Approval Date: May 30, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-080

B. Sponsor

Deprenyl Animal Health, Inc.
7101 College Blvd., Suite 580
Overland Park, KS 66210

C. Proprietary Name

Anipryl®

D. Established Name

selegiline hydrochloride, the levorotatory form of deprenyl HCl

E. Dispensing Status

Rx

F. Indication

Anipryl tablets are indicated for the control of clinical signs associated with uncomplicated canine pituitary dependent hyperadrenocorticism (PDH).

G. Dosage

After confirmation of the diagnosis of PDH, Anipryl is recommended orally once daily at an initial dose of 1 mg/kg (0.45 mg/lb) body weight, administered in the morning. During the first two months of therapy, the patient should be re-evaluated regularly for clinical response by history and physical examination. If no improvement in clinical signs or physical examination findings is evident after 2 months of therapy, the dose can be increased to a maximum of 2 mg/kg once daily. While increasing the dose from 1.0 to 2.0 mg/kg in a particular patient may not improve the effectiveness of the drug, favorable responses were seen in dogs treated at both 1.0 and 2.0 mg/kg in clinical trials. Patients should be monitored closely for possible adverse events associated with any increase in dose.

If there is no improvement after 1 month at the increased dose or if at any time clinical signs progress, the patient should be evaluated for the presence of concurrent disorders, including performance of appropriate laboratory tests or other studies as warranted. In dogs whose clinical signs of PDH progress despite Anipryl therapy in the absence of concurrent disease, alternative therapy should be considered.

II. EFFECTIVENESS

A. PDH2, Therapeutic Effect of L-Deprenyl in the Management of Canine Pituitary Dependent Hyperadrenocorticism Open Label Dose Range Trial

Type of study: Open label, multi-site dose range pilot clinical trial

Investigators		
Investigator Name	**City**	**State**
Dr. Barbara Atlee	Walnut Creek	CA
Dr. John Brees	Santa Clara	CA
Dr. David Bruyette	Manhattan	KS
Dr. Mike Cavanaugh	Topeka	KS
Dr. Tad Coles	Overland Park	KS
Dr. Gary Cowan	Wichita	KS
Dr. Pat Denney Dr. Julia Finlayson	Fairfax	VA
Dr. FM Gaddie	Lenexa	KS
Dr. Jack Garman	Stanford	CT
Dr. Laura Larson Dr. Kathy Gaughan	Abilene	KS
Dr. Alan Mundell	Seattle	WA
Dr. Jeff Myers	Topeka	KS
Dr. Vern Otte Dr. Cheryl Jones	Leawood	KS
Dr. Helen Power	Los Gatos	CA
Dr. Rob Raduzycki	Kansas City	MO
Dr. Nancy Sanders Dr. Carol Zerbe	Philadelphia	PA
Dr. Richard Schafer	Corpus Christi	TX
Dr. Dean Small	Overland Park	KS
Dr. Alan Stewart	Berkely	CA
Dr. Patricia Stewart	Kansas City	MO
Dr. Casey Thomas	Junction City	KS
Dr. John Van Zandt	Shawnee	KS
Dr. Jarvis Williams Dr. Sandi Leonard	Kansas City	MO
Dr. Sue Wingert	Wichita	KS
Dr. Karen Young	Salina	KS

Purpose: 1) to determine if administration of Anipryl® to dogs with PDH results in partial or complete resolution of this disorder [measured by amelioration of clinical signs and LDDS (low dose dexamethasone suppression) test results], 2) to determine the minimally effective dose, 3) to evaluate the clinical safety of Anipryl® therapy and 4) to optimize study procedures for later studies. Animals: 41 client-owned dogs (16 males and 25 females) of various breeds with spontaneously occurring PDH. The dogs ranged in age from 6 to 16 years (mean = 10.8 years) and weighed between 5.5 and 104.4 pounds (mean = 34.3 pounds).

Controls: The animals served as their own control because of the lack of other approved therapies and the progressive nature of the disease.

Diagnosis: The diagnosis of PDH was confirmed in each dog by: a) an abnormal LDDS test result and b) results of HDDS (high dose dexamethasone suppression) test

Dosage form: Anipryl® formulated into 2 mg, 5 mg, and 15 mg tablets

Route of administration: Oral

Dosage: Three dose groups were studied: the first 12 dogs enrolled received an initial dose of 0.5 mg/kg orally once daily; the 13 dogs enrolled into the second group initially received 1.0 mg/kg orally once daily; and 9 dogs in the third group received 2.0 mg/kg orally once daily throughout the trial. Dogs in the first two groups (dogs receiving 0.5 mg/kg and 1.0 mg/kg once daily) were considered for dose increases to 2.0 mg/kg at each re-exam if the owners or investigators were dissatisfied with the dogs' response.

Study Duration: Six months

Results: A total of 34 dogs were included in the evaluation of effectiveness (seven dogs from 1 investigator were eliminated due to investigator non-compliance). Thirteen of these 34 dogs completed less than 6 months of the study. Seven of the dogs were withdrawn due to lack of efficacy (as determined by either the veterinarian by lack of clinical response or as determined by the owner with dissatisfaction with the treatment); 4 developed disease unrelated to PDH (trauma, fibrosarcoma, disc disease, immune mediated disease); and 2 were withdrawn due to owner non-compliance.

The following table shows the number of dogs in each treatment group that completed the study to month 6 at their initial dose, i.e., those that had no increase in dose.

Dose	**Number Completing Study at The Initial Dose**
0.5 mg/kg	1/8 (12.5%)
1.0 mg/kg	7/8 (87.5%)
2.0 mg/kg	5/5 (100%)

In an extension of the original study, 11 dogs were continued on Anipryl therapy for up to at least month 12 with 5 of the dogs continuing up to at least month 15. Conclusions: The data suggest that the dose of 0.5 mg/kg is not as effective as the higher doses of 1.0 and 2.0 mg/kg for the control of clinical signs associated with PDH.

Adverse Reactions: Within a few days of starting therapy at 0.5 mg/kg, one dog presented with vomiting and diarrhea and was listless. The dog was dismissed from the trial. See page 12 for the adverse event data calculated from all field trials.

B. PDH3, Study of L-Deprenyl in the Management of Canine Pituitary Dependent Hyperadrenocorticism

Type of study: Open label, multi-site clinical field trial

Investigators		
Investigator Name	**City**	**State**
Dr. Randy Aronson	Green Valley	AZ
Dr. Nels E. Baclund	Omaha	NE
Dr. Ruth Boll	Portsmouth	Oh
Dr. Lex Bonam	Downers Grove	IL
Dr. Tim Cantrell	Ulysses	KS
Dr. Ron Carsten	Glenwood Springs	CO
Dr. Mike Cavanaugh	Topeka	KS
Dr. Melinda Chambers	Louisville	CO
Dr. David Clegg	Liverpool	NY
Dr. Kris Clothier	Antioch	CA
Dr. A.J. Collingwood	Beloit	KS
Dr. Diane Cosko	Lebec	CA
Dr. Tonya Curtis	Greensboro	NC
Dr. Pat Denney	Fairfax	VA
Dr. Wallace Diehl	Chapel Hill	NC
Dr. Dennis Drager	Marshalltown	IA
Dr. Maurine DuFault Fritch	Vancouver	WA
Dr. Joan Graulich	Syracuse	NY
Dr. Sheree J. Hughes	Bakersfield	CA
Dr. K. Kelly Jones	Wichita	KS
Dr. Mary C. Kelley	Cincinnati	OH
Dr. David Knaak	Bartonville	IL
Dr. Koen Loeven	Middlebury	CT
Dr. Craig Mabray	Albuquerque	NM
Dr. Duane Moore	Oakdale	CA
Dr. Linda Nickens	Roseville	CA
Dr. Albert Nunez	Coral Springs	FL
Dr. Dennis Olin	Stockton	CA
Dr. Patricia Parker	Friendswood	TX
Dr. Sarah Pratt	Sedgwick	KS
Dr. Jenny Silva	Austin	TX
Dr. William Skaer	Wichita	KS
Dr. W.T. Sternecker	Medina	OH
Dr. John Sundstrom	Gainesville	GA
Dr. Lianne Tabata	Bremmerton	WA
Dr. Sheila Taylor	Pekin	IL
Dr. Suzanne Terrent	Columbus	OH
Dr. Barbara Teter	Omaha	NE
Dr. Patricia Van Decoevering	Wilsonville	OR
Dr. Dean Vicksman	Denver	Co
Dr. Edward Wakem	Bristol	RI
Dr. Steve White	Fairway	KS

Purpose: 1) to confirm that 1.0 mg/kg of Anipryl® administered orally once daily is efficacious in the treatment of PDH and 2) to evaluate the clinical safety of Anipryl® in dogs. Animals: 52 client-owned dogs (16 males and 36 females) of various breeds with spontaneously occurring PDH were enrolled. The dogs ranged in age from 3.5 to 16 years (mean = 10.5 years) and weighed between 5.6 and 158.4 pounds (mean = 33.5 pounds).

Control: The animals served as their own control because of the lack of other approved therapies and the progressive nature of the disease.

Diagnosis: Each dog enrolled met the following criteria: 1) Presence of one or more of the following clinical signs of PDH: thinning of the skin, decreased elasticity of the skin, alopecia, thinning of the hair coat, and abdominal distention; 2) Diagnosis of PDH confirmed by: a) abnormal LDDS test results from at least 2 consecutive LDDS tests, and b) results of HDDS test, and other tests if warranted.

Dosage form: Anipryl® formulated into 2 mg, 5 mg, and 15 mg tablets

Route of administration: Oral

Dosage: 1 mg/kg administered orally once daily

Study Duration: Six months

Results: Nineteen of the 52 dogs enrolled completed less than 6 months of the study. Eleven of these dogs were withdrawn due to lack of efficacy (as determined by either the veterinarian by lack of clinical response or as determined by the owner with dissatisfaction with the treatment) and 8 developed injuries or concurrent illnesses unrelated to PDH or Anipryl therapy. Those dogs that responded to Anipryl tended to do so within 1-2 months after treatment was initiated.

Investigator monthly assessments. The veterinarians recorded their clinical assessments of each dog's response to therapy at each monthly re-examination. As summarized in the following table, during the first month of therapy, 34 of 52 dogs (65%) were assessed as either slightly improved or improved and 88% were either slightly improved or improved by month 2.

Assessment	**1**	**2**	**3**	**4**	**5**	**6**
Slightly Improved to Improved	34 (65%)	44 (88%)	42 (89%)	38 (88%)	35 (100%)	32 (97%)
Same	15 (29%)	5 (10%)	4 (9%)	3 (7%)	0 (0%)	1 (3%0)
Worse	3 (6%)	1 (2%)	1 (2%)	2 (5%)	0 (%)	0 (0%)
N	**52**	**50**	**47**	**43**	**35**	**33**

Investigator final assessments. Each dog was given a final assessment at the time of dismissal from the study. These subjective assessments indicated that 43 of 52 dogs (83%) improved overall with Anipryl therapy. In the following table, `improved' is broken down into `improved' and `slightly improved' in order to display the veterinarians' assessments more precisely.

Assessment	**Final Assessment**
Improved	25 (48.1%)
Slightly Improved	18 (34.6%)
No Change	6 (11.5%)
Worse	2 (3.9%)
Discontinued	1 (1.9%)
N	52

After 1 month of therapy, 33 of 52 dogs (63%) were reported by their owners to have an improved quality of life. By month 6 of the study, 29 of 33 dogs still enrolled in the study were reported to have an improved quality of life. This represents 88% of the dogs remaining in the study at month 6 or 56% of the original study population. Clinical signs of PDH monitored included: skin thickness, skin elasticity, alopecia, abdominal conformation, body weight changes, increased water consumption, signaling to go out to eliminate, appetite changes, activity level changes, sleep pattern changes, panting, decreased responsiveness to attention and enthusiasm of greeting. Based on the scores provided by the veterinarians and dog owners for all of the clinical variables observed, the response most assessed as improved was abdominal conformation by the veterinarians and activity level by the owners. The response varied from dog-to-dog with some dogs showing improvement in all of their presenting clinical signs but others showing improvement in only 1 or 2 parameters.

Endocrine Function Tests. The response to therapy was also evaluated by comparing the LDDS test results prior to treatment with those obtained at each monthly exam. For each dog, 2 LDDS tests were performed during the enrollment period and these results (the 8 hr. post dexamethasone value) were averaged and then compared to each monthly LDDS test result. The following table shows the least square means and their standard errors for the monthly LDDS test results.

Month 0	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
130.2	106.0	106.2	101.9	109.4	104.6	113.4
(9.3)	(9.3)*	(9.4)*	(9.6)*	(9.8)*	(10.5)*	(10.5)**

***** significant at the 0.05 level, two sided by pairwise difference t tests versus Month 0
****** significant at the 0.10 level, two sided by pairwise difference t tests versus Month 0

While the LDDS test results for the study population showed a return toward normal, there was no correlation between clinical response and the LDDS test results on an individual patient basis. There was no evidence of adrenal insufficiency.
Compassionate Use: Of the 33 dogs completing the study to month 6, 27 were eligible for enrollment in the compassionate use study. The owners of 26 of the 27 eligible dogs opted to continue treatment for an additional 3 months. Two doses were used in this compassionate study, 1.0 mg/kg and 2.0 mg/kg. The following table shows the number of dogs at each dose that completed the study.

Dose	**Number of Dogs**	**Nmber Completing Compassonate Use Study to Month 9**
1.0 mg/kg	15	12 (80%)
2.0 mg/kg	11	7 (63.6%)

Four dogs (3 in the 1.0 mg/kg group and 1 in the 2.0 mg/kg group) were dismissed from the compassionate use study due to the development of concurrent disease (pancreatitis, generalized weakness/ataxia, renal failure, and cataracts). Three dogs in the 2.0 mg/kg group were dismissed from the trial due to progression of PDH/lack of efficacy. It should be noted that 3 dogs in the 2.0 mg/kg group had their dose lowered back to 1.0 mg/kg due to possible adverse effects of the drug (diminished hearing in 1 dog and restlessness in 2 dogs). Conclusions: The data demonstrate that when dogs with uncomplicated PDH were treated with Anipryl at 1.0 mg/kg once daily, 65% responded clinically in 1 month and 88% responded clinically in 2 months. Response was variable and not necessarily permanent with a 21% failure rate. There was a statistically significant improvement in the LDDS test result for the study population. However, since there was no correlation demonstrated between an individual dog's clinical response to Anipryl and that dog's LDDS test results, monitoring should be based on history and physical examination findings.

Adverse Reactions: No dogs were withdrawn from the study due to adverse events, though 3 dogs dosed at 2.0 mg/kg in the compassionate phase of the study had their dose lowered back to 1.0 mg/kg due to possible adverse events (diminished hearing in 1 dog and restlessness in 2 dogs). See page 12 for the adverse event data calculated from all field trials.

C. PDH4, Study of L-Deprenyl in the Management of Canine Pituitary Dependent Hyperadrenocorticism

Type of study: Open label, multi-site clinical field trial

Investigators		
Investigator Name	**City**	**State**
Dr. Debra Anderson	Topeka	KS
Dr. Mike Berkenblit	North Palm Beach	FL
Dr. Garry Cowan	Wichita	KS
Dr. Bill Craig	San Antonio	TX
Dr. Pat Denney	Fairfax	VA
Dr. Sue Dougherty	San Jose	CA
Dr. Becky Elfers	Colfax	WA
Dr. Beth Gordon	Ramona	CA
Dr. Brian Harvick	Central Valley	CA
Dr. Beth Henry	DuBois	PA
Dr. Robert Johnson	Berryton	KS
Dr. David Knaak	Bartonville	IL
Dr. Gary Landsberg	Thornhill	Ontario, Canada
Dr. Brian McKee	Westminster	CO
Dr. Brian Melius	Metairie	LA
Dr. Lori Mitchell	Wichita	KS
Dr. Jory Olsen	Marietta	GA
Dr. Gail Ordun	Bishopville	MD
Dr. Carol Pitts	Lincoln	NE
Dr. Helen Power	Los Gatos	CA
Dr. Nelson Priddy Dr. Dan McIlhany	San Antonio	TX
Dr. James Rohleder Dr. Steve Mosier	Hays	KS
Dr. Ann Allen Salter	Montgomery	AL
Dr. Dean Small	Leawood	KS
Dr. Wendy Wallner	Lilburn	GA
Dr. Sue Wingert	Wichita	KS
Dr. Karen Young	Salina	KS

Purpose: 1) to confirm that 2.0 mg/kg of Anipryl® administered orally once daily is efficacious in the treatment of canine PDH and 2) to evaluate the field safety of Anipryl® in dogs. Animals: 39 client-owned dogs (15 males and 24 females) of various breeds with spontaneously occurring PDH were enrolled. The dogs ranged in age from 6 to 15 years (mean = 10.6 years) and weighed between 9.5 and 161.6 pounds (mean = 37 pounds).

Control: The animals served as their own control because of the lack of other approved therapies and the progressive nature of the disease

Diagnosis: Each dog enrolled met the following criteria: 1) Presence of one or more of the following clinical signs of PDH: thinning of the skin/decreased elasticity, pyoderma, alopecia or thinning of the hair coat, and abdominal distention; 2) Diagnosis of PDH confirmed by: a) abnormal LDDS test results from at least 2 LDDS tests, and b) results of HDDS test, and other tests if warranted.

Dosage form: Anipryl® formulated into 2 mg, 5 mg, and 15 mg tablets

Route of administration: Oral

Dosage: 2 mg/kg administered orally once daily

Study Duration: Three months initially with the option of extending the trial to 6 months for those dogs exhibiting a response to treatment.

Results: Nineteen of the 39 dogs enrolled completed less than 6 months of the study. Seven of the dogs were withdrawn due to lack of efficacy (as determined by either the veterinarian by lack of clinical response or as determined by the owner with dissatisfaction with the treatment); 5 developed diseases related to PDH (diabetes, pituitary macroadenoma, thromboembolism); 5 developed diseases unrelated to PDH (gastroenteritis, rear limb weakness, renal failure, pancreatitis, hepatocellular carcinoma); 1 had an adverse event (disorientation) and the diagnosis of PDH could not be confirmed in 1 dog. Those dogs that responded to Anipryl tended to do so within 1-2 months after treatment was initiated.

Investigator monthly assessments. The veterinarians recorded their clinical assessments of each dog's response to therapy at each monthly re-examination. As summarized in the following table, during the first month of therapy, 20 of 37***** dogs (54%) were assessed as slightly improved to improved and 61% were slightly improved to improved by month 2.

Assessment	**1**	**2**	**3**	**4**	**5**	**6**
Slightly Improved to Improved	20 (54%)	22 (61%)	18 (62%)	20 (87%)	19 (86%)	16 (84%)
Same	17 (46%)	9 (25%)	7 (24%)	3 (13%)	3 (14%)	3 (16%)
Worse	0 (0%)	5 (14%)	4 (14%)	0 (0%)	0 (0%)	0 (0%)
N	37	36	29	23	22	19

*****Number of assessments at each month are lower than the 39 enrolled due to investigator error or study drop-outs. *Investigator final assessments*. Each dog was given a final assessment at the time of dismissal from the study. These assessments indicated that 24 of 35 dogs (69%) improved with Anipryl therapy during months 1-3, 20 of 21 (95%) improved during months 4-6 and 11 of 15 (73%) improved during the compassionate phase of the study after month 6. In the following table, `improved' is broken down into `improved' and `slightly improved' in order to display the veterinarians' assessments more precisely.

Assessment	**Months 1-3**	**Months 3-6**	**Compassionate Use (6-15 months)**
Improved	10 (29%)	15 (71%)	8 (53%)
Slightly Improved	14 (40%)	5 (24%)	3 (20%)
No Changed	5 (14%)	0 (0%)	3 (20%)
Worse	4 (11%)	0 (0%)	0 (0%)
Discontinued	2 (6%)	1 (5%)	1 (7%)
N	**35**	**21**	**15**

After 1 month of therapy, 21 of 38 dogs (55%) were reported by their owners to have an improved quality of life. By month 6 of the study, 17 of 19 dogs still enrolled in the study were reported to have an improved quality of life. This represents 89% of the dogs remaining in the study at month 6 or 44% of the original study population. Clinical signs of PDH monitored included: skin thickness and elasticity, pyoderma, alopecia, regrowth of clipped hair, abdominal conformation, body weight changes, increased water consumption, signaling to go out to eliminate, appetite changes, activity level changes, sleep pattern changes and panting. Based on the scores provided by the veterinarians and dog owners for all of the clinical variables observed, the response most assessed as improved was abdominal conformation by the veterinarians and activity level by the owners. The response varied from dog-to-dog with some dogs showing improvement in all of their presenting clinical signs but others showing improvement in only 1 or 2 parameters.

Endocrine Function Tests. The response to therapy was also evaluated by comparing the LDDS test results prior to treatment with those obtained at each monthly exam. For each dog, 2 LDDS tests were performed during the enrollment period and these results (the 8 hr. post dexamethasone value) were averaged and then compared to each monthly LDDS test result. The following table shows the least square means and their standard errors for the monthly LDDS test results.

Month 0	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
111.8	102.8	102.2	101.5	93.1	103.4	98.1
(9.5)	(9.5)	(9.7)	(10.4)	(11.5)	(11.5)	(11.9)

While the LDDS test results for the study population showed a return toward normal, there was no correlation between clinical response and the LDDS test results on an individual patient basis. There was no evidence of adrenal insufficiency. Conclusions: The data demonstrate that when dogs with uncomplicated PDH were treated with Anipryl at 2.0 mg/kg once daily, 54% responded clinically in 1 month and 61% responded clinically in 2 months. Response was variable and not necessarily permanent with a 18% failure rate. While the LDDS test results for the study population showed a return toward normal, since there was no correlation demonstrated between an individual dog's clinical response to Anipryl and that dog's

LDDS test results, monitoring should be based on history and physical examination findings.

Adverse Reactions: One dog was withdrawn from the study at month 2 because it was displaying disorientation that was believed to be associated with the drug. One other dog experienced diarrhea that resulted in it being temporarily discontinued from treatment on 3 separate occasions. After the third bout of diarrhea, the dose was lowered to 1.0 mg/kg, which the dog tolerated well. See page 12 for the adverse event data calculated from all field trials.

Adverse Reactions from PDH2, PDH3 and PDH4: Because the clinical experience with Anipryl is limited to these 132 dogs, no placebo control was used and all dogs enrolled were compromised due to their underlying PDH, only a limited estimate of the potential adverse event rate for Anipryl can be provided. We acknowledge that many of the observations listed may be associated with the underlying disease, the advanced age of many of the patients or development of concurrent, unrelated disease. The following table lists the adverse events reported in 3 or more dogs from all three field trials (> 2%), in decreasing order of frequency. A total of 132 dogs were enrolled in these 3 trials.

Prevalence of adverse events reported
in 3 open-label clinical field trials Number of Dogs N = 132
vomiting20diarrhea18restlessness/repetitive
movements6lethargy5salivation5anorexia5diminished
hearing/deafness3pruritus3licking 3shiver/tremble/shake3 Six dogs (5%) experienced the adverse events that lead either to discontinuation of therapy, dismissal from the study, or a reduction in dose: 1) diarrhea, vomiting and listlessness; 2) disorientation, 3) diarrhea, 4) diminished hearing, and 5) restlessness in 2 dogs.

The following list provides all other events reported by the investigators in the three trials as being either remotely or possibly due to the study drug.

Allergic skin disease, anemia, ataxia, bronzing of the hair, blindness, cardiac disease, circling, coughing, dermatitis, dry mouth, elevated BUN and phosphorus, epistaxis, fever, flatulence, gagging, hardening of the stools, hepatitis/bilirubinuria, Horner's syndrome, keratoconjunctivitis sicca (KCS), labored breathing, lick granuloma, mydriasis, nystagmus, otitis, pale membranes, pancreatitis, panting, polydipsia, pyoderma, rash, renal casts, respiratory distress, seborrhea, tachypnea, thrombocytopenia, uremia, urinary incontinence, urinary tract infection, weak in rear and weight gain.

III. TARGET ANIMAL SAFETY

Target Animal Safety Study With Anipryl® in Dogs

Type of Study: Target Animal Safety

Investigator:
David L. Heimbichner
Fermenta Animal Health Company
Research Center
1512 Webster Court
Fort Collins, CO 80524

Purpose: to determine the safety of Anipryl® when administered, per os, at 0.5, 1, 1.5 and 3 times the maximum daily level to adult dogs over a period of 6 months, as compared to a placebo control. Animals : 40 beagle dogs (20 male and 20 female) were assigned to one of five treatment groups with each group containing 4 males and 4 females. The dogs ranged in age from 2 to 7 years.

Control: Placebo tablets, indistinguishable from tablets containing active ingredient

Dosage Form: Anipryl® formulated into 2 mg, 5 mg, and 15 mg tablets

Route of administration: Oral

Dosage: Group 1 received placebo tablets, Group 2 received the study drug (Anipryl®) at a rate of 1 mg/kg/day, Group 3 received the study drug at a rate of 2 mg/kg/day, Group 4 received the study drug at a rate of 3 mg/kg/day, and Group 5 received the study drug at a rate of 6 mg/kg/day. All dogs were dosed for 183 consecutive days.

Test Duration: Six months

Pertinent parameters measured: 1) Daily behavioral observations - stereotypic (repetitive) behavior, attention to observer as observer approaches, anxiety, and aggression; 2) Daily clinical observations - feces, excessive salivation, condition of eyes, pupillary response, mucous membranes, hydration, respiration, skin irritation, and presence or absence of vomitus; 3) General physical examinations; 4) Ophthalmic examinations; 5) Rectal temperatures; 6) Body weights; 7) Feed consumption; 8) ECG and blood pressure; 9) Urinalysis; 10) Hematology and clinical chemistry screens. Parameters 1, 2 and 5 were evaluated twice daily, just prior to treatment in the morning and 4 hours after treatment.

Two dogs from each group were euthanized and necropsied each day over 4 consecutive days, beginning on Day 183 and concluding on Day 186. Collected tissues were examined microscopically from all animals in the placebo and high (3X) dose groups. Any gross lesions observed in the low and mid-dose groups (0.5X, 1X, and 1.5X) were also examined histologically.

Results:

Behavioral observations:
At a dose of 6 mg/kg, the incidence of stereotypic (repetitive) behavior as evidenced by weaving back and forth in the cage, was statistically significant ($p < 0.0171$) compared to placebo. The occurrence of weaving was more prevalent following treatment than prior to treatment. This constant, repetitive movement in the cages and exercise runs led to abrasions on the legs, nose and/or foot pads of 6 dogs (1 in the 1 mg/kg group, 3 in the 3 mg/kg group and 2 in the 6 mg/kg group).

There was a significant dose by time effect for the attention parameter, which was demonstrated by the fact that the least square means showed a decreasing dose trend in the morning prior to treatment whereas they showed an increasing dose trend following treatment. This trend suggests that the dogs given the higher doses were more likely to show no motor response in the morning and an active response following treatment. However, there was sufficient variability in the responses to prevent any group comparisons to control from being statistically significant.

Clinical observations:

Observation	**Statistical Significance**	**Before or After Daily Treatment**
Hypersalivation	1, 3 and 6 mg/kg	After
Decreased Pupillary Light Response	1, 3 and 6 mg/kg	---
Rectal Temperatures	6 mg/kg (males only)	Decreased Befre Incrased After
Pale Mucous Membranes	1.2, 3 and 6 mg/kg	Before
Panting	6mg/kg	After

Mean body weights were decreased for the 3 and 6 mg/kg groups relative to control from months 3 to the end of the study. The 6 mg/kg group was statistically significantly lower than control at month 2, and by the end of the study the 2 mg/kg group was also statistically significantly lower than control. While body weights decreased with increasing dose, feed consumption was increased in the 2, 3 and 6 mg/kg groups in months 2 and 3 of the study.

Two dogs in the 6 mg/kg group were responsible for a majority of the clinical observations and best demonstrate the toxic effects of Anipryl. These 2 dogs displayed repetitive, purposeless weaving in their cages and in the exercise runs which led to abrasions and foot pad injuries. They were responsible for the majority of the hypersalivation noted in the high dose group, both showed slight dehydration throughout the study beginning at weeks 4 and 10, respectively, and both showed increased panting following administration of the daily dose.

There were no significant changes noted in blood pressure, heart rate and ECG parameters, nor were there any ophthalmic changes.

Laboratory findings:

Red cell mass - RBC, Hb, and HCT: The baseline values for these parameters were highly variable and had more of an effect on the subsequent values than did treatment. The effect of Anipryl on these parameters was not significant over time.

Hepatic enzyme activities - Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Alkaline phosphatase (ALP): The range for ALT was 11 - 164 IU/L for all dogs on the study and the published reference range is 1 - 130 IU/L (Kirk and Bonagura, eds., Current Veterinary Therapy, 11th. Ed., 1992, Saunders, Philadelphia). The only statistically significant treatment effect was an increase in ALT activity for dogs receiving 6 mg/kg. No statistically significant differences were detected in the activities of AST or ALP.

Conclusions: Anipryl is safe for use in dogs at the recommended daily dose range of 1.0-2.0 mg/kg. Anipryl causes toxicity at 3 and 6 mg/kg (1.5X and 3X the maximum recommended daily dose) when administered daily for 6 months to dogs. Significant

effects seen at the 3 and 6 mg/kg doses include decreased body weight despite normal to increased feed consumption, increased incidence of hypersalivation and decreased pupillary light response. Additional statistically significant effects at the 6 mg/kg dose include increased stereotypic behavior (predominantly weaving, which in some dogs led to abrasions on the legs, face and foot pads), increased ALT, and an increased incidence of panting and dehydration.

IV. HUMAN FOOD SAFETY

Human Safety Relative to Food Consumption: Data on human safety, pertaining to consumption of drug residues in food, were not required. This drug is to be labeled for use in dogs, which are non-food animals.

Human Safety Relative to Possession, Handling and Administration:
Labeling contains an adequate caution statement.
Labeling states: "Keep out of reach of children."

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that Anipryl (selegiline hydrochloride), when used under labeled conditions of use is safe and effective.

The drug is restricted for use by or on the order of a licensed veterinarian because professional expertise is required for the diagnosis of pituitary dependent hyperadrenocorticism and for the monitoring of adverse events and response to therapy.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval for non-food producing animals qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

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