T4VCA0622

Eight hundred sixteen (816) Nicholas 88 finishing tom turkeys were evaluated at this study site. Arithmetic means for the claim variables and feed intake are presented in Table 8, Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4VCA0622. The live phase for this study site was Nutreco, Ontario, Canada (Dr. Heather Bruce, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of one room with 48 available pens. Animals were allotted to the 48 pens and there were 17 animals/pen. The usable pen space was 6.38 m^2 (0.38 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 79.7 to 80.9 º F (26.51 to 27.17 º C) and mean daily low temperatures ranged from 66.7 to 66.8 ºF (19.28 to 19.33 º C). Relative daily high humidity ranged from 70.73 to 70.81% and relative daily low humidity ranged from 39.08 to 39.53%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 or 13 ppm. After completing ractopamine treatment, animals were manually loaded and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight.

Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 8. Performance of Finishing Tom Turkeys Fed Diets Containing Ractopamine – Study Site T4VCA0622

		Ractopamine (ppm)			
Variables[1]	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.120 (0.009)	0.123 (0.015)	0.134 (0.013)	0.136 (0.012)
	14	0.126 (0.006)	0.139 (0.025)	0.150 (0.012)	0.145 (0.017)
Gain Efficiency (G/F)	7	0.239 (0.020)	0.232 (0.021)	0.246 (0.020)	0.262 (0.019)
	14	0.238 (0.010)	0.258 (0.031)	0.289 (0.021)	0.279 (0.017)
Average Daily Feed Intake (kg/d)	7	0.503 (0.029)	0.530 (0.019)	0.544 (0.023)	0.518 (0.016)
	14	0.531 (0.014)	0.537 (0.039)	0.520 (0.023)	0.520 (0.031)

[1]Means are arithmetic means

3. Summary of Pooled Hen Effectiveness Study Sites

Hens

A single clinical effectiveness study was conducted at six sites. The study sites were located in five different geographic locations, representing the major turkey producing regions in the United States and one in Canada. In addition, breast meat samples were collected and shipped from all study sites to a single laboratory for Kramer Shear Force evaluation. Three study sites used the Hybrid Converter finishing hen turkeys and three sites used either Nicholas 88 or Nicholas 700 finishing hen turkeys.

The effectiveness study design employed at each study site was a randomized complete block design with pen location as the blocking factor. The treatment structure was factorial in nature with two factors (2 x 4 complete factorial in each block): RAC concentration and Duration. There were four ractopamine concentrations and two durations. Animals were fed ractopamine concentrations of 0, 5, 9 or 13 ppm for either 7 or 14 days using an industry standard diet (0.96% lysine). Birds were either 15 weeks ($\pm$ 3 days) of age or 16 weeks ($\pm$ 3 days) of age at the initiation of the treatment phase for the 14 day or 7 day duration, respectively. Initial weights were measured at treatment initiation and final weights were measured at the end of the treatment period. Feed offered and remaining in the feeders at the end of

the medicated treatment period was recorded. Pens at each site contained 14 to 29 animals to achieve an animal density of approximately 0.223 m^2 (2.4 ft^2) per hen.

At five of the six study sites, all animals were loaded and transported for a minimum of 4 hours. At the sixth study site, only animals selected for necropsy and breast meat quality evaluation were transported. Forty-eight birds at each site were pre-selected for breast meat quality evaluation which included Minolta L* Color score and ultimate pH measurements taken from turkey breast meat that had been chilled overnight. Breast meat samples were also sent to Iowa State University for Kramer shear force evaluation. Sixteen birds were randomly pre-selected at each site for necropsy and appropriate tissues were collected by a board-certified veterinary pathologist for histological evaluation.

Data Analysis Summary

Data from the six study sites were pooled and analyzed. Results were calculated for each variable on a pen basis. The claim variables of Average Daily Gain and Gain Efficiency were analyzed using a linear mixed model, Proc Mixed SAS®, version 9.1. Fixed effects for the mixed model analysis were RAC, Duration, and RAC x Duration, and random effects of Site, Block (Site), Site x RAC and Site x Duration. Linear contrasts were used to compare the non-zero concentrations of RAC to controls and to each other within Duration.

Initial animal body weights were not different, so no covariate adjustment was made for the claim variables. A test of heterogeneity of variance among sites and among blocks within sites was conducted. Residual heterogeneity was detected ($P < 0.001$), but no random heterogeneity was detected, for Average Daily Gain (ADG; no P-value generated) and Gain Efficiency (G:F; $P = 0.180$) (claim variables).

Pooled Hen Effectiveness Results

ADG and G:F were improved ($P < 0.001$; Table 3) for animals fed a diet containing a non-zero concentration of RAC for both 7 and 14 days, when compared to controls. As RAC fed at the 5 ppm concentration was the smallest non-zero dose different from control, 5 ppm RAC was identified as the minimum effective dose for both the 7 and 14 day duration.

In addition to the contrasts comparing each non-zero dose of RAC to control, contrasts were conducted to determine an appropriate dose response model. A linear dose model from 0 to 13 ppm was significant for both durations ($P < 0.001$) and both ADG and G:F ($P <0 .001$). Additional contrasts between the non-zero doses supported the linear response. Therefore, the dosage range for both Average Daily Gain and Gain Efficiency for animals fed 7 or 14 days was determined to be 5 to 13 ppm RAC.

An unweighted mixed model analysis was conducted for Ultimate pH (Table 4) and linear contrasts showed no differences ($P \geq 0.092$) for animals fed a diet containing 5

ppm or 9 ppm RAC for 7 days or a non-zero concentration of RAC for 14 days when compared to controls. In contrast, animals fed a diet containing 13 ppm RAC for 7 days had increased (P = 0.003) Ultimate pH measures when compared to controls. However, the range of Ultimate pH values observed in this study demonstrated acceptable pH values. Therefore, RAC did not negatively impact pH values.

An unweighted mixed model analysis was conducted for Minolta L* Color (Table 4) and linear contrasts showed no differences ($P \geq 0.127$) for animals fed a diet containing a non-zero concentration of RAC for 7 days or 5 ppm or 9 ppm RAC for 14 days when compared to controls. However, animals fed a diet containing 13 ppm RAC for 14 days had lower (P = 0.024) Minolta L* Color measures when compared to controls. For the range of Minolta L* values, all scores demonstrate acceptable color. Therefore, RAC did not negatively impact color.

An unweighted mixed model analysis was conducted for Kramer Shear Force (Table 4) and linear contrasts showed no RAC differences in Kramer Shear Force ($P \geq 0.120$) for animals fed 5 ppm or 9 ppm RAC for 7 days or any non-zero concentration of RAC for 14 days when compared to controls. However, animals fed a diet containing 13 ppm RAC for 7 days had higher (P = 0.043) Kramer Shear Force measures when compared to controls. All of the observed shear force values appear to be within an acceptable range based on an acceptable range established in chickens. However, users should be aware that use of the 13 ppm treatment for 7 days results in higher Kramer Shear Force values.

Table 9. Pooled Analysis – Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine: Primary Claim Variables

		Ractopamine (ppm)					P-value		
Variables	Duration	0	5	9	13	SE	0 vs. 5	0 vs. 9	0 vs. 13
Average Daily Gain (kg/d)	7	0.090	0.105	0.109	0.111	0.005	<0.001	<0.001	<0.001
	14	0.100	0.111	0.117	0.123	0.005	<0.001	<0.001	<0.001
Gain Efficiency	7	0.241	0.276	0.283	0.290	0.005	<0.001	<0.001	<0.001
	14	0.259	0.285	0.300	0.316	0.005	<0.001	<0.001	<0.001

Table 10. Pooled Analysis – Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine: Breast Meat Quality Evaluation

		Ractopamine (ppm)				SE	P-value		
Variables	Duration	0	5	9	13		0 vs 5	0 vs 9	0 vs 13
Ultimate pH	7	5.777	5.790	5.780	5.839	0.058	0.521	0.880	0.003
	14	5.777	5.806	5.812	5.786	0.058	0.165	0.092	0.682
Minolta L*	7	56.91	56.42	56.48	56.67	0.687	0.360	0.421	0.647
	14	57.09	56.45	56.27	55.87	0.687	0.229	0.127	0.024
Kramer Shear Force (kg/g)	7	6.800	7.175	7.176	7.601	0.458	0.339	0.338	0.043
	14	7.000	7.026	6.995	6.388	0.458	0.947	0.991	0.120

Pooled Hen Effectiveness Conclusions

Ractopamine fed at concentrations of 5, 9, and 13 ppm improved ADG and feed efficiency in a linear fashion above control levels. Feeding levels of 5, 9 and 13 ppm of RAC did not negatively impact the carcass quality measures of pH, Kramer Shear Force, and Minolta L* color values.

4. Summary of Individual Hen Effectiveness Study Sites

Hens – Study Site T4V060701

Eight hundred sixty-four (864) Hybrid Converter finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 11, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V060701. The live phase for this study site was HMS Veterinary Development, Tulare, CA (Dr. Terry TerHune, Investigator). The facility was an open-sided naturally ventilated barn with solid concrete floors and supplemental mechanical ventilation (as needed). A single barn was used with 72 available pens; animals were allotted to 48 pens. There were 18 animals/pen and usable pen space was 3.97 m^2 (0.22 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 75.1 to 76.1^{o} F (23.96 to 24.54^{o} C) and mean daily low temperatures ranged from 54.4 to 55.7^{o} F (12.43 to 13.15^{o} C). Relative daily high humidity ranged from 70.39 to 73.65% and relative daily low humidity ranged from 35.65 to 36.81%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

After transport, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 11. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V060701

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.095 (0.009)	0.114 (0.006)	0.114 (0.007)	0.123 (0.006)
	14	0.109 (0.004)	0.124 (0.003)	0.127 (0.005)	0.137 (0.007)
Gain Efficiency (G/F)	7	0.245 (0.019)	0.283 (0.010)	0.286 (0.020)	0.296 (0.027)
	14	0.266 (0.008)	0.295 (0.012)	0.302 (0.006)	0.323 (0.016)
Average Daily Feed Intake (kg/d)	7	0.388 (0.016)	0.404 (0.015)	0.398 (0.016)	0.419 (0.031)
	14	0.408 (0.014)	0.422 (0.019)	0.421 (0.016)	0.425 (0.014)

Hens – Study Site T4V080704

Seven hundred twenty (720) Hybrid Converter finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 12, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V080704. The live phase for this study site was Colorado Quality Research, Wellington, CO (Dr. Stephen Davis, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of one room with 48 available pens and animals

were allotted to the 48 pens. There were 15 animals/pen and usable pen space was 3.41 m^2 (0.23 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 69.6 to 70.3^o F (20.91 to 21.29^o C) and mean daily low temperatures ranged from 64.3 to 65.0^o F (17.93 to 18.31^o C). Relative daily high humidity ranged from 61.97 to 62.68 % and relative daily low humidity ranged from 40.27 to 40.93%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 12. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V080704

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.086 (0.007)	0.107 (0.007)	0.110 (0.008)	0.113 (0.010)
	14	0.096 (0.002)	0.106 (0.007)	0.118 (0.006)	0.121 (0.004)
Gain Efficiency (G/F)	7	0.225 (0.024)	0.265 (0.014)	0.268 (0.018)	0.284 (0.014)
	14	0.240 (0.006)	0.272 (0.017)	0.293 (0.017)	0.303 (0.006)
Average Daily Feed Intake (kg/d)	7	0.384 (0.015)	0.406 (0.024)	0.410 (0.015)	0.397 (0.027)
	14	0.400 (0.009)	0.389 (0.010)	0.403 (0.010)	0.399 (0.021)

Hens – Study Site T4V180705

Seven hundred twenty (720) Nicholas 88 finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 13, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V180705. The live phase for this study site was Purdue University, West Lafayette, IN (Dr. Todd Applegate, Investigator). The

facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of four rooms with 24 available pens in each room. Animals were allotted to 16 pens in three of the four rooms (48 pens total). There were 15 animals/pen and usable pen space was 3.36 m^2 (0.22 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 77.0 to 79.7^o F (25.01 to 26.52^o C) and mean daily low temperatures ranged from 66.5 to 68.4^o F (19.17 to 20.24^o C). Relative daily high humidity ranged from 77.89 to 81.60 % and relative daily low humidity ranged from 60.54 to 68.53%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, animals were commingled and loaded by block with a commercial loader and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 13. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V180705

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.094 (0.022)	0.127 (0.017)	0.125 (0.012)	0.130 (0.010)
	14	0.109 (0.021)	0.117 (0.020)	0.133 (0.010)	0.146 (0.008)
Gain Efficiency (G/F)	7	0.232 (0.052)	0.300 (0.040)	0.309 (0.031)	0.318 (0.013)
	14	0.271 (0.042)	0.285 (0.038)	0.321 (0.016)	0.344 (0.013)
Average Daily Feed Intake (kg/d)	7	0.406 (0.016)	0.423 (0.024)	0.406 (0.036)	0.408 (0.026)
	14	0.401 (0.022)	0.409 (0.042)	0.414 (0.021)	0.425 (0.021)

Hens – Study Site T4V270706

Nine hundred twelve (912) Hybrid Converter finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 14, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V270706. The live phase for this study site was University of Minnesota, St. Paul, MN (Dr. Sally Noll, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of one room with 50 available pens. Animals were allotted to 48 pens. There were 19 animals/pen and usable pen space was 4.18 m^2 (0.22 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 81.4 to 81.6^o F (27.43 to 27.55^o C) and mean daily low temperatures ranged from 63.0 to 64.3^o F (17.21 to 17.95^o C). Relative daily high humidity ranged from 62.02 to 62.25% and relative daily low humidity ranged from 38.99 to 40.37%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, a portion of the animals were manually loaded and transported in a livestock trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 14. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V270706

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.088 (0.006)	0.093 (0.007)	0.100 (0.008)	0.095 (0.010)
	14	0.085 (0.008)	0.094 (0.003)	0.100 (0.003)	0.104 (0.006)
Gain Efficiency (G/F)	7	0.263 (0.011)	0.281 (0.022)	0.297 (0.021)	0.280 (0.025)
	14	0.256 (0.022)	0.280 (0.007)	0.292 (0.009)	0.305 (0.014)
Average Daily Feed Intake (kg/d)	7	0.334 (0.012)	0.332 (0.012)	0.337 (0.009)	0.340 (0.015)
	14	0.331 (0.007)	0.337 (0.006)	0.343 (0.017)	0.342 (0.010)

Hens – Study Site T4V370702

Six hundred seventy-two (672) Nicholas 700 finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 15, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V370702. The live phase for this study site was Diamond K Research, Marshville, NC (Dr. Kenneth Krueger, Investigator). The facility was a curtain-sided, naturally ventilated barn with solid concrete floors, and supplemental mechanical ventilation (as needed). The barn consisted of one room with 48 available and animals were allotted to the 48 pens. There were 14 animals/pen and usable pen space was 3.12 m^2 (0.22 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 88.1 to 89.0^o F (31.18 to 31.67^o C) and mean daily low temperatures ranged from 69.33 to 70.52^o F (20.74 to 21.40^o C). Relative daily high humidity ranged from 91.58 to 94.41% and relative daily low humidity ranged from 52.21 to 53.38%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, animals were commingled and loaded by block a tractor that used a loader and box and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight. Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 15. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4V370702

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.082 (0.006)	0.102 (0.015)	0.101 (0.008)	0.099 (0.011)
	14	0.104 (0.004)	0.112 (0.002)	0.113 (0.006)	0.124 (0.004)
Gain Efficiency (G/F)	7	0.228 (0.020)	0.265 (0.033)	0.260 (0.037)	0.268 (0.034)
	14	0.272 (0.013)	0.275 (0.033)	0.299 (0.024)	0.323 (0.019)
Average Daily Feed Intake (kg/d)	7	0.359 (0.018)	0.387 (0.063)	0.396 (0.074)	0.373 (0.057)
	14	0.383 (0.020)	0.413 (0.049)	0.378 (0.018)	0.386 (0.017)

Hens – Study Site T4VCA0703

One thousand three hundred ninety-two (1392) Nicholas 88 finishing hen turkeys were evaluated at this study site. Arithmetic means and standard deviations for the claim variables and feed intake are presented in Table 16, Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4VCA0703. The live phase for this study site was Nutreco Ag Research - Canada, Ontario, Canada (Dr. Heather Bruce, Investigator). The facility was a totally enclosed, mechanically ventilated building with solid concrete floors consisting of one room with 48 available pens. Animals were allotted to 48 pens and there were 29 animals/pen and usable pen space was 6.38 m^2 (0.22 m^2/animal).

Temperature monitoring in the barns indicated that the mean daily high temperature ranged from 80.0 to 81.8^o F (26.67 to 27.64^o C) and mean daily low temperatures ranged from 67.7 to 67.9^o F (19.82 to 19.93^o C). Relative daily high humidity ranged from 79.52 to 80.05% and relative daily low humidity ranged from 54.75 to 56.15%.

Animals were fed ractopamine for either 7 or 14 days at concentrations of 0, 5, 9 and 13 ppm. After completing ractopamine treatment, animals manually loaded and transported in a commercial trailer for at least 4 hours.

Upon completion of transportation, the animals that were pre-selected for breast meat quality evaluation (n=48) or necropsy (n=16) were euthanized. Minolta L* Color score and pH measurements were taken from turkey breast meat chilled overnight.

Breast meat samples were sent to Iowa State University for Kramer shear force evaluation.

Table 16. Performance of Finishing Hen Turkeys Fed Diets Containing Ractopamine – Study Site T4VCA0703

		Ractopamine (ppm)			
Variables	Duration	0 (SD)	5 (SD)	9 (SD)	13 (SD)
Average Daily Gain (kg/d)	7	0.090 (0.015)	0.093 (0.009)	0.104 (0.011)	0.106 (0.009)
	14	0.096 (0.007)	0.108 (0.006)	0.112 (0.006)	0.113 (0.008)
Gain Efficiency (G/F)	7	0.242 (0.040)	0.267 (0.028)	0.287 (0.027)	0.294 (0.023)
	14	0.258 (0.021)	0.290 (0.011)	0.301 (0.010)	0.311 (0.009)
Average Daily Feed Intake (kg/d)	7	0.378 (0.070)	0.350 (0.015)	0.363 (0.014)	0.362 (0.028)
	14	0.374 (0.013)	0.373 (0.018)	0.374 (0.011)	0.363 (0.023)

III. TARGET ANIMAL SAFETY:

For each gender, target animal safety was determined using data from two studies, a non-clinical laboratory study and a clinical field study. Observations with a significance level of $P<0.10$ were further examined to determine potential animal safety concerns.

A. Pivotal Study – Toms – Study Number T4V060518

Study Title: Non-Clinical Laboratory Study (GLP): Safety Evaluation of Ractopamine in Finishing Tom Turkeys.

a. Type of Study:
GLP-Target Animal Safety Study

b. Study Director:
T.N. TerHune, DVM, PhD, HMS Veterinary Services, Inc, Tulare, CA

c. General Design:

1. Purpose:

To determine the toxicity, if any, associated with feeding ractopamine hydrochloride (RAC) at 10X the maximum proposed dose to Nicholas and Hybrid finishing tom turkeys during the final 14 days of the growing-finishing period.

2. Experimental Design:

The design of this study was a randomized complete block. The study consisted of eight blocks with six pens per block. Each block included three contiguous pens for each of the two strains. For each strain within a block, each of the three treatment groups (0, 13, and 130 ppm RAC) was represented by one pen. There were a total of 48 pens. There were eight pen replications for each Strain X RAC combination with eight animals per pen during the Treatment Phase of the study.

3. Animals:

192 Nicholas 85 and 192 Hybrid Converter finishing tom turkeys, 20 weeks of age.

4. Experimental Unit:

Pen was the experimental unit.

5. Control

Control animals were fed the same basal diet as treated animals, but it did not contain RAC.

6. Dosage Form:

Type A Medicated Feed containing 9 g/lb RAC was used to make a Type C Medicated feed containing 13 or 130 ppm RAC.

7. Dosages:

0, 13, and 130 ppm RAC

8. Route of Administration:

Oral, *ad libitum*

9. Study Durations:

RAC was fed for 14 days

10. Pertinent Measurements/Observations:

Clinical observations, adverse events, body weight, feed consumption, blood chemistry, coagulation and hematological measurements, bone strength measurements, and gross necropsy/histopathology

d. Data Analysis Summary

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

e. Results Summary

No abnormal health concerns were identified.

Average Daily Feed Intake was reduced in the 130 ppm group from 0.61 to 0.58 kg/animal/day (P=0.016) compared to controls without a difference in average daily gain (P=0.104) or final weight (P=0.104).

The treatment-related effects associated with muscle were: an increase in the number of animals with mononuclear cell infiltrate and myofiber degeneration (Tables 17 and 18) and an increase in the concentration of serum creatine kinase (Table 19). Feeding RAC at 13 or 130 ppm to Hybrid finishing tom turkeys during the final 14 days of the production cycle (i.e., slaughter) was associated with an increase in the number of animals with microscopic muscle alterations. The muscle lesions were of the type reported in clinically normal populations of rapidly growing turkeys. They did not cause any apparent clinical signs (mobility or postural), the muscle was grossly normal, and the alterations were minimal in severity, affecting approximately less than 1% of muscle fibers within a given section.

Table 17. Number of Animals with Myofiber Degeneration and Mononuclear Cell Infiltrates in Hybrid Converter Toms

Ractopamine Concentration in Feed:	**0 ppm**	**13 ppm**	**130 ppm**
n:	**16**	**16**	**16**
Skeletal Muscle, pectoralis major:			
Degeneration, myofiber	6 (38%)	11* (69%)	13* (81%)
Infiltrate, mononuclear cell	6 (38%)	13* (81%)	14* (88%)
Skeletal Muscle, quadriceps femoris:			
Degeneration, myofiber	7 (44%)	8 (50%)	11 (69%)
Infiltrate, mononuclear cell	8 (50%)	12 (75%)	13* (81%)

*Significantly different from control ($P \leq 0.10$)

The number in parenthesis represents percentage of total

Table 18. Number of Animals with Myofiber Degeneration and Mononuclear Cell Infiltrates in Nicholas 85 Toms

Ractopamine Concentration in Feed:	**0 ppm**	**13 ppm**	**130 ppm**
n:	**16**	**16**	**16**
Skeletal Muscle, pectoralis major:			
Degeneration, myofiber	9 (56%)	7 (44%)	6 (38%)
Infiltrate, mononuclear cell	12 (75%)	7 (44%)*	8 (50%)
Skeletal Muscle, quadriceps femoris:			
Degeneration, myofiber	3 (19%)	7 (44%)	5 (31%)
Infiltrate, mononuclear cell	7 (44%)	11 (69%)	7 (44%)

*Significantly different from control ($P \leq 0.10$).

The number in parenthesis represents percentage of total

Additional clinical chemistry, coagulation and hematology variable differences were detected between treatment groups but were considered clinically insignificant because they did not correlate to any gross pathologic or histopathologic findings (Table 19). These differences were within the normal reference range or were of such small magnitude that they were negligible. Therefore, the differences between treatments were considered incidental.

Table 19. Summary of Statistically Significant Clinical Chemistry, Coagulation and Hematology Variables

Variable		Hybrid 13 ppm	Hybrid 130 ppm	Nicholas 13 ppm	Nicholas 130 ppm	Reference Range
Albumin (g/dL)	Compared to Control	- 1.51	- 1.41			1.2 – 2.4
Phosphorus (mg/dL)	Compared to Control		+ ***5.63***	+ 5.14	+ ***5.5***	3.3 – 5.3
Lactic Acid (mmol/L)	Compared to Control				+ 5.71	3.0 – 8.9
Total Protein (g/dL)	Compared to Control	- 3.31	- 3.20			2.5 – 5.2
Creatinine (mg/dL)	Compared to Control		- 0.39			0.3 – 0.7
Creatine Kinase (U/L)	Compared to Control		+ 94,266		+ 79,665	Reference range not established
Glucose (mg/dL)	Compared to Control		- 245.4		- 246.4	211 - 320
Globulin (mg/dL)	Compared to Control	- 1.79	- 1.79			1.3 – 2.8
Aspartate Aminotransferase (U/L)	Compared to Control		+ ***1732***		+ ***1675***	660 - 1588
Alanine Amino-transferase (U/L)	Compared to Control	+ 18.40	+ ***23.45***		+ ***21.97***	7 - 21
Bicarbonate (mmol/L)	Compared to Control				- ***32.29***	17 - 32
Prothrombin Time (sec)	Compared to Control		- 71.50			47.7 – 93.7
Partial Thromboplastin Time (sec)	Compared to Control		- 81.84			54.7 – 220.6

Packed Cell Volume (%)	Compared to Control			+ 44.51	38.6 – 47.7
White Blood Cell ($x10^3$ µL)	Compared to Control	- 20.71			11.7 – 44.9
WBC Differential Heterophil ($x10^3$ µL)	Compared to Control		+ 12.63	+ 13.50	5.4 – 29.1
WBC Differential % Heterophil (%)	Compared to Control		+ 61.73		+ 59.90	Reference range not established
WBC Differential Lymphocyte ($x10^3$ µL)	Compared to Control	- 7.22	- 6.02			1.16 – 14.5
WBC Differential % Lymphocyte (%)	Compared to Control		- 27.53			Reference range not established
Hemoglobin (g/dL)	Compared to Control	+ 12.38				9.7 – 13.1

Note: Bold and italicized values indicate the LS Mean value was out of the reference range. A "+" indicates the LS Mean value was greater compared to control, and the "-" indicates the LS Mean value was lower compared to control. Shaded cells indicate LS Means were not significantly different from control.

The source of reference values were values from healthy animals obtained at:

- Iowa State University (hematology variables except hemoglobin)
- Purdue University (hemoglobin)
- Physicians Reference Laboratory (serum chemistry and coagulation variables)

Additionally, differences were detected between treatments for some organ weights. Heart weight differences were detected, ($P \leq 0.046$), for Hybrid birds receiving RAC at 13 ppm, and Nicholas birds receiving RAC at 130 ppm, as compared to control. A smaller average kidney weight was detected ($P = 0.056$) for Nicholas birds receiving 130 ppm RAC compared to controls. A heart weight as a percent of final body weight difference was detected ($P = 0.014$) for Hybrid birds receiving RAC at 130 ppm compared to controls. A kidney weight as a percent of final body weight difference was detected ($P \leq 0.013$) for birds receiving 130 ppm RAC compared to controls for both strains. However, the magnitude of the organ weight differences was small and there were no micro- or macroscopic observations or clinical chemistry results associated with these weight differences. Therefore, the differences in organ weights were considered incidental.

Table 20. Organ Weight Variables with Significant Differences*

	Ractopamine (ppm)			P values		Strain
	0	**13**	**130**	**0 vs. 13**	**0 vs. 130**	
Heart Weight (g)	77.63	80.25	83.44	0.341	**0.040**	Nicholas
Heart Weight (g)	80.50	84.63	81.41	**0.039**	0.640	Combined
Heart weight (g)	83.38	89.00	79.38	**0.046**	0.150	Hybrid
Heart weight as % of body weight	0.40	0.42	0.37	0.114	**0.014**	Hybrid
Kidney weight (g)	70.53	71.19	65.78	0.726	**0.015**	Combined
Kidney weight (g)	71.31	71.75	66.13	0.869	**0.056**	Nicholas
Kidney weight as % of body weight	0.33	0.33	0.30	0.961	**0.013**	Hybrid
Kidney weight as % of body weight	0.34	0.34	0.31	0.768	**<.001**	Combined
Kidney weight as % of body weight	0.35	0.34	0.31	0.713	**0.006**	Nicholas

*Bold P values indicate significantly different LS Means ($P \leq 0.10$)

f. Conclusions

Feeding ractopamine hydrochloride up to 130 ppm to finishing tom turkeys during the final 14 days of the finishing period is safe under the conditions set forth in this study.

B. Multiple Location Field Effectiveness Study – Toms – Study Numbers T4V060621, T4V080625, T4V180623, T4V270624, T4V370620, and T4VCA0622

Study Title: Clinical Study (GCP): The Effectiveness of Ractopamine Hydrochloride on Growth Performance in Finishing Turkeys Fed for the Last 7 to 14 Days Prior to Slaughter – Toms

a. Design

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

b. Health Observations

Daily health observations were recorded for each pen of animals during the treatment phase. Additionally, animals were observed for moribundity and mortality during the loading and unloading of the transportation phase. Gross necropsy and histopathology were also examined on a subset of animals (16 per study site for the total of 96 per entire study).

c. Results Summary

In the combined durations (7 and 14 days), the total number of animals that died or were culled in this study was increased in the 9 ppm group (P=0.038) compared to the controls. When evaluated individually, only the number of deaths was increased in the 9 ppm group (P = 0.049) compared to controls, but not the number of culled animals (P = 0.563). The increase in removals (culls and deaths) was influenced by study site (T4V060621) which experienced a period of extreme heat during the course of the study, see Table 21. At this study site, internal barn temperatures exceeded 29.50°C (85°F) for 8 days on the north side of the barn and all 14 days of the treatment phase on the south side of the barn. The highest measured internal barn temperature was 38.97°C (102°F). In addition, the external temperatures reached 43.9°C (111°F). Analysis of the data from five sites (excluding the site T4V060621) demonstrated no statistically significant differences among treatments for the number of culled/dead in the combined medicated period and transportation phase. In conclusion, the significant increase in the removal rate (deaths and culls) for the study appears to be due to the period of excessive heat at study site T4V060621. Therefore, feeding RAC to turkeys under environmental conditions of excessive heat resulted in increased mortality.

Table 21. Number of Removed Animals (Found Dead and Culled) during Medicated Period and Transportation Phase in the Effectiveness study, Combined Duration

	Ractopamine (ppm)				**Total**
Study Site	**0**	**5**	**9**	**13**	
T4V080625	4	2	9	1	16
T4V180623	2	3	3	4	12
T4V270624	1	4	5	2	12
T4V370620	4	0	0	2	6
T4VCA0622	1	1	2	4	8
Total for 5 Sites (T4V060621 Excluded)	12	10	19	13	54
T4V060621	7	6	12	15	40
Total for all 6 Sites (T4V060621 Included)*	19	16	31**	28	94

* Overall effect (P=0.240)

**Significantly different from control P=0.038

No differences were observed in the number of animals with gross findings for any of the tissues examined during the Scheduled Necropsies from animals fed a diet containing a non-zero concentration of RAC for 14 days when compared to controls ($P \geq 0.145$).

The only differences in organ weights of tom turkeys in the combined analysis of both strains were increased absolute and relative (to total body weight) kidney weights in treated groups compared to controls, and increased liver weight. However, these differences were biologically negligible. No significant macro- or microscopic findings were found in any of these organs and, therefore, these differences were not considered a health concern.

Another observation was an increase in the incidence of cysts on the bursa of Fabricius in the 14 day feeding duration group for the 5 ppm RAC, 9 ppm RAC, and the combined non-zero RAC treatment groups compared to controls ($P \leq 0.060$). Based on the other variables analyzed in both the safety and effectiveness studies, these cysts were not associated with any disease or toxicity and were not considered a health concern.

d. Conclusions from the Effectiveness Study

This multi-location field effectiveness study demonstrated that ractopamine hydrochloride when fed at concentrations of up to 13 ppm in the diet to finishing tom turkeys at internal barn temperatures of up to 29.5°C (85°F) is clinically safe. However, the use of RAC in tom turkeys during periods of excessive heat (i.e. internal barn temperatures above 29.5°C (85°F) for multiple days) can result in increased mortality.

C. Pivotal Study – Hens – Study Number T4V060519

Study Title: Non-Clinical Laboratory Study (GLP): Safety Evaluation of Ractopamine in Finishing Hen Turkeys.

a. Type of Study:
GLP-Target Animal Safety Study

b. Study Director:
T.N. TerHune, DVM, PhD, HMS Veterinary Services, Inc, Tulare, CA

c. General Design:

1. Purpose:

To determine the toxicity, if any, associated with feeding ractopamine hydrochloride (RAC) at 10X the maximum proposed dose to Nicholas and Hybrid finishing hen turkeys during the final 14 days of the growing-finishing period.

2. Experimental Design:

The design of this study was a randomized complete block. The study consisted of eight blocks with six pens per block. Each block included three

contiguous pens for each of the two strains. For each strain within a block, each of the three treatment groups (0, 13, and 130 ppm RAC) was represented by one pen. There were a total of 48 pens. There were eight pen replications for each Strain X RAC combination with eight animals per pen during the Treatment Phase of the study.

3. Animals:
192 Nicholas 85 and 192 Hybrid Converter finishing hen turkeys, 15 weeks of age.

4. Experimental Unit:
Pen was the experimental unit.

5. Control
Control animals were fed the same basal diet as treated animals, but it did not contain RAC.

6. Dosage Form:
Type A Medicated Feed containing 9 g/lb RAC was used to make a Type C Medicated feed containing 13 or 130 ppm RAC.

7. Dosages:
0, 13, and 130 ppm RAC

8. Route of Administration:
Oral, *ad libitum*

9. Study Durations:
RAC was fed for 14 days

10. Pertinent Measurements/Observations:
Clinical observations, adverse events, body weight, feed consumption, blood chemistry, coagulation and hematological measurements, bone strength measurements, and gross necropsy/histopathology

d. Data Analysis Summary

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

e. Results Summary

No abnormal health concerns were identified.

The treatment-related effects associated with muscle were: an increase in the number of animals with mononuclear cell infiltrate and myofiber degeneration (Tables 22 and 23) and an increase in the concentration of serum creatine kinase (Table 24). Additionally, feeding RAC at 13 or 130 ppm to Hybrid finishing hen turkeys was associated with an increase in the number of animals with microscopic muscle alterations. The muscle lesions were of the type reported in clinically normal populations of rapidly growing turkeys. They did not cause any apparent clinical signs (mobility or postural), the muscle was normal at gross examination, and the microscopic alterations were minimal in severity, affecting approximately less than 1% of muscle fibers within a given section.

Table 22. Number of Animals with Myofiber Degeneration and Mononuclear Cell Infiltrates in Hybrid Converter Hens

Ractopamine Concentration in Feed:	**0 ppm**	**13 ppm**	**130 ppm**
n:	**16**	**16**	**16**
Skeletal Muscle, pectoralis major:			
Degeneration, myofiber	3 (19%)	5 (31%)	9* (56%)
Infiltrate, mononuclear cell	4 (25%)	6 (38%)	9* (56%)
Skeletal Muscle, quadriceps femoris:			
Degeneration, myofiber	6 (38%)	9 (56%)	10 (63%)
Infiltrate, mononuclear cell	10 (63%)	10 (63%)	11 (69%)

*Significantly different from control ($P \leq 0.10$)
The number in parenthesis represents percentage of total

Table 23. Number of Animals with Myofiber Degeneration and Mononuclear Cell Infiltrates in Nicholas 85 Hens

Ractopamine Concentration in Feed:	**0 ppm**	**13 ppm**	**130 ppm**
n:	**16**	**16**	**16**
Skeletal Muscle, pectoralis major:			
Degeneration, myofiber	6 (38%)	4 (25%)	12* (75%)
Infiltrate, mononuclear cell	8 (50%)	4 (25%)	13* (81%)
Skeletal Muscle, quadriceps femoris:			
Degeneration, myofiber	8 (50%)	11 (69%)	14* (88%)
Infiltrate, mononuclear cell	9 (56%)	14* (88%)	15* (94%)

*Significantly different from control ($P \leq 0.10$).The number in parenthesis represents percentage of total

Cysts in the bursa of Fabricius were found in 3, 8, and 10 Nicholas hens from the 0, 13 (P=0.078), and 130 (P=0.021) ppm RAC groups, respectively. However, there were no differences in lymphocyte numbers in blood or in the incidence of infections in this study or in the effectiveness study. For the above reasons, the histological observations in the bursa are not considered a health issue.

Additional clinical chemistry, coagulation and hematology variable differences were detected between treatment groups but were considered clinically insignificant because they did not correlate to any gross pathologic or histopathologic findings (Table 24). Some differences in values, such as those in creatine kinase, glucose, lactic acid, albumin, globulin and total protein, may be a result of higher muscle anabolism, which is the intended action of the drug. The majority of these differences was within the normal reference range or was of such small magnitude that they were considered negligible or incidental. Therefore, treatment differences were not considered a health concern.

Table 24. Summary of Statistically Significant Hen Clinical Chemistry Variables

Variable		Hybrid 13 ppm	Hybrid 130 ppm	Nicholas 13 ppm	Nicholas 130 ppm	Reference Range
Albumin (g/dL)	Compared to Control		- 1.45	- 1.53	- 1.38	1.2 - 2.4
Potassium (mEq/L)	Compared to Control		+ 4.15			3.8 – 6.8
Chloride (mEq/L)	Compared to Control		+ 117.3	+ 116.5	+ 116.1	108 – 132
Sodium (mEq/L)	Compared to Control			+ 156.3		121 – 172
Lactic Acid (mmol/L)	Compared to Control		+ 6.67	+ 6.25		3.0 – 8.9
Total Protein (g/dL)	Compared to Control		- 2.92	- 3.12	- 2.88	2.5 – 5.2
Uric Acid (mg/dL)*	Compared to Control		- ***1.67***		- ***1.91***	4.7 – 9.1
Creatinine (mg/dL)	Compared to Control				- 0.36	0.3 – 0.7
Creatine Kinase (U/L)	Compared to Control				+ 68,675	Reference range not established
Glucose (mg/dL)	Compared to Control		- 260.7		- 261.6	211 – 320
Globulin (mg/dL)	Compared to Control			- 1.59	- 1.49	1.3 – 2.8
Aspartate Amino-transferase (U/L) †	Compared to Control		+ ***939.7***		+ ***1201***	218 – 568
Cholesterol (mg/dL)	Compared to Control		- 108.1	- 116.8	- 102.8	77 – 165
Alanine Amino-transferase (U/L)	Compared to Control		+ 10.29		+ 13.12	7 – 21

Note: Bold and italicized values indicate the LS Mean value was out of the reference range. A "+" indicates the value was greater compared to control, and the "-" indicates the value was lower compared to control. Shaded cells indicate LS Means were not significantly different (P > 0.10) from control.

*All LS mean values for all treatment groups for uric acid were lower than the reference range.

†All LS mean values for all treatment groups for aspartate aminotransferase were greater than the reference range.

The reference values were from Physicians Reference Laboratory

Additionally, differences between treatments were detected for liver weight, both absolute and relative to the body weight (Table 25). Absolute and relative liver weights were lower in Nicholas hens, but these differences were not associated with any macro- or microscopic alteration, or any differences in clinical chemistry variables. In addition, the magnitude of the organ weight differences was small. Therefore, the differences in organ weights were considered not clinically relevant.

Table 25. Organ Weight Variables with Significant Difference

Variable	Ppm RAC			P values		Strain
	0	13	130	0 vs. 13	0 vs. 130	
Liver weight[1]	127.9	118.6	111.6	**0.046**	**<0.001**	Nicholas
	121.3	117.8	111.3	0.279	**0.003**	Combined
Liver weight as % of body weight[2]	1.15	1.11	1.04	0.377	**0.017**	Hybrid
	1.19	1.06	0.96	**0.006**	**<0.001**	Nicholas
	1.17	1.08	1.00	**0.011**	**<0.001**	Combined

[1]Dose effect P=0.011
[2]Dose effect P<0.001

f. Conclusions

Feeding ractopamine hydrochloride up to 130 ppm to finishing hen turkeys during the final 14 days of the finishing period is safe under the conditions set forth in this study.

D. Multiple Location Field Effectiveness Study – Hens – Study Numbers T4V060701, T4V080704, T4V180705, T4V270706, T4V370702, and T4VCA0703

Study Title: Clinical Study (GCP): The Effectiveness of Ractopamine Hydrochloride on Growth Performance in Finishing Turkeys Fed for the Last 7 to 14 Days Prior to Slaughter – Hens

a. Design

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

b. Health Observations

Daily health observations were recorded for each pen of animals during the treatment phase. Additionally, animals were observed for morbidity and mortality during the loading and unloading of the transportation phase. Gross necropsy and histopathology were also examined on a subset of animals (16 per study site for the total of 96 per entire study).

c. Results Summary

No differences were observed in the number of animals with gross findings for any of the tissues examined during the Scheduled Necropsies from animals fed a diet containing a non-zero concentration of RAC for 14 days when compared to controls ($P \geq 0.539$).

Significant differences in organ weights of hen turkeys in the combined analysis of both strains were: lower absolute and relative (to total body weight) kidney weights in treated groups compared to controls, and lower heart weight relative to body weight in treated groups compared to controls. These changes were small and not associated with any macro- or microscopic findings on these organs or clinical chemistry differences and thus do not raise a concern.

d. Conclusions from the Effectiveness Study

This multi-location field effectiveness study demonstrated that ractopamine hydrochloride when fed at concentrations of up to 13 ppm in the diet to finishing hen turkeys is clinically safe.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

Studies to establish an acceptable daily intake (ADI) for humans are summarized in the Freedom of Information Summary for PAYLEAN Type A medicated article for

swine, NADA 140-863, approved December 22, 1999. The ADI for total residues of ractopamine is 1.25 micrograms ractopamine hydrochloride per kilogram of body weight per day. 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.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Study to Establish Steady State

Study Title and Number: "Determination of the Decline of Total Residues and Ractopamine HCl in Liver of Turkeys Fed ^{14}C-Ractopamine HCl," Study T4V739101

Investigators: J. E. Dalidowicz, Ph.D.
T. D. Macy, and
R.L. Cochrane
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

The length of time required for radioactive residues to reach steady state in turkey tissues was determined. The relationship between parent ractopamine (marker residue) and the total radioactive residue was established in the target tissue (liver) so that the total residue in a tissue could be calculated by measuring only the marker residue in turkey liver tissue. Twenty turkeys (10 hens and 10 toms) received ^{14}C-ractopamine hydrochloride in the feed at 20 ppm (1.5x the intended use level) for seven days and groups of four birds (2 hens and 2 toms) were sacrificed at a practical zero-time withdrawal (6 hours) and at 24, 48, 72, and 96-hour withdrawal periods. Additionally, two groups of four birds (2 hens and 2 toms) received ^{14}C- ractopamine hydrochloride in the feed at 20 ppm for 4 and 10 days, respectively, and were sacrificed at a practical zero-time withdrawal (6 hours). After each sacrifice, the ^{14}C-residue concentration in liver, muscle, skin with adhering fat, and abdominal fat and the ractopamine concentrations in liver were determined.

The mean total radioactivity (RA) and the mean concentrations of ractopamine (Ract) in turkey livers after the different withdrawal times, calculated as net ppb of ractopamine, are summarized in the following table:

Table 26. Mean Total Radioactivity (RA) and Mean Concentrations (ppb) of Ractopamine (Ract) in Turkey Livers

	Days Dosed		
Withdrawal	4	7	10

Time (hrs)	RA	Ract	RA	Ract	RA	Ract
6	479	239	681	273	513	190
24			166	72		
48			77	16		
72			99	18		
96			64	13		

Muscle and skin with adhering fat had very low residues (16-18 and 18-22 ppb, respectively) at all feeding periods after a practical zero-time withdrawal. At the same time, abdominal fat did not contain any detectable residues. With the exception of liver, all tissues had no detectable residues at all the other withdrawal times.

Analysis of the practical zero-time withdrawal data showed that steady state residue concentrations were reached in five days in liver, muscle, skin with adhering fat, and abdominal fat.

The amount of ractopamine, as a percentage of total ^{14}C residues, was 40% in liver at zero-time withdrawal following 7 days of feeding ractopamine hydrochloride.

b. Study to Demonstrate Comparative Metabolism

Study Title and Number: "Comparative metabolism of ^{14}C ractopamine HCl in turkeys, dogs, and rats", Study T4V739102

Investigator: J. E. Dalidowicz, Ph.D.
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

The purpose of this study was to compare the metabolism of ractopamine hydrochloride in turkeys, dogs, and rats. Radiochemically equivalent amounts of two lots of ≥98% pure ^{14}C-ractopamine hydrochloride, one uniformly labeled in Ring A, the other uniformly labeled in Ring B, were mixed with unlabeled ractopamine hydrochloride to make the test article for these studies.

Tissue data from rats and dogs are from Study ABC-0369. The description of that study is reported in the FOI for NADA 140-863, PAYLEAN for swine, dated December 22, 1999.

Liver and kidney tissues from the turkeys, dogs, and rats were analyzed by HPLC and scintillation counting.

Figure 1. ^{14}C-Ractopamine Hydrochloride, uniformly labeled in Ring A and uniformly labeled in Ring B

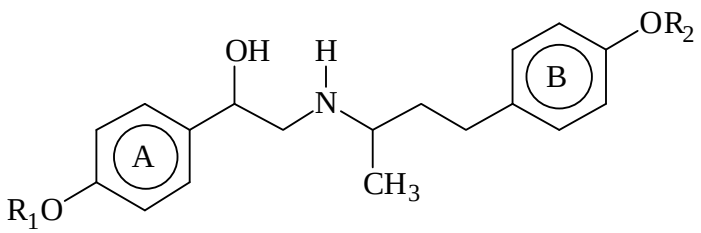

Table 27. Metabolites from HPLC Analysis of Liver and Kidney Tissues from Turkeys

	R_1	R_2	Isomers
Ractopamine	H	H	Mixture
Metabolite A	H	Glucuronide	RS, SR
Metabolite B	H	Glucuronide	RR,SS
Metabolite C	Glucuronide	H	Mixture
Metabolite D	Glucuronide	Glucuronide	Mixture

The mean amounts in ppm of ractopamine and its metabolites (calculated as ractopamine) in liver tissues were:

Table 28. Total Residues of Ractopamine and Metabolites in Liver Tissue from Turkeys, Dogs, and Rats

	Residues in liver (ppm)		
	Turkey	Dog	Rat
Ractopamine	0.22	0.59	0.40
Metabolite A	0.09	0.46	0.17
Metabolite B	0.10	0.77	0.15
Metabolite C	0.02	1.76	0.10
Metabolite D	0.01	0.71	0.17

It was concluded that the dogs and rats used in the toxicological studies were exposed to the same metabolites as those found in the edible tissues of turkeys. The animals chosen for the chronic, subchronic, and acute toxicity studies, therefore, have been exposed to the same metabolites as those found in the edible tissues of turkeys.

c. Study to Demonstrate the Withdrawal Period

Study Title and Number: "Ractopamine Tissue Residue Study in Turkeys," Study T4V699801

Investigators: J. W. Moran and S.C. Fossler
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

This non-radiolabeled tissue residue study was conducted to determine the liver and muscle concentrations when turkeys are fed 13 or 20 ppm ractopamine hydrochloride in the diet. Two groups of Nicholas Cross turkeys were dosed with ractopamine hydrochloride provided in their feed. One group (01) of 12 birds (6 of each gender) had *ad libitum* access to feed containing 13 ppm of ractopamine hydrochloride for seven days. Another group (02) of 6 birds (3 of each gender) had *ad libitum* access to feed containing 20 ppm of ractopamine hydrochloride for seven days. Control birds (00) were a group of 6 birds (3 of each gender) which had *ad libitum* access to basal feed containing no ractopamine hydrochloride for seven days. Birds were sacrificed at a practical zero withdrawal (6 hours after their feed was removed).

Whole liver, minus the gall bladder, and pooled samples of thigh and breast muscle were collected from each bird. All tissues were assayed for ractopamine by HPLC. Mean residues in liver and muscle from birds ingesting ractopamine hydrochloride are presented in the following table. Control birds did not have residues above background.

Table 29. Mean Ractopamine Concentrations (ppb) in Liver and Muscle of Turkeys

				Mean Residues [ppb (range)]	
W/D Time (Days)	Diet Conc. (ppm)	Gender	Number of birds	Liver	Muscle
0	13	Male	6	74.6 (37-139)	2.8 (1.8-5.6)
0	13	Female	6	138.9 (125-155)	4.5 (4.1-4.7)
0	20	Male	3	150.7 (125-191)	5.4 (4.5-6.1)
0	20	Female	3	206.4 (117-300)	6.8 (5.0-9.1)

2. Target Tissue and Marker Residue Assignment

The marker residue is ractopamine and the target tissue is liver.

3. Tolerance Assignments

As indicated in Section IV.B.1a., parent ractopamine is 40% of the total residue in liver. The safe tissue concentration for total residues in liver is 0.75 ppm; therefore the tolerance (R_m) for ractopamine parent in liver could be set at 0.30 ppm (40% of 0.75 ppm). However, after examining the data base for ractopamine, it appeared that an occasional liver sample could contain greater than 0.30 ppm, but, because the drug qualifies for a zero withdrawal period, this

still does not represent a safety issue. To prevent compliance issues having no safety implication, FDA established the tolerance for ractopamine in liver at 0.45 ppm.

The safe concentration for total residues in muscle is 0.25 ppm. In the absence of a direct correlation for ractopamine parent to total residue in muscle, FDA used the conservative value of 40% observed for liver. Therefore, the tolerance for ractopamine parent in muscle is set at 0.10 ppm (40% of 0.25 ppm).

4. Withdrawal Time(s)

The residue data summarized in Section IV.B.1a. and Section IV.B.1c. support the assignment of a zero withdrawal period for the use of up to 13 ppm ractopamine hydrochloride in the diet of turkeys. A statistical analysis of the liver data for the Group 01 birds from the study in Section IV.B.1c. showed that the 99% tolerance limit with 95% confidence was well below the tolerance of 0.45 ppm at zero withdrawal.

C. Microbial Food Safety:

The Agency considered the impact of the use of ractopamine hydrochloride Type A Medicated article in turkeys (5 to 13 ppm in Type C Medicated feed for the last 7 to 14 days prior to slaughter for increased weight gain and improved feed efficiency) on antimicrobial resistance development among bacteria of public health concern. The Agency determined that a microbial food safety assessment was not necessary at this time.

D. Analytical Method for Residues:

1. Determinative Method

The determinative procedure for the analysis of ractopamine residues in turkey tissue consists of extraction of the ractopamine from liver or muscle, and measurement of the parent drug in the extract by high performance liquid chromatography (HPLC) with fluorescence detection.

2. Confirmatory Method

To confirm the identity of ractopamine in tissues, an extract of turkey liver or muscle is prepared according to the determinative procedure. An aliquot of the samples are subjected to analysis by reversed-phase HPLC/ electrospray ionization triple tandem quadrupole mass spectrometry (LC/ESI-MS-MS). The mass spectrometer operating parameters are set to monitor for four structurally specific ions. Chromatographic retention time and ion abundance ratios in extracts are compared with those associated with a ractopamine reference standard and are used to confirm the presence of ractopamine in the extracts.

3. Availability of Method

The methods are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TOPMAX 9:

WARNING: The active ingredient in TOPMAX 9, ractopamine hydrochloride, is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of the reach of children. The TOPMAX 9 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling TOPMAX 9, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse eyes thoroughly with water. If irritation persists, seek medical attention. The material safety data sheet contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

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 TOPMAX 9, when used according to the label, is safe and effective for increased rate of weight gain and improved feed efficiency in finishing tom turkeys fed for the last 14 days prior to slaughter. Additionally, data demonstrate that residues in food products derived from turkeys treated with TOPMAX 9 will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

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:

The sponsor did not submit any patent information with this application.

VI. ATTACHMENTS:

Facsimile Labeling:

Medicated Article Type A Label
Ractopamine Medicated Hen Turkey Feed Type B Medicated Feed
Ractopamine Medicated Tom Turkey Feed Type B Medicated Feed
Ractopamine Medicated Hen Turkey Feed Type C Medicated Feed
Ractopamine Medicated Tom Turkey Feed Type C Medicated Feed