Date of Approval: December 12, 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-260

SLENTROL Oral Solution

Dirlotapide

For the management of obesity in dogs

Sponsored by:

Pfizer, Inc.

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-260
b.	Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
c.	Established Name:	Dirlotapide
d.	Proprietary Name:	SLENTROL
e.	Dosage Form:	Oral Solution
f.	How Supplied:	SLENTROL Oral Solution is supplied in 20, 50, and 150 mL bottles
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Each mL contains 5 mg of dirlotapide
i.	Route of Administration:	Oral
j.	Species/Class:	Dog
k.	Recommended Dosage:	The initial dosage is 0.01 mL/kg (0.0045 mL/lb) body weight for the first 14 days. After the first 14 days of treatment, the dose volume is doubled to 0.02 mL/kg (0.009 mL/lb) body weight for the next 14 days (days 15 to 28 of treatment). Dogs should be weighed monthly and the dose volume adjusted every month, as necessary, to maintain a target percent weight loss of ≥ 0.7% per week. If the dog has gained weight or lost <0.7% per week since the last visit, the dose volume should be increased by 100% at the first dose increase and then by 50% at subsequent months as necessary. The monthly adjustments should continue in this way until the desired weight determined at the start of therapy is reached.

A 3 month weight management phase is recommended to successfully maintain the weight loss achieved with treatment. During the weight management phase, the veterinarian and the dog owner should establish the optimal level of food intake and physical activity needed. To dose for weight management, body weight should continue to be assessed at monthly intervals. The dose is adjusted monthly by 50% at the first dose adjustment and then by 25% at subsequent months to maintain the body weight achieved at the end of weight loss.

The dose should not exceed a maximum daily dose of 0.2 mL/kg (0.09 mL/lb), based on the dog's current body weight, during any part of treatment.

l. Pharmacological Category: Microsomal triglyceride transfer protein inhibitor

m. Indications: For the management of obesity in dogs

2. EFFECTIVENESS:

a. Dosage Characterization:

The objective of the dosage characterization was to identify an initial dosage and a dose adjustment regimen that permitted each dog to be individually dosed to effect to target a safe rate of weight loss for the management of obesity in dogs. All studies were conducted with the commercial liquid solution formulation that contains 5 mg/mL of dirlotapide. The dosage characterization includes three studies utilizing different initial dosages. All initial dosages and dose regimens produced or appeared to produce effective weight loss at the end of the treatment period studied. However, each study tested a sequentially lower initial dosage in order to minimize the vomiting and anorexia produced by the test article. This characterization supports an initial dose of 0.01 mL/kg of dirlotapide oral solution administered once daily by mouth for 14 days followed by 0.02 mL/kg for the next 14 days. This characterization also supports the adjustment of the dose volume after the first month of therapy based on the amount of weight loss achieved.

The first study is a laboratory effectiveness study in neutered male and spayed female obese adult beagles. Dr. M. Anne Hickman of Pfizer Research and Development was the investigator for the study entitled: "Efficacy of dirlotapide administered to obese spayed and neutered beagles at doses that produce weight

loss and weight maintenance." The study included 12 dirlotapide-treated dogs and 4 control dogs (administered medium chain triglyceride oil) that received the test article for an 84 day weight reduction period and 28 day weight management phase. In the weight reduction period, the dogs received an initial dosage 0.045 mL/lb. The investigators weighed the dogs every 2 weeks and adjusted the dose by 25% to produce 1 to 2% body weight loss per week. On entering the weight management period, the investigators decreased the dose each individual dog received by 25% and then adjusted the dose 14 days later to maintain the reduced body weight plus or minus 1%. All dogs received a dry food diet *ad libitum*. The dirlotapide-treated dogs revealed a least squares mean decrease in body weight of 18.8% during the weight reduction period compared to the control dogs which did not lose weight. The initial dosage of 0.045 mL/lb produced greater than 2% weight loss per week in all treated dogs. In the weight management phase, the treated dogs lost an average of 1.8% to 0.8% per week. However, the dogs did gain bodyweight once they stopped receiving treatment. The dirlotapide-treated dogs also had a reduction in food intake. No serious adverse drug reactions or mortalities occurred during the study. Seven of the treated dogs had episodes of vomiting in the weight reduction phase and 4 treated dogs had soft stool. Three dogs exhibited anorexia during the first 2 weeks of treatment and one dog had an elevation in serum hepatic transaminases and bile acids that was maximal around day 28. Overall mean changes in the treated dogs included a decreased total protein, decreased albumin, decreased BUN, decreased cholesterol, and increased AST. This study revealed that the dosage of 0.045 mL/lb is effective at producing weight loss in dogs treated for twelve weeks; however, it is too high of an initial dose to maintain a loss of body weight of 1-2% per week.

The second study is a field effectiveness study in a total of 28 client owned obese dogs that did not have evidence of an endocrine gland disorder. Dr. Jay Butan, and Dr. David Lukof were the investigators in the study entitled: "Efficacy of dirlotapide administered once daily to obese dogs presented as veterinary patients." This study only evaluated weight reduction and consisted of two phases each testing a different initial dose of the test article. Phase I evaluated an initial dosage of 0.035 mL/lb in 18 dogs for 56 days and included a control group of 10 dogs. The control dogs received medium chain triglyceride oil. In phase I, the investigators lowered the dose on day 14 by 20% if the body weight loss exceeded 3% per week. Phase II extended the dosing period for 8 treated dogs from phase I to 84 days and evaluated an initial dose of 0.018 mL/lb in an additional 8 dogs. Phase II did not include a control group. Both phases included dose adjustments of 10 or 20% at day 28 and/or 56 to produce weight loss between 1 and 3% per week. All dogs received nutritionally complete and balanced commercial dog foods. After 56 days of treatment (phase I), dogs treated with an initial dosage of 0.018 mL/lb dirlotapide had lost a mean of 9.0% body weight compared to a mean loss of 0.5% body weight in the control dogs. The mean weight loss in the treated dogs did not change between day 28 (8.7%) and day 56 (9.0%) and the final dosage (0.41 mg/kg) was approximately the same as the initial dosage (0.40 mg/kg). The dogs did have excessive weight loss (>3% per week) during the first two weeks of treatment which required most dogs to have a 20% decrease in dose at day 14. In phase II the dogs treated for 3 months with an initial dosage of 0.018 mL/lb dirlotapide had a mean weight loss of

10.0% at day 56 and 6.3% at day 84. The rate of weight loss decreased with time and some dogs regained body weight the last month with 10% to 20% dose increases. There were no mortalities in the study. Vomiting (33.3% of dogs at 0.035 mL/lb initial dose and 12.5% of dogs at 0.018 mL/lb initial dose) was the most frequently encountered abnormal clinical sign. At an initial dosage of 0.018 mL/lb three dogs had anorexia (16.7%) and one dog was reported with depression (5.6%). One dog at an initial dosage of 0.035 mL/lb had a seizure-like episode. Some treated dogs at an initial dosage of 0.018 mL/lb had mild elevations in transaminases. This study revealed that the initial dosages of 0.035 and 0.018 mL/lb are effective at producing weight loss in the treated dogs; however, the study suggests that monthly 10-20% adjustments in dosage may be too small to allow dogs to maintain weight loss.

The third data source for the dosage characterization is the Weight Loss phase of a field effectiveness study that consisted of three phases. The Substantial Evidence section of this document includes the design of this study which is titled "Field effectiveness and safety of dirlotapide (CP-742,033) administered once daily to produce weight loss and maintain body weight for 7 months in obese dogs presented as veterinary patients." This study revealed a mean weight loss of 13% and 14.2% for dosing regimens 1B and 2 respectively. The percent of treated dogs successfully achieving 13% weight loss were 54% and 51.2% in regimens 1B and 2 respectively. These results were better than the final dosing regimen; however, the incidence of adverse reactions in the Weight Loss phase was also increased compared to the rates of adverse reactions with the final dosing regimen. There were no mortalities in the 154 dogs that completed this phase of the study. Vomiting was the most frequently encountered adverse reaction in the Weight Loss phase; 54.7% of dirlotapide-treated dogs had at least one episode of vomiting compared to 20.8% of the control dogs. Other adverse reactions in the dirlotapide-treated dogs included anorexia (18.9%), lethargy (17%), and diarrhea (16%). Both the number of animals and the occurrences of vomiting, anorexia, lethargy and diarrhea were lower in dosing regimen 2 than in dosing regimen 1B. These adverse reactions were observed primarily during the first month of treatment in all dose regimens. Eight dogs in regimen 1B and five dogs in regimen 2 were withdrawn from the study for adverse reactions. The treated dogs had higher mean values of ALT and AST, and lower means of alkaline phosphatase, cholesterol, total protein, albumin, and globulin levels. This study revealed that the initial dosing and subsequent dose adjustment regimens tested produced effective weight loss but the larger initial doses had a high incidence of adverse reactions. This led to the selection of a more gradual increase in dosage with an initial dose of 0.0045 mL/lb for 14 days followed by 0.009 mL/lb for the next 14 days.

b. Substantial Evidence:

(1) FIELD STUDY: DIRLOTAPIDE WEIGHT LOSS EFFICACY AND SAFETY

(a) Study Title and Number: Field Effectiveness and Safety of Dirlotapide (CP-742,033) to Produce Weight Loss when Administered Once Daily to Obese Dogs Presented as Veterinary Patients. Study Number: 1962C-60-03-671

(b) Type of Study: Field Effectiveness and Safety Dose Confirmation Study

(c) Study Dates: March 2004 – September 2004

(d) Locations and Investigators:

Name	**City**	**State/Province**
Dr. Susan Baker	West Palm Beach	Florida
Dr. Kristi Bradley	Lawrence	Kansas
Dr. Kevin Cederberg	Andover	Kansas
Dr. Daniel Core	Bossier City	Louisiana
Dr. Sam Geller	Quakertown	Pennsylvania
Dr. Allen Gignac	Toronto	Ontario
Dr. William Greene	Nashville	Tennessee
Dr. Richard Hahn	Fort Wayne	Indiana
Dr. Larry Hendricks	Germantown	Tennessee
Dr. Susan Hubbard	Rochester	New York
Dr. Robert Jackson	Caledonia	Michigan
Dr. Stephen Jones	Moncks Corner	South Carolina
Dr. Joseph Kinnarney	Reidsville	North Carolina
Dr. Sharon Lachette	White Haven	Pennsylvania
Dr. Mark Lelli	Muskegon	Michigan
Dr. Susan Moon	Memphis	Tennessee
Dr. Timothy Patterson	Bristol	Pennsylvania
Dr. Andrew Pickering	Terre Haute	Indiana
Dr. Rodney Pierson	Davison	Michigan
Dr. Kendra Reynolds	Clio	Michigan
Dr. Mark Spiegle	Toronto	Ontario
Dr. Karen Updike	Portage	Michigan
Dr. Philip VanVranken	Battle Creek	Michigan

(e) General Design

1. Purpose of Study: To evaluate the effectiveness and safety of dirlotapide for weight loss in obese dogs presented as veterinary patients.

2. Description of Test Animals: The study included 258 client owned obese dogs (119 males and 139 females) of various breeds and age (range of 1 to 14 years) presented to 23 veterinary clinics in the US and Canada for weight loss.

3. Control and Treatment Groups: The study was randomized, masked, and controlled. Control dogs received corn oil. Cases were allotted in the ratio of 1 control: 2 dirlotapide cases within clinics and blocks based on order of enrollment.

Table 1. Treatment Groups

Treatment	Dosage[a]	Number of Animals
Control	0.0045 mL/lb once daily from day 0 to 14, Then 0.009 mL/lb once daily from day 15 to 28, Then adjusted according to weight loss on days 29 to 112	88
Dirlotapide	0.0045 mL/lb (0.023 mg/lb) once daily from day 0 to 14, Then 0.009 mL/lb (0.045 mg/lb) once daily from day 15 to 28, Then adjusted according to weight loss on days 29 to 112	170

[a] The initial escalating dosage was administered once daily from day 0 to 28. After day 28, the dog was weighed monthly and the once daily dose was increased if the rate of weight loss was less than the target rate of 0.7% body weight per week, otherwise the dose remained the same. Owners administered the treatment to the dog at home.

4. Feeding Practices: All dogs were offered commercially available and nutritionally complete and balanced dog food, treats and snacks in the same amounts and at the same times as prior to the study.

5. Inclusion Criteria:
   i. Generally healthy based on medical history, physical examination, and blood and urine analyses. Dogs with select medical conditions that were stable or dogs receiving stable doses of allowed medications were included on study.
   ii. The dog was obese with a Body Condition Score (BCS) $\geq$ 8/9 point scale[1].
   iii. The dog was at least 1 year of age.
   iv. The dog was eating or will eat nutritionally complete and balanced commercial dog food.

6. Exclusion Criteria:
   i. Male or female dogs intended for breeding, or female dogs that were pregnant or lactating.

[1] LaFlamme, D.P. Development and validation of a body condition scoring system for dogs. Canine Practice 1997; 22:10-15.

ii. Dogs with metabolic disease, endocrine disease or with signs of organ failure based on physical examination, blood and urine analyses. The study excluded all dogs with a pre-treatment alkaline phosphatase level greater than 325 IU/L.
iii. Dogs treated with long-acting steroid medications 30 days prior to starting the study.
iv. Dogs receiving disallowed medications such as long-acting glucocorticoid preparations and anabolic steroids.
v. Dogs that had evidence of weight loss from unknown reasons during the 6 months prior to entering the study.
vi. Dogs that had a medical disease or received medication(s) associated with reduced appetite or affected the endocrine systems.
vii. Dogs diagnosed with epilepsy prior to entering the study.

7. Dosage Form: 5 mg/mL dirlotapide solution (commercial formulation). Control group received corn oil.

8. Drug Administration: Once daily, directly into the mouth or on a small amount of food, with or without the main meal.

   i. Dosage amount, frequency, and duration: An initial escalating dosage was administered for the first 28 days and thereafter the dose volume remained the same or was increased monthly (100% first adjustment and 50% subsequently) to produce individual weight loss >0.7% body weight per week.
   ii. Route of administration: oral

9. Variables Measured: Body weight, body condition score (BCS), and physical examinations were evaluated monthly. Hematology and serum chemistry panels were evaluated prior to treatment and at the end of treatment. Urinalysis was performed only prior to treatment. The owner was asked one question at the end of treatment to compare the dog's current activity level to the activity level prior to treatment.

10. Criteria for Success/Failure: The treatment effectiveness was evaluated after the four months of treatment. The effectiveness evaluation was based on two endpoints, the total percentage body weight loss at day 112 and the percent of dogs that successfully achieved 13% body weight loss at day 112. Thirteen percent weight loss is an amount that has been shown to provide a health benefit in dogs.[2] The two endpoints were analyzed with and without imputation of the missing data for cases that withdrew before the end of the study.

[2] Impellizeri, J.A., Tetrick, M.A., and Muir, P. Effect of weight reduction on clinical signs of lameness in dogs with hip osteoarthritis. J. Am. Vet. Med. Assoc. 2000, 216(7):1089-1091.

11. Statistical Methodology: For the analysis of the two endpoints listed above, the following models were used:

    i. Total percent weight change data were analyzed using a linear mixed model. Treatment was included in the model as a fixed effect. Clinic, block within clinic, and clinic-by-treatment were included as random effects.

    ii. The percentage of dogs that successfully achieved at least 13% body weight loss was modeled using a generalized linear mixed model with a logit link and binomial error term. Treatment was the only fixed effect. Clinic, block within clinic, and the clinic-by-treatment interactions were included as random effects.

(f) Results:

Table 2. Summary of Weight Loss Efficacy after 4 months of treatment:

Treatment	Control	Dirlotapide
% Total Weight Change[a]	-3.9	-11.8*
% Dogs with ≥ 13% Weight Change[b]	5.3	39**
Final mean dosage mL/lb[c](range)	0.03 (0.01 – 0.05)	0.02 (0.01 – 0.05)
Final mean dosage mg/lb[c] (range)	-	0.12 (0.05 – 0.24)

[a] Percent total weight change. Control n =74, Dirlotapide n = 132.
[b] Percent of dogs that successfully lost ≥ 13% body weight. Control n =75, Dirlotapide n = 141.
[c] Final dosage based on current body weight.
* P<0.0001, **P=0.0002

Treatment with dirlotapide for 4 months produced least squares mean body weight change of -11.8%. Thirty nine percent of dogs treated were successful in achieving ≥ 13% weight loss. An improvement in BCS was observed for most dogs after 4 months of dirlotapide treatment. Thirty six percent of the treated dogs decreased to a BCS of 7. Six percent decreased to a BCS of 6 or less. In the dirlotapide treatment group, 58% of owners reported an increase in activity level for their dogs. At the end of the study, the mean dirlotapide dosage being administered was 0.12 mg/lb with a range from 0.05 mg/lb to 0.24 mg/lb (0.26 mg/kg and range 0.11 mg/kg to 53 mg/kg). Dirlotapide was administered by two methods, directly into the mouth (78%) or on a small amount of food (22%). Dirlotapide was also administered with a meal (53%) and without a meal (47%). There was a slight improvement in weight loss if dirlotapide was given with a meal or with food when compared to oral administration only.

(g) Adverse Reactions: The most common adverse reactions in the study were vomiting, diarrhea, lethargy and anorexia. Vomiting was the most common adverse reaction in both the control and dirlotapide treatment groups. The incidence of vomiting was the highest during the first month of treatment. Owners were instructed to keep giving the medication at the same dose volume when vomiting, diarrhea, lethargy, or anorexia were reported. Some owners changed the time of dosage administration or changed whether the dose was given with or without a meal in response to adverse reactions.

Twelve cases were withdrawn for reasons related to adverse reactions including owner intolerance of vomiting, diarrhea, or lethargy. Two cases, one control and one dirlotapide-treated dog, were withdrawn from the study with a presumptive diagnosis of pancreatitis. One dirlotapide-treated case was withdrawn for adverse reactions including vomiting and a hepatopathy. The case was a 5-year old male castrated Dachshund that developed vomiting and diarrhea after 2 months of dirlotapide treatment. After discontinuing dirlotapide treatment the dog was hospitalized for anorexia. This dog had elevated ALT (665 IU/L, reference range 0-120 IU/L), ALP (829 IU/L, reference 21-125), AST (84 IU/L, reference 10-60), and LDH (661 IU/L, reference 25-460). The dog was withdrawn at day 86, and subsequent testing revealed that the ALT continued to rise over the next several weeks though the dog was acting normally. After several months the owner did not continue further testing because the dog was asymptomatic. A definitive diagnosis was not obtained for this case and the dog remained clinically normal.

Table 3. Adverse Reactions:

Adverse Reaction	**Percentage of Patients Reporting Sign**	
	Control (n = 88)	**Dirlotapide (n = 170)**
Vomiting	21.6%	24.7%
Diarrhea	6.8%	12.4%
Lethargy	3.4%	9.4%
Anorexia	2.3%	7.6%
Constipation	1.1%	2.4%
Dehydration	0%	1.2%

Although the above table reveals a similar incidence of vomiting and diarrhea in the dirlotapide-treated and control dogs, the treated dogs with these signs generally had an increased frequency and duration of the signs compared to the control dogs. Also, administration of medium chain triglyceride oil (the vehicle control) in the safety studies produced vomiting and diarrhea.

One dog in the dirlotapide-treatment group, a 5 year old Beagle with no medical history of seizures, had a seizure on Day 52 of the study. The dog continued to receive dirlotapide until additional seizures occurred 11 and 12 days later. The investigator stopped the dirlotapide therapy and referred the case to a neurologist. The seizures continued approximately twice weekly when off dirlotapide. The neurologist found no lesions that support the causality of the seizures.

In addition to the signs listed above, there were numerous other abnormal findings. Many dogs in both groups had dental disease, abnormal skin and ear findings, and lameness/arthritis. The incidence of these findings was similar in both treatment groups and most dogs had similar lesions noted pre-treatment. Two dogs in the dirlotapide treatment group developed corneal ulcers. One dirlotapide-treated dog developed inappropriate urination and defecation and another treated dog developed polyuria and polydipsia.

The serum chemistry results for variables that were outside the normal laboratory reference ranges are listed below. The dirlotapide-treated dogs had a greater incidence of increased ALT (9.9%) and AST (9.2%) post-treatment compared to the control dogs (4.8% and 6.0% respectively). Three treated dogs had ALT elevated greater than 2 times the high end of the reference range (0-120 IU/L) post-treatment. Three treated dogs had AST elevated greater than 2 times the high end of the reference range (0-60 IU/L) post-treatment. One dirlotapide-treated dog had the highest values of all dogs in ALT (983 IU on Day 127), AST (354 IU on Day 127), GGT (46 IU on Day 127), and alkaline phosphatase (829 IU on Day 82). Overall, the dirlotapide-treated dogs had lower alkaline phosphatase values post-treatment than the control dogs. The dirlotapide-treated dogs, as a group, had decreased serum cholesterol, total protein, albumin, and globulin levels compared to the control dogs.

Table 4. Select Elevated Serum Chemistry Results

Serum Analyte	Percentage of Dogs			
	Control (n = 88)		Dirlotapide (n = 170)	
	Pre[b]	Post[c]	Pre[b]	Post[c]
ALT > 60 IU/L	3.4%	6.0%	4.7%	9.9%
AST > 120 IU/L	0	4.8%	3.5%	9.2%
ALP[a] > 125 IU/L	11.4%	16.9%	17.6%	9.9%
Cholesterol > 320 mg/dL	14.8%	9.6%	14.7%	4.6%

[a]ALP = serum alkaline phosphatase. Dogs with ALP > 325 IU/L pre-treatment were excluded from the data analysis.
[b]Pre = Percent of dogs with values above the laboratory reference range at pre-treatment.
[c]Post = Percent of dogs with values above the laboratory reference range after 4 months of treatment.

(h) Conclusions: Treatment with dirlotapide was safe and effectively produced weight loss at an initial escalating dosage of 0.023 mg/lb (0.0045 mL/lb), adjusted individually each month by 100% initially then 50% at subsequent months, when administered orally once daily to obese dogs presented as veterinary patients. The most common adverse reactions associated with dirlotapide treatment were vomiting, anorexia, diarrhea, and lethargy.

(2) FIELD STUDY: DIRLOTAPIDE EFFICACY AND SAFETY FOR WEIGHT STABILIZATION AND POST-TREATMENT

(a) Study Title and Number: Field Effectiveness and Safety of Dirlotapide (CP-742,033) Administered Once Daily for 7 Months to Obese Dogs Presented as Veterinary Patients. Study Number: 1962C-60-02-636

(b) Type of Study: Field effectiveness and safety study for weight stabilization and dose selection for the initial dosage and dosing regimen for weight loss.

(c) Study Dates: December 2002 – February 2004

(d) Locations and Investigators:

Name	City	State/Province
Dr. Douglas Andrews	Falmouth	Maine
Dr. Brett Berryhill	Baton Rouge	Louisiana
Dr. Jay Butan	Lake Worth	Florida
Dr. Scott Buzhardt	Zachary	Louisiana
Dr. Christopher Ficke	Chester	Connecticut
Dr. John Kelley	Eastham	Massachucetts
Dr. David Lukof	Harleysville	Pennsylvania
Dr. John Means	North Hampton	New Hampshire
Dr. Samuel Quiaoit	Bolingbrook	Illinois
Dr. Dean Rund	Springfield	Missouri
Dr. Jay Schweizer	Independence	Missouri
Dr. David Serra	Wyoming	Rhode Island
Dr. Roger Sifferman	Springfield	Missouri
Dr. Melissa Wiest	O'Fallon	Missouri

(e) General Design

1. Purpose of Study: To select a dirlotapide initial dosage and dose regimen for weight loss (see Dose Characterization Section for weight loss results for this study), confirm a dosage that stabilizes body weight, and evaluate body weight changes when dirlotapide was discontinued in obese dogs presented as veterinary patients.

2. Description of Test Animals: One hundred fifty-four obese dogs (60 male and 94 female) of various breeds and age presented to 14 veterinary clinics in the US for weight loss participated in the first phase of the study. Sixty-nine dogs (6 control and 63 dirlotapide) that had achieved at least 0.5% weekly weight loss continued treatment in the weight stabilization and post-treatment phases. All dogs were offered nutritionally complete and balanced commercial dog food including treats and snacks. In the weight

stabilization phase the owner observed how much food the dog actually consumed each day.

3. Control and Treatment Groups: The initial phase of the study was randomized, masked, and controlled. The control dogs received corn oil. Cases were allotted in the ratio of 1 control: 2 dirlotapide cases and enrolled sequentially into dosing regimen 1A, 1B, or 2. The 3 regimens were different only during the initial 28 days of treatment. All doses were given once daily.

Table 5. Treatment Groups During Weight Loss Phase (Days 0 to 112)

Dosing Regimen	Treatment	Dosage[a]	Number of Animals
1A	Control	0.027 mL/lb from day 0 to 28, then adjusted based on weight loss from day 29 to 112	1
	Dirlotapide	0.027 mL/lb (0.135 mg/lb) from day 0 to 28, then adjusted based on weight loss from day 29 to 112	3
1B	Control	0.009 mL/lb, from day 0 to 6, 0.018 mL/lb from day 7 to 14, 0.027 mL/lb from day 15 to 28, then adjusted based on weight loss from day 29 to 112	24
	Dirlotapide	0.009 mL/lb (0.045 mg/lb), from day 0 to 6, 0.018 mL/lb (0.09 mg/lb) from day 7 to 14, 0.027 mL/lb (0.135 mg/lb) from day 15 to 28, then adjusted based on weight loss from day 29 to 112	49
2	Control	0.0045 mL/lb, from day 0 to 14, 0.018 mL/lb from day 15 to 28, then adjusted based on weight loss from day 29 to 112	23
	Dirlotapide	0.0045 mL/lb (0.023 mg/lb), from day 0 to 14, 0.018 mL/lb (0.09 mg/lb) from day 15 to 28, then adjusted based on weight loss from day 29 to 112	54

[a]At each monthly recheck after the first month of treatment, the dose volume was increased by 50% the first month and 25% at subsequent months if the weight loss was < 1% per week. If the weight loss was ≥ 1% per week, the dose volume remained the same as the previous month for the next month.

During the weight stabilization phase (day 112 to 196), the study was essentially open label since most control dogs completed the study at the end of weight loss (see inclusion criteria below).

Table 6. Treatment Groups During Weight Stabilization Phase (Days 112 to 196)

Treatment	Dosage	Number of Animals
Control	Unchanged or adjusted by 50% then by 25% based on weight loss[a]	6
Dirlotapide	Unchanged or adjusted by 50% then by 25% based on weight loss[a]	63

[a] Beginning at the end of the weight loss phase, if the dog had lost ≥ 1% body weight the previous month (study day 84 to 112), the dose was decreased by 50%, if the dog had lost between 0 and 1% the dose remained the same, and if the dog had gained weight the dose was increased by 50%. The dose could be increased or decreased by 50% once, at the first dose adjustment. All subsequent adjustments performed at monthly intervals were by 25% of the dose. If the percent weight change was -5% to +5%, the dose remained unchanged. If the dog lost >5% body weight, then the dose was decreased by 25%. If the dog gained >5% body weight, then the dose was increased by 25%.

4. Feeding Practices: All dogs were offered nutritionally complete and balanced dog food, treats and snacks in the same amounts and at the same times as prior to the study.

5. Inclusion Criteria:

   i. Generally healthy based on physical examination and blood analyses. Conditions permitted on the study (such as cardiovascular disease or skeletal disease) are stable with any medical treatments at stable doses, and the conditions are not associated with metabolic disease.
   ii. Obese with a BCS of greater than or equal to 8 on a 9 point scale, or the dog is heavy with a BCS score of 7 and a body weight that is >120% of body weight at 12 to 18 months of age, or for giant breeds at 18 to 24 months of age.
   iii. One year of age or older.
   iv. The dog was eating or started eating a nutritionally complete and balanced commercial dog food.
   v. For inclusion into the weight stabilization phase, the dog must have achieved an average of > 0.5% body weight loss per week during the 4 month Weight Loss Phase.

6. Exclusion Criteria:

   i. Dogs intended for breeding and dogs pregnant or lactating.
   ii. Dogs with clinical evidence of metabolic disease, endocrine disease, or organ failure.

iii. Dogs treated with long-acting steroid medications within 30 days prior to starting the study.
iv. Dog receiving disallowed medications (long-acting glucocorticoid preparations or anabolic steroids).
v. Dogs with unexplained weight loss during the 6 months prior to the study.

7. Dosage Form: 5mg/mL dirlotapide solution (commercial formulation). Control group received corn oil.

8. Drug Administration: Once daily, directly into the mouth or on a small amount of food, with or without the main meal.

   i. Dosage amount, frequency, and duration: For the weight loss phase an initial escalating dosage was administered for the first 28 days and thereafter the dose volume remained the same or was increased monthly (100% first adjustment and 50% subsequently) to produce individual weight loss >0.7% body weight per week. For the weight stabilization phase the dosage was adjusted monthly (50% first adjustment and 25% subsequently) to maintain the desired body weight plus or minus 5%.
   ii. Route of administration: oral
   iii. Other Comments: The goal of the weight stabilization phase was to allow for the owner to determine the optimal amount of food and exercise necessary to maintain the dog's desired body weight. This would allow the dog to maintain the lower body weight when it stopped receiving dirlotapide at the end of the 3 month period.

9. Variables Measured: Body weight, body condition score (BCS), and physical examinations were evaluated monthly. Hematology and serum chemistry panels were evaluated prior to treatment, at the end of the weight loss phase, at the end of the weight stabilization phase, and at the end of the post-treatment phase. Urinalysis was performed only prior to treatment.

10. Criteria for Success/Failure: For the weight loss phase, the treatment effectiveness was evaluated after the four months of treatment. The effectiveness evaluation was based on two endpoints, the total percentage body weight loss at day 112 and the percent of dogs that successfully achieved 13% body weight loss at day 112. The two endpoints were analyzed with and without imputation of the missing data for cases that withdrew before the end of the study

    For the weight stabilization phase, success was defined as maintaining the Day 112 body weight plus or minus 5% for 3 months.

11. Statistical Methodology: In the analysis of the weight stabilization phase, the mean weight loss was reported between study day 112 and each subsequent study visit (days 140, 168, and 196). For the comparability analysis, the dosing regimens from studies 1962C-60-02-636 (regimens 1B and 2) and 1962C-60-03-671 were compared based on the 95% confidence intervals (CIs) for the endpoints (i) total percent weight change and (ii) proportion of dogs losing at least 13% body weight. For a given endpoint, the CIs for regimens 1B and 2 were checked to see if they overlapped with the middle half of the corresponding CI of the regimen in study 671. The CIs for the 636 regimens were determined to be overlapping with the 671 regimen if the middle 50% of the CI for the 671 regimen had any common values with the CI for the 636 regimens. If such an overlapping occurred, then the dosing regimens were considered similar.

(f) Results:

The results of the weight stabilization and post-treatment phases are summarized below. The results from the weight loss phase are summarized under the Dosage Characterization section of this document.

1. Comparability Analysis: The results are summarized for each endpoint below:

   i. Percent weight change: The 95% CI for the study 671-regimen was (-13.0%, -10.5%), and the middle 50% of this CI was (-12.4%, -11.1%). For study 636, the 95% CI for regimen 1B was (-15.3%, -10.9%), and the CI for regimen 2 was (-16.2%, -12.2%). The CIs for regimens 1B and 2 each overlap with the middle 50% of the CI for the regimen in study 671. The conclusion is that the dosing regimens are similar.

   ii. Percentage of dogs with 13% weight loss: The 95% CI for the study 671-regimen was (31%, 52%), and the middle 50% of this CI was (36%, 47%). For study 636, the 95% CI for regimen 1B was (39%, 68%), and the CI for regimen 2 was (34%, 69%). The CIs for regimens 1B and 2 each overlap with the middle 50% of the CI for the regimen in study 671. The conclusion is that the dosing regimens are similar.

2. Weight Stabilization: A total of 59 dogs completed the weight stabilization phase. Of these dogs, 54 received dirlotapide and 5 were controls. The dirlotapide-treated dogs lost a mean of 4.6% body weight from Day 112 to Day 196. Twenty-five treated dogs (46.3%) lost greater than 5% of their Day 112 body weight with a maximum loss of 20% during the 3 month phase. One treated dog (1.9%) gained 6.4% of its Day 112 body weight.

At the end of the weight stabilization phase, the mean dirlotapide dosage being administered was 0.14 mg/lb with a wide range from 0.03 mg/lb to 0.34 mg/lb of current body weight. The dosage at the end of the weight stabilization phase was approximately 25% less than the dosage at the end of the weight loss phase.

3. Post-Treatment: A total of 53 dogs, including 4 control dogs, correctly completed the post-treatment phase until Day 252. The mean weight change in the treated dogs on Day 252 was a 2.9% gain from the Day 196 body weight (range of -16.7% to a gain of 15.5%). In the treated dogs that completed the study, the mean weight change in the first month post-treatment was 2.1%. Of the 53 dirlotapide-treated dogs, 77.6% gained weight at the end of the post-treatment phase and 38% gained at least 5% of their Day 196 body weight during this period.

(g) Adverse Reactions: There were fewer adverse reactions during the weight stabilization phase. Vomiting was still the most frequently observed adverse reaction. There were no adverse reactions reported in the 6 control dogs.

Table 7. Adverse Reactions:

Adverse Reaction	Percentage of Patients Reporting Sign Dirlotapide (n = 62)
Vomiting	16.1%
Lethargy	4.8%
Diarrhea	1.6%
Anorexia	1.6%
Ataxia	1.6%

In addition to the signs listed above, there were numerous other abnormal findings. Many dogs in both groups had dental disease, abnormal skin and ear findings, and lameness/arthritis; the incidence of these findings was similar in both treatment groups and most dogs had similar lesions noted pre-treatment.

Post-Treatment: When dirlotapide was discontinued, some owners reported increased appetite in their dogs in the month following treatment.

One dog, a 6-year-old Chihuahua was found dead on the 8th day of the post-treatment phase. The owner reported the dog acting normally the night before. The investigator performed a necropsy but the cause of death was not conclusive.

(h) Conclusions: After 4 months of weight loss, daily oral treatment with dirlotapide was safe, and stabilized or further reduced body weight, when adjusted monthly by 50% the first month and then by 25% as needed based on individual body weight changes. Dirlotapide therapy caused vomiting as the

most frequent adverse reaction during weight stabilization. Cessation of dirlotapide therapy was associated with an increase in body weight emphasizing the need for proper dietary management after the 7 month dosing period.

3. TARGET ANIMAL SAFETY:

a. Toxicity and Tolerance Studies:

(1) Acute Tolerance Study in Adult Dogs:

(a) Study Title and Number: 14-Day Oral Toxicity Study of CP-742,033 (dirlotapide) in Dogs, Study # 01-2098-03

(b) Type of Study: Target Animal Safety: toxicity/tolerance study at 0, 2.5, 5.0, or 10 mg/kg in adult dogs.

(c) Study Dates: July 2001 to July 2002

(d) Location and Investigator:

Theodore J. Schmahai, Ph. D.
Pfizer Inc.
Groton, Connecticut

(e) General Design:

1. Purpose of Study: To provide information on the toxic effects of dirlotapide following oral administration in beagle dogs at doses up to 10 mg/kg/day for 14 days.

2. Description of Test Animals: 12 male and 12 female Beagle dogs

3. Control and Treatment Groups: The 24 animals were allocated into 4 replicates of 6 dogs each (3 males and 3 females).

Table 8. Treatment Groups

Treatment Group	Number of dogs	Male	Female
0 mg/kg	6	3	3
2.5 mg/kg	6	3	3
5.0 mg/kg	6	3	3
10.0 mg/kg	6	3	3

4. Dosage Form: Dirlotapide in oil solution. Control Group, medium chain triglyceride oil (vehicle) solution only.

5. Drug Administration:

i Dosage amount, frequency, and duration: 0, 2.5, 5.0 and 10.0 mg/kg dirlotapide was administered once daily for 14 consecutive days one hour after feeding.

ii Route of administration: Oral gavage.

6. Variables Measured: Daily observations for clinical signs of abnormal health and food intake were conducted. Body weights were measured prior to treatment, and on days 1, 3, 6, 9, 12, and 15. Vital signs and electrocardiograms were measured prior to treatment and on day 9. Hematology and clinical chemistry were measured prior to treatment and on days 7 and 14, and urinalyses were conducted prior to treatment and on day 13/14. Plasma dirlotapide concentrations were determined on days 1 and 14 and metabolite concentrations were determined from bile/urine samples taken at necropsy on day 15. All animals were necropsied on day 15, select organs were weighed, and a comprehensive set of tissues were evaluated by histopathology. Treatment means and standard deviations were calculated for electrocardiogram measurements, vital signs, body weights, organ weights, hematology and serum chemistry data. General health, clinical observations, and gross and microscopic pathology findings were summarized. Mean dirlotapide concentrations in plasma, bile and urine and standard deviations were calculated.

(f) Results:

1. Clinical Observations and Physical Exams: Dirlotapide administration produced reductions in food intake, organ weights, and body weight. Clinical signs, observed in all dose groups including the controls that received the medium chain triglyceride oil, included vomiting and loose stools. The incidence of vomiting was greatest on the first 3 days of dosing. Vomiting generally occurred within 4 hours of dosing. The occurrence of loose stools, observed intermittently throughout the study, was comparable between controls and treated animals. Clinical observations, physical examinations, ophthalmologic examinations, vital signs (respiration, body temperature, heart rate, blood pressure), and electrocardiograph examination revealed no adverse effects of treatment.

2. Clinical Pathology: Dirlotapide administration resulted in a dose-related decrease in mean serum cholesterol and high-density lipoprotein (HDL) that was observed at day 7 and was not progressive at day 14. Treated dogs revealed decreases in mean total protein, mean albumin, mean serum calcium, mean blood urea nitrogen (females), and mean serum glucose (females); however, most values for individual dogs usually remained within normal ranges. All treated groups revealed a mild to moderate increase in mean alanine aminotransferase (ALT) activity and aspartate aminotransferase (AST) activity. Mean ALT activity was increased over baseline only for the mid-dose males (5 mg/kg) at day 14 and mean AST activity was increased for the mid-dose females at the same time. One high-dose (10 mg/kg) female had an

elevation in both ALT activity (257 U/L) and AST activity (99 U/L) and one mid-dose female had mild increases in ALT activity (102 U/L), AST activity (71 U/L) and a moderate increase in bile acids (57.0 mcmol/L), without accompanying microscopic evidence of hepatic degeneration or necrosis.

3. Pathology: On microscopic examination, accumulation of lipid vacuoles in the apical third of enterocytes in the small intestine (duodenum, jejunum and/or ileum) was present in all treated dogs. Minimal to mild periportal fatty change in the liver was also present in five treated dogs.

4. Plasma Drug Levels: A high level of between-animal variability in dirlotapide plasma concentrations was observed at all three dose levels. C_{max} and $AUC_{0\text{-last}}$ showed a dose-related but less-than-dose-proportional increase with increased dose. The ratios of $AUC_{0\text{-last}}$ on Day 14 and $AUC_{0\text{-inf.}}$ on Day 1 for higher dose groups suggest non-linear absorption and the possibility of drug accumulation. The mean elimination half-life ranged between 5 and 18 hours, and it seemed to increase with dose and with repeated administration. Dirlotapide was detected in both urine and bile.

(g) Conclusions: Dirlotapide administered at 2.5, 5, and 10 mg/kg produced signs of toxicity in all the treated groups. In addition to the decrease in body weight and decrease in food consumption, the main findings associated with dirlotapide administered at high doses to healthy dogs included vomiting, soft stool, an increase in serum hepatic transaminases, a mild decrease in serum total protein, dose related decreases in serum cholesterol and HDL levels, and mild to moderate lipid accumulation in the enterocytes of the small intestine and periportal hepatic cells.

(2) Margin of Safety Study in Obese Dogs:

(a) Study Title and Number: Three Month Oral Toxicity Study of CP-742,033 (dirlotapide) in Obese Beagle Dogs. Study # 01-2098-05

(b) Type of Study: Target Animal Safety: GLP margin of safety study at 0, 0.5, 1.5 and 2.5 mg/kg dirlotapide administered once daily in obese Beagle dogs.

(c) Study Dates: August 2001 to February 2003.

(d) Location and Investigator:

Theodore J. Schmahai, Ph. D.
Pfizer Inc.
Groton, Connecticut

(e) General Design:

1. Purpose of Study: To provide information on the toxic effects of dirlotapide following oral administration in adult obese neutered Beagle dogs at doses up to 2.5 mg/kg/day for 12 weeks.

2. Description of Test Animals: Nineteen male and nineteen female adult Beagle dogs.

3. Control and Treatment Groups: The 38 animals were allocated into 4 groups of dogs. Selected dogs from the 1.5 mg/kg treatment group and 0.3 mL/kg control group were maintained for a 1-month post-treatment period following 3 months of dirlotapide treatment. Dosages in the low-dose (0.5 mg/kg) were reduced by 20% for all 6 dogs at day 14 and at different times for 5 of the 6 dogs after day 14 so that the final dosage ranged from 0.36 to 0.4 mg/kg for the low-dose group. Dosage adjustments were intended to prevent individual body weight loss in excess of 2.2% per week.

Table 9. Treatment Groups

Treatment Group	Number of Dogs	Male	Female
0 mg/kg	10	5	5
0 mg/kg	4	2	2
0.5/0.4 mg/kg	6	3	3
1.5 mg/kg	12	6	6
2.5 mg/kg	6	3	3

4. Dosage Form: Dirlotapide in oil solution. Control Group, medium chain triglyceride oil (vehicle) solution only.

5. Drug Administration:

   i Dosage amount, frequency, and duration: 0, 0.5, 1.5 or 2.5 mg/kg dirlotapide was administered once daily for 90 consecutive days one hour after feeding. Ten control dogs received an equivalent volume as the 1.5 mg/kg (0.3 mL/kg) treatment group and 4 control dogs received an equivalent volume as the 2.5 mg/kg (0.5 mL/kg) treatment group.

   ii Route of administration: oral gavage.

6. Variables Measured: Clinical health observations and food intake were monitored daily. Body weights were recorded weekly. Ophthalmic examinations, electrocardiograms, vital signs, physical examinations, body condition score assessments, and clinical pathology, including plasma concentrations of vitamins A and E, were performed approximately monthly. Serial plasma and urine dirlotapide concentrations were measured once monthly and bile dirlotapide metabolite concentrations were determined at the end of the study. Dogs were necropsied on day 91 at the end of dosing or on day 118/119 at the end of the post-treatment period and evaluated by gross examination. Select organs were weighed

and a comprehensive set of tissues were examined microscopically by a veterinary pathologist. Treatment means and standard deviations were calculated for electrocardiogram measurements, vital signs, body weight, organ weights, feed consumption estimates, plasma vitamin concentrations, and clinical pathology data.

7. Methodology of Analysis: Statistical analyses were conducted on body and organ weight, vitamin and clinical pathology data. Mean dirlotapide concentrations in plasma, bile and urine, and standard deviations were calculated, and necropsy findings were summarized. A mixed linear model was used for endpoints measured once, and a mixed linear model with repeated measures was used for endpoints measured multiple times. The pre-treatment values were used as covariates in the analysis where appropriate. A two-stage Fisher's protected least significant difference was used for pair-wise treatment comparisons.

(f) Results:

1. Clinical Observations and Physical Exams: Dirlotapide administration resulted in a decrease in body weight, body condition score, and food intake in the treated dogs. Body weight decreased between 17% and 39% from baseline for dirlotapide-treated dogs. Loose stools and vomiting were the most common clinical signs. Loose stools were sporadic and occurred at different times throughout the study in all treatment groups. Vomiting was observed in all treatment groups and tended to occur within 3 hours of dosing. Vomiting was dose-related and was more frequent during the first 2 to 4 weeks of treatment. During the first 14 days of treatment, 5 of 6 dogs (87%) in the 2.5 mg/kg group, 9 of 12 (75%) in the 1.5 mg/kg group, and 2 of 6 (33%) in the 0.5 mg/kg treatment group vomited. Excessive salivation was noted on physical examination for two male dogs in the high-dose group at the 2-month evaluation. Sagging skin was also noted on physical examination for some dogs during the treatment period. There were no electrocardiograph or ophthalmologic changes observed. All changes had a reversing trend during the 1-month recovery period.

2. Clinical Pathology: Dogs treated with dirlotapide revealed a dose-related decrease in serum cholesterol ($P=0.0001$) and high-density lipoprotein (HDL) concentration ($P=0.0001$) by day 28 that remained relatively constant for the remainder of the 3-month treatment period. Most measurements for individual dogs were within reference ranges. Decreases in vitamin A and E plasma concentrations were observed early in treatment for all dirlotapide-treated groups. No clinical or histopathological signs of vitamin deficiency were observed.

   All dogs receiving 1.5 mg/kg and 2.5 mg/kg of dirlotapide revealed a mild to moderate increase in hepatic transaminases activity (ALT and AST) compared to the control dogs and individual baseline values. AST activity in the dirlotapide-treated dogs was mildly elevated throughout the treatment period compared to the controls ($p<0.0807$). ALT elevations

were highest after one month of treatment in the 1.5 and 2.5 mg/kg treatment groups (P=0.0106 and P=0.0001 for the 1.5 and 2.5 mg/kg groups respectively). Alkaline phosphatase activity (ALP) decreased in the treated dogs compared to the controls ($p<0.0516$). In the high dose (2.5 mg/kg) group, two of six dogs (one male and one female) had AST elevations >100 U/L combined with ALT elevations >500 U/L and a mild increase in bile acids. In the female, there were also mild increases in gamma-glutamyltransferase activity (GGT) and alkaline phosphatase activity (ALP) in the first month of treatment.

The total serum protein and albumin levels in treated dogs declined compared to the controls ($p<0.0018$ and $p<0.0296$ for total protein and albumin respectively) and pre-treatment means. Other changes in the treated dogs include a mild decrease in the mean serum calcium and BUN levels. However, most values remained within the reference range.

The urinalysis data revealed an increase in urine bilirubin levels in the dirlotapide-treated dogs compared to the control dogs. Also, two dogs in the high dose group tested positive for ketones on Day 86. All of the clinical pathology findings reverted to the normal range in the dogs selected for the post-treatment period when dirlotapide treatment was withdrawn.

3. Pathology: The liver and kidney weights, as well as the final body weights, were lower in the treated dogs compared to the control dogs. A white diffuse gelatinous material, presumably unabsorbed lipid, was visible on the mucosal surface of the small intestine. This change was observed more frequently in the mid and high dose groups. On histopathological examination, the enterocytes of the small intestine contained lipid vacuoles in the villus tips. Dilated lacteals were observed in some dogs. Hepatic glycogen accumulation was observed in all treatment groups. There were no significant treatment-related findings at the end of the 1-month recovery period.

4. Plasma Drug Levels: Dirlotapide was measured in blood samples taken on Days 1, 29, 58 and 87 to confirm exposure. Substantial intra- and inter-animal variability was observed in blood levels from all treated groups, but it was most notable in the 5X group. Systemic exposure based on C_{max} and $AUC_{0\text{-last}}$ was dose proportional for the 1X to 3X dose, but less-than-dose-proportional for the highest dose group. C_{max} on Day 1 at the 0.5 mg/kg dose was 63.5 (+ 27.7 SD) ng/mL and $AUC_{0\text{-last}}$ was 304 (+ 134) ng*h/mL.

   Systemic exposure was highest on Day 29, and decreased during the subsequent two months of treatment. Very high doses may result in drug accumulation. Dirlotapide and one metabolite were detected in the bile in a greater-than-dose-proportional manner. Dirlotapide clearance appears to be primarily via biliary secretion.

(g) Conclusions: Dirlotapide was well-tolerated when administered once daily for three months at 0.4 mg/kg to healthy beagle dogs. The product caused occasional vomiting at the proposed dose level, especially within the first few days of dosing. At higher doses the product caused an increased incidence of vomiting and increased salivation. Dirlotapide significantly affected the absorption and transport of lipids in the body and produced a significant reduction of body weight. Use of the product may affect liver function and the absorption and transport of fat-soluble nutrients including fat-soluble vitamins. These effects reversed after one month of stopping dirlotapide therapy.

(3) 1-Year Safety at the "Use" Dose in Obese Dogs:

(a) Study Title and Number: "Confirmation of efficacy and safety of CP-742,033 (dirlotapide) in the treatment of excessive body weight in dogs given diets of differing fat contents." Study Number 5960C-36-02-269 and 5960E-60-04-294 (clinical pathology analysis).

(b) Type of Study: Efficacy and Safety of dirlotapide at the use-dose regimen (0.1 mg/kg for 28 days, adjusted monthly to produce between 1 and 3% weekly weight loss for approximately 6 months, then adjusted monthly to produce constant body weight ± 5% for another 6 months) in obese Labrador Retriever dogs. The study included a maximum dose of 1 mg/kg.

(c) Study Dates: 09 December 2002 to 18 February 2004.

(d) Location and Investigator:

James McKenna, MVB, MRCVS
Charles River Biolabs.
Glenamoy,
County Mayo
Republic of Ireland

(e) General Design:

1. Purpose of Study: The purpose of this efficacy study was to provide long-term safety of the 1X dose range of dirlotapide in dogs. The study was conducted to confirm the efficacy and safety of the commercial formulation of dirlotapide, administered once daily for up to 52 weeks in the treatment of obesity in Labrador Retriever dogs given diets of differing fat contents. This study was conducted according to GCP guidelines.

2. Description of Test Animals: 43 neutered male and 29 spayed female adult obese Labrador Retriever Dogs.

3. Control and Treatment Groups: The 72 dogs were blocked by body condition score (BCS) and body weight and randomly allocated to one of nine treatments (see Table 10. Study Design below). Depending on treatment group, the dogs received either the control for 168 days (T1, T2

and T3, initial dosage of 0.02 mL/kg), dirlotapide for up to 168 days followed by control for up to 196 days (T4, T5 and T6, initial dosage of 0.1 mg/kg), or dirlotapide for up to 364 days (T7, T8 or T9, initial dosage of 0.1 mg/kg). Finally there was a 1 month post-treatment phase (T7, T8, or T9) in which all treatment with dirlotapide was discontinued. The dogs in each treatment group were fed diets with varying fat contents of 5% (T1, T4 and T7), 10% (T2, T5 and T8), or 15% (T3, T6 and T9) on an air dry matter basis.

Table 10. Study Design

	Dosage received in each phase			
Treatment	Weight loss	Retraining	Post-treatment	Fat% of diet
T1	Control	-	-	5
T2	Control	-	-	10
T3	Control	-	-	15
T4	Dirlotapide	Control	-	5
T5	Dirlotapide	Control	-	10
T6	Dirlotapide	Control	-	15
T7	Dirlotapide	Dirlotapide		5
T8	Dirlotapide	Dirlotapide		10
T9	Dirlotapide	Dirlotapide		15

4. Dosage Form: Dirlotapide solution in oil; control received corn oil only.

5. Drug Administration:

   i The dosage and dosage adjustments were intended to simulate the 1X or "use" dosage for dirlotapide. The study consisted of three consecutive phases. The weight loss phase was up to 168 days (6 months). The initial dose of 0.1 mg/kg of dirlotapide administered once daily was adjusted monthly based on weight loss to produce 1 to 3% body weight loss per week for treatment groups T4 to T9. The retraining phase was up to 196 days (7 months). It followed the weight loss phase for treatment groups T7 to T9. The dose was adjusted monthly to maintain the dog's body weight at the end of the weight loss phase ± 5%. The treatment was changed from dirlotapide to control for treatment groups T4 to T6 during the retraining phase. The post-treatment phase was up to 31 days (1 month) for treatment groups T7 to T9 and the treatment with dirlotapide was discontinued. The maximum dose allowed was 1.0 mg/kg daily based on current body weight.

   ii Route of administration: Dirlotapide liquid solution was administered directly into the mouth with a dosing syringe once daily prior to the morning feeding.

6. Variables Measured: Dogs were weighed, assessed for body condition, sampled for clinical chemistry, and clinically examined

at least every 28 days throughout the weight loss and retraining phases, and at the end of the post-treatment phase. Dogs that received 12 months of dirlotapide treatment (T7 to T9) were assessed for body composition by dual energy X-ray absorptiometry (DXA) scans pretreatment, after 40 weeks of dirlotapide treatment, and at the end of the post-treatment phase. Ophthalmologic examinations were performed at the end of the retraining phase. Subcutaneous adipose tissue samples were collected from the dogs that received 6 or 12 months of dirlotapide treatment (T4 to T9) at the end of the retraining phase, and on the final day of study (T7 to T9). Blood samples were analyzed for vitamins A and E after 1 month, 6 months, and 12 months of dirlotapide treatment and 1 month post-treatment. Blood samples were analyzed for prothrombin times at the end of the retraining phase and at the end of the post-treatment phase.

7. Methodology of Analysis: Changes in body weight and food intake were statistically compared between dirlotapide-treatment and control. Treatment means and standard deviations were calculated for plasma vitamin A and E concentrations, tissue vitamin E, and clinical pathology results. Abnormal clinical signs, fecal consistency, prothrombin times, body condition and body composition were summarized for each treatment and phase of study. A mixed linear model was used to analyze data. The pre-treatment value was used as covariates in the analysis where appropriate. The data were analyzed by phase.

(f) Results:

1. Clinical Observations and Physical Exams: Body weight decreased statistically significantly from baseline in the dirlotapide-treated dogs compared to the controls ($p=0.0001$) during the weight loss phase (18.4% to 22.3%) and the retraining phase (5.0% to 6.4%), corresponding with a comparable decrease in food intake ($p<0.0061$). Body weight increased at all levels of dietary fat from 0.13% to 0.74% per week during the post-treatment phase when feed was not limited (T7-T9). Body condition scores (based on a 9-point scale[3]) decreased between one and three points for 89% of dogs during weight loss; weight lost in the dirlotapide-treated dogs was due to a decrease in fat mass, sparing lean mass (based on DXA data).

   One dog was removed from study due to severe anorexia. The anorexia in this dog began three days prior to dirlotapide therapy and persisted for 63 days of treatment. Following removal from the study, the dog was offered a canned food diet and ate eagerly.

[3] LaFlamme, D.P. Development and validation of a body condition scoring system for dogs. Canine Practice 1997; 22:10-15.

The most frequently observed clinical signs were vomiting, diarrhea and salivation. Diarrhea or soft stool was more frequent in the dirlotapide-treated dogs, occurred intermittently throughout the study, and appeared more often during the retraining phase when the dose was still high. Episodes of soft stools resolved without treatment. Intermittent vomiting was observed throughout the study in control and dirlotapide-treated dogs. Dirlotapide-treated dogs vomited more frequently during the first month of treatment than the rest of the study. During the retraining phase the incidence of vomiting for dirlotapide-treated dogs was similar to the control dogs. Vomiting was usually of short duration of one or two days; two control and three dirlotapide-treated dogs vomited for 3 or 4 days duration. Excessive salivation was noted only in 4% to 8% of dirlotapide-treated dogs and primarily during the first month of treatment.

Ophthalmologic examinations conducted only at the end of the study, revealed focal or multi-focal retinopathies, or diffuse retinal degeneration in eight dogs receiving dirlotapide for 12 months and two dogs receiving dirlotapide for six months. Generalized progressive retinal atrophy (PRA) was diagnosed in one dog receiving dirlotapide for 12 months and one dog receiving dirlotapide for six months. Post-polar or diffuse cataracts were observed in four dogs receiving dirlotapide for 12 months and one dog receiving dirlotapide for six months. Both dogs diagnosed with PRA had diffuse cataracts. In addition, one dog treated for 12 months had bilateral posterior suture lines visible. Pretreatment ophthalmologic examinations were not available.

2. Clinical Pathology: The mean cholesterol level was statistically significantly lower in the dirlotapide-treated dogs over time in the weight loss phase compared to the controls (the lowest 1.858 mmol/L for dirlotapide-treated dogs and the highest 4.785 mmol/L for the controls, respectively, $p=0.0001$), and the decrease in serum cholesterol was greater for the dogs on the high fat diet than for those on the low fat diet ($p=0.0198$). Serum cholesterol returned to normal concentrations when dirlotapide treatment was discontinued. Mean serum triglyceride concentrations were not significantly affected by treatment.

   The overall serum alanine aminotransferase (ALT) concentrations of the treated dogs tended to be mildly increased compared to the control dogs. Mean ALT concentration in the dirlotapide-treated dogs were statistically significantly higher than the controls on Day 139 of treatment (34.6 U/L for controls and 39.3 U/L for dirlotapide-treated dogs, respectively, $p=0.0609$). Except for one dog that had an elevated alkaline phosphatase prior to treatment and a sustained ALT elevation during treatment, 9 of 48 dogs had individual ALT measurements that exceeded the normal range (maximum was 366 U/L) during the first 6 months of dirlotapide treatment and 4 of 24 dogs had an elevated value during the subsequent 6 months of dirlotapide treatment. Generally, for each individual dog, the elevations in ALT activity were sporadic and not progressive. ALT activity was also sporadically increased in the control dogs (maximum was 233 U/L). All

observed changes reversed within one month of discontinuing dirlotapide treatment.

Mean aspartate aminotransferase (AST) levels in the dirlotapide-treated dogs were statistically significantly higher than the controls (24.9 U/L for controls and 31.5 U/L for dirlotapide-treated dogs, respectively, p=0.0001) during the weight loss phase. The AST elevations were mild and not sustained, only 1 of 48 dogs had an individual AST concentration that was above the normal range (23 – 66 U/L) with a maximum value of 84 U/L. The maximum AST value observed in the control dogs was 116 U/L. All of the changes reversed within one month of discontinuing dirlotapide treatment. No individual animals had increased hepatic transaminases that were accompanied by increases in other hepatic function measurements.

Mean serum alkaline phosphatase activity (ALP) in the dirlotapide-treated dogs was statistically significantly lower than the controls over time in the weight loss phase (the lowest 27.1 U/L for dirlotapide-treated dogs and the highest 34.3 U/L for the controls, respectively, p =0.0128). The serum ALP activity also tended to decrease during 6 months of dirlotapide treatment in the retraining phase.

GGT activity was not changed during 13 months of treatment, except on Days 55 and 167; mean GGT was statistically significantly higher on Day 55 (p=0.0960) and lower on Day 167 (p=0.0002) in the dirlotapide-treated dogs compared to the controls. There was no difference between treatment groups detected in total bilirubin during the first 6 months of dirlotapide treatment in the weight loss phase, but mean total bilirubin level in the dirlotapide-treated dogs was significantly lower than the controls during the 6 months of dirlotapide treatment in the retraining phase.

Other changes included low total protein, low serum albumin and globulin, low blood urea nitrogen**,** and low serum creatinine compared to control dogs. Mean and individual values were usually within the normal range.

3. Fat Soluble Vitamins: Median plasma vitamin A concentrations in dirlotapide-treated dogs were lower (~50%) than control during the first 6 months of dirlotapide treatment at the weight loss dosage. The concentrations tended to increase during the retraining as the dirlotapide dosage was decreased. However, the median plasma concentrations of the treated dogs remained below the control dogs. The median vitamin A concentrations returned to the control range when dirlotapide treatment was discontinued. Median plasma vitamin E concentrations were lower in dirlotapide-treated dogs than in control dogs and they tended to decrease progressively during the first 6 months of dirlotapide treatment at the weight loss dosage roughly parallel to the decrease in serum cholesterol concentrations. As the dirlotapide dose was decreased during the retraining phase, the median plasma vitamin E concentrations tended to increase but did not return to the control range until dirlotapide was

discontinued. All of the low serum vitamin concentrations reversed within one month of discontinuing dirlotapide treatment.

Adipose tissue vitamin E concentrations after 12 months of dirlotapide treatment were higher in the treated dogs compared to the control dogs.

Mean prothrombin clotting times at the end of 12 months of dirlotapide treatment were 11.2 seconds for control dogs and 12.0 seconds for dirlotapide-treated dogs. At the end of the post-treatment phase, T7 to T9 dogs had a prothrombin clotting time of 11.5 seconds.

(g) Conclusions: Dirlotapide was safe when administered at an initial dose of 0.1 mg/kg and adjusted based on weight loss over 168 days with a maximum dose of 1.0 mg/kg. Dirlotapide administration resulted in 18-22% weight loss in obese adult dogs. Dirlotapide was also well tolerated for an additional 196 days of treatment with adjusted doses that maintained the bodyweight within 5% (retraining phase dosing). However, dirlotapide may produce or exacerbate severe anorexia that requires the discontinuation of the product. Dirlotapide significantly affects the absorption and transport of lipids in the body and produces a significant reduction of body weight in obese dogs. Use of dirlotapide may affect liver function and the absorption and transport of fat-soluble nutrients. These effects reversed after one month of stopping dirlotapide therapy.

The ocular lesions observed in this study are considered incidental to the Labrador breed. This conclusion is supported by a 9-month chronic dosing study in Beagles.

(4) 9-month Oral Safety Study in Obese Beagle Dogs:

To further address the ocular lesions observed in the 1-year safety study described above, the sponsor submitted an additional study that tested the safety of chronic daily administration of dirlotapide. Theodore J. Schmahai, Ph. D. of Pfizer, Inc. was the investigator of the study entitled: "9- Month Oral Toxicity Study of CP-742,033 (dirlotapide) in Dogs with a 2-month Recovery Period." The study evaluated dirlotapide in a self-emulsifying drug delivery system (SEDDS). Although, the study did not use the final formulation of dirlotapide, the overall results in the treated dogs were comparable to studies performed with the final formulation in terms of the clinical response, serum levels of fat soluble vitamins, and pharmacokinetic parameters. The similarities of the studies supported the ocular safety of dirlotapide.

The study included 34 dirlotapide-treated dogs and 14 control dogs (administered SEDDS vehicle only) 18-24 months of age with a BCS of 6-8. The dogs received the test article or control once daily for 9 months. See Table 11 below for the dosing groups, initial doses, dose ranges, and average daily dose. Dosages in all treatment groups were adjusted to prevent excessive weight loss. The dose was adjusted if weight loss for the high-dose group averaged $\geq$ 1% per week. Selected dogs (3 dogs/sex) from the high dose group and the control group were

maintained for a 2-month post-treatment period following 9 months of dirlotapide treatment.

Table 11. Treatment Groups

Treatment Group	Initial Dose (mg/kg)	Dose Range (mg/kg)	Average Daily Dose (mg/kg)	Number of Dogs
Control	0	0	0.25 mL/kg	14
Low Dose	0.025	0.025 – 0.05	0.03 mg/kg	10
Mid Dose	0.10	0.075 - 0.25	0.14 mg/kg	10
High Dose	0.25	0.15 – 1.0	0.35 mg/kg	14

The results of the study revealed that the effects of chronic administration of dirlotapide in the SEDDS vehicle at the mid and high doses were clinically similar to the results of safety studies with the final formulation. Findings during the treatment period in the mid and high dose groups included vomiting, discolored stools, loose/liquid stools, decreased body weight, decreased feed consumption, and decreased body condition scores. Clinical pathology, serum levels of vitamins A and E, and pathology results were similar to previous studies except for a few findings. Hematology revealed a slight number of burr cells noted on Day 91 and a slight number of target cells noted on Day 182 in 1 male dog euthanized 1 week early due to significant weight loss (30%) and decline in body condition (BCS of 2). On histopathology, all groups had a similar incidence of thymic atrophy but the mid and high dose groups had an increase in severity.

Mean dirlotapide systemic exposure (as assessed by $AUC_{0\text{-last}}$ and C_{max}) showed a dose-related but not dose-proportional increase with increased dose. Systemic exposure in dogs administered the product in the SEDDS formulation was similar to or higher than the systemic exposure observed with the commercial dirlotapide formulation.

In the dogs selected for the study, the veterinarian performing the ophthalmic examinations did not observe any ocular lesions at any time during the study. The lack of ocular lesions in this study supports the safety of dirlotapide. Based on this study and the nature of the lesions in the 1-year study, the ocular lesions observed in the 1-year study most likely represent common lesions or genetic defects known to exist in the Labrador breed.

4. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

5. USER SAFETY:

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

> **Not for human use. Keep this and all drugs out of the reach of children.**
>
> Adverse reactions associated with human consumption include: abdominal distention, abdominal pain, diarrhea, flatulence, headache, increased serum transaminases, nausea, and vomiting.
>
> SLENTROL may cause eye-irritation. If accidental eye exposure occurs, flush the eyes immediately with clean water.

One single dose and 3 short term multiple dose studies performed in humans evaluating a different formulation of dirlotapide revealed adverse reactions. The main adverse reactions following human consumption included, in alphabetical order: abdominal distention, abdominal pain, diarrhea, flatulence, headache, increased serum transaminases, nausea, and vomiting.

A single application of dirlotapide to a non-irrigated eye in 3 New Zealand White rabbits produced iridial inflammation and moderate conjunctival irritation. All treated eyes were normal by 48 hours. The study, based on the findings, scored dirlotapide as a minimal irritant.

6. 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 SLENTROL, when administered according to the label, is safe and effective for the management of obesity in dogs.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to provide adequate dosing instructions and to monitor the safe use of the product.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

U.S. Patent Number	Date of Expiration
6,720,351	October 12, 2022

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Package insert
Vial label (20 mL, 50 mL, and 150 mL)
Carton label (20 mL, 50 mL, and 150 mL)