Approval Date: December 10, 1998

FREEDOM OF INFORMATION SUMMARY

ANIPRYL® (selegiline hydrochloride) Tablets
for use in dogs

NADA 141-080

Pfizer, Inc.
Groton, CT 06340

Freedom of Information Summary

ANIPRYL® TABLETS

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1. General Information:

NADA Number:	141-080
Sponsor:	Pfizer, Inc. 812 Springdale Dr. Exton, PA 19341
Generic Name:	selegiline hydrochloride, the levorotatory form of deprenyl HCl
Trade Name:	Anipryl®
Marketing Status:	Rx: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Effect of Supplement:	This supplement changes the original approval by adding a second claim for use in cognitive dysfunction syndrome at a new dose of 0.5-1.0 mg/kg.

2. Indications for Use:

   Anipryl® tablets are indicated for the control of clinical signs associated with canine Cognitive Dysfunction Syndrome (CDS).

3. Dosage Form, Route of Administration, and Recommended Dosage(s):

   The recommended dosage for oral administration for the control of clinical signs associated with cognitive dysfunction is 0.5 -1.0 mg/kg once daily, preferably administered in the morning. Initially, dogs should be dosed to the nearest whole tablet. Adjustments should then be made based on response and tolerance to the drug.

4. Effectiveness:

   CD/HT- Study of Anipryl Effects on Cognitive Dysfunction in Aged Dogs

Type of study:	Phase 1 - Placebo controlled, multi-site, dose range clinical field trial Phase 2 - Open label, dose confirmation study

Investigators:

Investigator Name	City	State
Dr. Kimberly Anderson	Redford	MI
Dr. Tim Anderson	Bakersfield	CA
Dr. Joan Antle	Lyndhurst	OH
Dr. Gari-Anne Austin	Lawrenceville	GA
Dr. Richard Austin	Kissimmee	FL
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Dr. Megan Bamford	Covina	CA
Dr. Glen Baron	Matthews	NC
Dr. Mildred Bass	Farragut	TN
Dr. Pete Beeman	San Francisco	CA
Dr. Lark Behrens	Tucson	AZ
Dr. James Bianco	Ardmore	PA
Dr. Gwen Bilyk	Saint Louis	MO
Dr. James Blackert	Sugarland	TX
Dr. Julie Bobb	Lexington	KY
Dr. Diana Bochenski	Buellton	CA
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Dr. Susan Ferraro	Chicago	IL
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Purpose: 1) To assess the efficacy of Anipryl® administered orally once daily for control of clinical signs associated with CDS and 2) To evaluate the clinical safety of Anipryl® in dogs.

Animals: 199 client-owned dogs (82 males and 117 females) of various breeds with acquired cognitive dysfunction were enrolled. The dogs ranged in age from 7 to 20 years (mean = 13.9 years) and weighed between 4.5 and 152 pounds (mean = 36.7 pounds).

Control: During the first 4 week phase, one group received placebo tablets comprised of the formulation excipients without active ingredient The placebo tablets were indistinguishable from Anipryl® tablets.

Enrollment: Each dog enrolled met the following criteria:

1) Presence of acquired cognitive dysfunction, as documented by the presence of at least 3 of the following cognitive problems: disorientation; decreased activity; increased sleep or changes in sleep/wake cycle; loss of housetraining or reduced signaling behavior (i.e, signals less to go outside); decreased enthusiasm of greeting behavior; decreased responsiveness to attention.
2) Age 10 years or older; giant breed dogs, age 7 years or older.
3) No known concurrent debilitating disease that would preclude monitoring response to therapy.
4) No concurrent treatment or recent treatment with corticosteroids or other medication that could cause polyuria/polydipsia or substantially affect behavior.
5) No concurrent treatment with medications known to interact with Anipryl®.
Dogs were excluded if they had evidence of concurrent disease or concurrent drug therapy that could preclude monitoring of response to therapy, or if they had other behavioral problems such as aggression.

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

Route of administration: Oral

Dosage: 0 mg/kg administered to one group of 67 dogs, 0.2 mg/kg administered to one group of 65 dogs, and 1.0 mg/kg administered to one group of 67 dogs once daily in the morning.

Study Duration: Three months, divided into two phases.

Phase 1:	Three dose groups (placebo, 0.2 mg/kg, or 1.0 mg/kg) were studied for 4 weeks.
Phase 2:	All dogs were administered 1.0 mg/kg of Anipryl® in open label fashion for 8 additional weeks.

Variables evaluated: Entrance and post-treatment evaluation criteria consisted of evaluation of the following behaviors: orientation, activity, sleep pattern, housetraining, responsiveness, and greeting behavior. The owner stated if each behavior had worsened, stayed the same, or improved. The owners' assessments of changes in behavior were obtained by telephone interview with the veterinary behavioral consultants at enrollment, week 4 and week 12.

Results: Phase 1-(4-week, placebo controlled dose range study):

Results of the 4-week study are based on 181 evaluable dogs. Table 1 shows proportions of dogs that improved following 4 weeks of treatment with Anipryl® or placebo. Improvement of individual parameters was evaluated in those dogs with the behavioral abnormality in question at the initiation of the study. Significant improvements were observed in sleep pattern, housetraining and activity.

Table 1. Proportion of Improved Dogs at Week 4 by Dose Group

Behavior (Number affected at enrollment)	**Control**	**0.2 mg/kg**	**1.0 mg/kg**	**Overall p-value***
Orientation (179)	22/62 (35.5%)	24/59 (40.7%)	32/58 (55.2%)	0.098
Activity (166)	16/56 (28.6%)	22/57 (38.6%)	29/53 (54.7%)	0.012
Sleep (164)	9/54 (16.7%)	17/55 (30.9%)	29/55 (52.7%)	0.001
Responsiveness (158)	23/55 (41.8%)	26/55 (47.3%)	25/48 (52.1%)	0.499
Housetraining (157)	15/57 (26.3%)	21/54 (38.9%)	16/46 (34.8%)	0.030
Greeting (145)	12/48 (25.0%)	20/51 (39.2%)	15/46 (32.6%)	0.584

*For the Cochran-Mantel-Haenszel test for nonzero correlation, indicating increased improvement with increasing dose.

Phase 2- (Open label dose confirmation study, continued to week 12):

Results of the 8-week open label phase of the study are based on 157 evaluable dogs. Analyses of week 12 evaluations compared the percent improvement at 12 weeks to that observed at 4 weeks of treatment. Table 2 results indicate some dogs that did not improve by week 4 showed improvement by week 12. This tendency to improve was observed in all 3 treatment groups by 12 weeks of treatment regardless of the initial treatment received during the first 4 week period (i.e. placebo, 0.2, or 1.0 mg/kg of Anipryl®), indicating that some increased improvement may be seen with extended use, even among high dose (1.0 mg/kg) group animals. Significant improvement occurred in activity, sleep pattern, and housetraining.

Table 2. Proportion of Improved Dogs at Week 12 Among Those Not Improved at Week 4

The headings for the proportions below refer to the dosage groups the dogs were in during the first phase of the trial. In phase 2, all dogs received 1.0 mg/kg.

Behavior (n)	Control	0.2 mg/kg	1.0 mg/kg
Orientation (86)	17/35 (48.6%)	18/29 (62.1%)	11/22 (50.0%)
Activity (83)	15/35 (42.9%)	15/31 (48.4%)	6/17 (35.3%)
Sleep (96)	12/41 (29.3%)	12/35 (34.3%)	6/20 (30.0%)
Responsiveness (68)	14/27 (51.8%)	12/24 (50.0%)	8/17 (47.1%)
Housetraining (90)	12/36 (33.3%)	18/29 (62.1%)	13/25 (37.1%)
Greeting (82)	7/32 (21.9%)	10/27 (37.0%)	8/23 (34.8%)

To assess the duration of effect, the change between week 4 and week 12 among those dogs who were evaluated as improved at week 4 was evaluated. The proportion of dogs that regressed at week 12 among those improved at week 4 was fairly consistent across the groups. The duration of effect may be as short as 8 weeks in about 50% of the cases.

Conclusions: In this clinical trial, Anipryl® administered at 1.0 mg/kg once daily was shown to provide safe and effective control of clinical signs associated with CDS in pet dogs. The onset, duration and magnitude of response varied with individual dogs. Based on the results in Table 1, trends indicate that the higher dose of 1.0 mg/kg is more effective than the lower dose of 0.2 mg/kg.

Adverse Reactions: Refer to the Safety section (page 12) for adverse events observed in clinical trials.

CD3, Multi-Site Clinical Trial of Anipryl® for Canine Cognitive Dysfunction

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

Investigators:

Investigator Name	City	State
Dr. W.A. Andrews	Bonner Springs	KS

Dr. Ward Brown	Kansas City	MO
Dr. Don Dinges	Leawood	KS
Dr. Rusty Erickson, Dr. Todd Goodman	Mission	KS
Dr. Karen Eyer-Stokes	Overland Park	KS
Dr. Wayne Hunthausen, Dr. Annette Frerking	Westwood	KS
Dr. Kevin Lesslie	Shawnee	KS
Dr. Scott Lichlyter	Brentwood	CA
Dr. Keven McShane, Dr. R. Brenton Smith	Austin	TX
Dr. Vern Otte, Dr. Cheryl Jones, Dr. Keith Longhofer	Leawood	KS
Dr. Dan Reimer, Dr. Mary Haitt	Sepulveda	CA
Dr. Brian Rind	Great Neck	NY
Dr. Jill Sandler	Overland Park	KS
Dr. Tom Shackelford	Carmel	IN
Dr. David Theiss	Lee's Summit	MO
Dr. Steve White, Dr. Scott Mickleson	Fairway	KS
Dr. Jarvis Williams, Dr. Sandi Leonard	Kansas City	MO

Purpose: The objectives of this clinical trial were to assess the efficacy and safety of Anipryl® for CDS in the dog.

Animals: 73 client-owned dogs (29 males and 44 females) of various breeds with spontaneously occurring CDS were enrolled. The dogs ranged in age from 7 to 19 years (mean = 15 years) and weighed between 8 and 80 pounds (mean = 31 pounds).

Controls: Each animal served as its own control.

Diagnosis: Diagnosis of CDS was based on the presence of one or more of the following clinical or behavioral signs: decreased appetite, decreased awareness of surroundings, decreased ability to recognize familiar places, people or other animals, decreased hearing, decreased ability to climb up and down stairs, decreased tolerance to being alone, development of compulsive behavior or repetitive behaviors or habits, circling, tremors or shaking, disorientation, decreased activity level, abnormal sleep wake cycles, loss of house training, decreased or altered responsiveness to family members, and decreased or altered greeting behavior. Dogs were excluded if they had evidence of concurrent disease or concurrent drug therapy that could preclude

monitoring of response to therapy, or if they had other behavioral problems such as aggression.

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

Route of administration: Oral

Dosage: One dose group was studied: dogs received 0.5 mg/kg orally once daily throughout the trial. Three dogs had an increase in dose to 1.0 mg/kg because of lack of efficacy and two dogs had the dosage halved due to adverse events (hyperactivity).

Study Duration: Three months.

Variable evaluated: Changes in the behaviors and clinical signs listed below in Table 3.

Results: To determine responses to 0.5 mg/kg once daily Anipryl® treatment, individual parameters were evaluated in this trial by methods similar to those used in the CD/HT clinical trial. A complete listing of response to individual parameters is displayed in Table 3. The sleep pattern improvement is consistent with the dose response pattern observed for this variable in the CD/HT study. The improvement rates for housetraining, activity, and orientation exceed that observed in 1.0 mg/kg dose group from the CD/HT study.

Table 3. Proportion Improved at 4 Weeks
Parameters in bold are the same parameters evaluated in CD/HT clinical trial.

Behavior	Proportion* (%)
Housetraining	**19/47 (40.4%)**
Activity/attention	**30/51 (58.8%)**
Orientation/awareness	**28/47 (59.6%)**
Recognition	15/41 (36.6%)
Tolerance to being alone	4/31 (12.9%)
Circling	8/20 (40.0%)
Sleep/wake	**13/46 (28.3%)**
Whining/whimpering	10/29 (34.5%)
Alertness	**31/55 (56.4%)**
Response to commands	12/60 (20.0%)
Recognizing people	11/46 (23.9%)
Memory	11/50 (22.0%)

Learning ability	3/50 (6.0%)
Interact with people	12/42 (28.6%)
Interact with other dogs	7/47 (14.9%)

*The proportions are the number improved over the number with the problem at the beginning of the study.

Conclusions: The results of this clinical trial support the inclusion of 0.5 mg/kg as the lower end of a dosage range.

5. Safety:

The safety of Anipryl® is based on data in the original approval (refer to the Freedom of Information Summary dated May 30, 1997). The information below describes the adverse events reported in the CDS clinical field trials.

In the CD/HT clinical trial, 132 dogs were monitored for adverse events while on Anipryl® for up to 12 weeks and 67 dogs were monitored on the drug for up to 8 weeks. In the CD3 trial, 73 dogs were monitored while on Anipryl® for up to 12 weeks.

The following table lists the adverse reactions reported in the 2 clinical trials. The 67 dogs that received placebo during Phase 1 of the CD/HT trial are included.

Table 4: Adverse events from 2 clinical field trials

Adverse Event	**Placebo (n=67)**	**Anipryl® (n=272)**
vomiting	14 (21%)	87 (32%)
diarrhea	7 (10%)	55 (20%)
hyperactive/restless*	4 (6%)	42 (15%)
anorexia	1 (1%)	29 (11%)
neurologic**	1 (1%)	26 (10%)
lethargy	1 (1%)	20 (7%)
urinary tract infection	1 (1%)	17 (6%)
salivation	3 (4%)	15 (6%)
weakness	0 (0%)	15 (6%)
pale gums	1 (1%)	14 (5%)
polyuria/polydipsia	1 (1%)	13 (5%)
pruritis/dermatologic	1 (1%)	13 (5%)
weight loss	0 (0%)	12 (4%)
panting	1 (1%)	10 (4%)
cardiovascular/resp***	0 (0%)	10 (4%)
diminished hearing	0 (0%)	7 (3%)

*includes hyperactive, irritable, anxious, restless, abnormal repetitive movements
**includes ataxia, incoordination, staggering, disorientation, decreased proprioception, seizure
***includes heart murmurs, tachycardia, collapse, dyspnea, pleural effusion, sneezing

In the CD/HT trial, 5 dogs had the drug discontinued because of the following adverse events: 1) vomiting and diarrhea, 2) hyperactivity, 3) increase in destructive behavior associated with separation anxiety, 4) anemia, and 5) stiffness and polydipsia.

In the CD3 trial, 2 dogs had the dosage halved because they became too active and 5 dogs had the drug discontinued because of the following adverse events: 1) vomiting (in 2 dogs); 2) agitation, 3) stargazing and trembling a few hours after the first tablet was given, and 4) possible drug interaction. After being on the drug for about a week one dog experienced weakness, confusion, incoordination and "seizure-like" activity. The dog was also on metronidazole, prednisone, and trimethoprim sulfa. All drugs were discontinued, and the dog returned to normal.

A trend in hematocrit levels was noticed during review of individual case reports. Some dogs experienced a drop in hematocrit during the clinical trials. The decreases seen were usually within the normal range and not accompanied by any clinical signs. One dog had a rapid drop below the normal range accompanied by lethargy and anorexia. The dog recovered after the drug was discontinued**.**

6. Human 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."

7. 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, L-deprenyl), when used under labeled conditions of use, is safe and effective.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application conducted or sponsored by the applicant.

The drug is restricted for use by or on the order of a licensed veterinarian because professional expertise is required for the diagnosis of clinical signs associated with cognitive dysfunction syndrome and for the monitoring of adverse events and response to therapy.

Patent information: The sponsor holds the following patents: 5,225,446 (expires 8-31-10); 5,276,057 (expires 1-4-11); 5,387,615 (expires 2-7-12); 5,565,495 (expires 10-15-13); 5,561,163 (expires 10-1-13); 5,151,449 (expires 8-31-10); and 5,192,808 (expires 8-31-10).

8. Labeling (attached):

Package Insert
Cartons for 2, 5, 10, 15 and 30 mg tablets
Blister package foil backing for 2, 5, 10, 15 and 30 mg tablets