Date of Approval: January 19, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-272

RECONCILE

Fluoxetine Hydrochloride
Chewable Tablets
Dogs

"For the treatment of canine separation anxiety in conjunction with a behavior modification plan."

Sponsored by:

Elanco Animal Health,
A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-272
B. Sponsor:	Elanco Animal Health, A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Name:	RECONCILE
D. Established Name:	fluoxetine hydrochloride
E. Pharmacological Category:	Selective serotonin reuptake inhibitor (SSRI)
F. Dosage Form:	Chewable tablets
G. Amount of Active Ingredient:	Four different strength tablets containing 8 mg, 16 mg, 32 mg, and 64 mg of fluoxetine hydrochloride per tablet
H. How Supplied:	Bottles containing 30 tablets
I. How Dispensed:	Rx
J. Dosage:	1-2 mg/kg once daily
K. Route of Administration:	Oral
L. Species/Class:	Dogs
M. Indication:	RECONCILE chewable tablets are indicated for the treatment of canine separation anxiety in conjunction with a behavior modification plan.

II. EFFECTIVENESS:

A. Dosage Characterization:

Results from controlled field studies and published clinical case reports support the premise that fluoxetine administered at a dose range of 0.5 to 4.0 mg/kg of body weight/day may be safe and effective to treat various canine behavioral disorders, including separation anxiety. For example, in a double-masked field study (Rapoport JL, et.al.; 1992), a mean fluoxetine dose range of 0.55 to 1.36 mg/kg of body weight/day administered over five weeks produced a 39% ($p<0.05$) reduction in mean licking behavior from baseline observations in fourteen dogs diagnosed with acral lick dermatitis (ALD). Adverse reactions subsided over time and included lethargy, hyperactivity and loss of appetite.

In a placebo-controlled field study (Wynchank D and Berk M, 1998a), 58 dogs diagnosed with ALD had a statistical improvement in licking behavior, lesion appearance and general condition when administered up to 4 mg/kg of body weight/day over the course of 6 weeks. No adverse reactions were noted in either the fluoxetine or the placebo group. When this study was extended another two months at the same doses (Wynchank D and Berk M, 1998b), four dogs were withdrawn from the extended trial; three were unexplained withdrawals, and one was attributed to vomiting associated with fluoxetine treatment.

In other studies, the following adverse reactions have been observed with the clinical use of fluoxetine in dogs. At 1 mg fluoxetine/kg of body weight/day, Melman (1995) reported lethargy (26%), hyperactivity (18%), polydipsia (16.9%), diarrhea (4.5%), and both an increase and decrease in appetite (21% each) as the most common adverse reactions. Dodman (1997) reported sedation and reduced appetite in dogs treated with fluoxetine at 0.5 to 1.0 mg/kg of body weight/day. A 23 kg dog maintained on 12.5 mg/kg of body weight/day for 28 months experienced dilated pupils, but the pupils remained responsive to light (Overall 1995).

Further characterization of the dose was demonstrated by a placebo-controlled study conducted in client-owned dogs with separation anxiety in 47 veterinary behavior referral practices or general practices with a behavior interest or expertise in France, Germany, and the United Kingdom. Following initiation of treatment with fluoxetine chewable tablets, improvement was observed in both the 1-2 and 2-4 mg/kg of body weight dose groups compared to placebo within two to four weeks with approximately 80% of all dogs showing improvement by study conclusion. The most frequently observed adverse reactions for fluoxetine were decreased appetite, lethargy, muscle tremors, constipation, and mydriasis. At the 2-4 mg/kg of body weight dose, these signs were not acceptable and were assessed as follows: 1) decreased appetite and lethargy were most frequent; 2) muscle tremor incidence was undesirably high and more severe compared to the lower doses; and 3) mydriasis was limited to the 2-4 mg/kg of body weight dose. One dog in the 0.25-0.5 mg/kg of body weight dose group, receiving 0.4 mg/kg of body weight/day for one month,

experienced a seizure one week after fluoxetine discontinuation. The results from this study demonstrated that 1-2 mg/kg of body weight of fluoxetine administered once daily in conjunction with behavior modification is effective for the treatment of separation anxiety while minimizing the frequency or severity of adverse reactions.

Based on the studies discussed above, a dose range of 1 to 2 mg/kg of body weight/day was chosen to evaluate in field studies to maximize the likelihood of successful amelioration of separation anxiety in dogs while minimizing the frequency and severity of adverse reactions.

References:

Rapoport JL, Ryland DH, and Kriete M. (1992). Drug Treatment of Canine Acral Lick: An Animal Model of Obsessive-Compulsive Disorder. *Arch Gen Psychiatry.* 49: 517-521.

Dodman NH. (1997). Prozac shows promise in treating behavior problems. *Vet Med.* pp318-319.

Melman SA. (1995). Use of Prozac in animals for selected dermatological and behavioral conditions. *Vet Forum.* pp19-27.

Overall KL. (1995). Animal Behavior Case of the Month. *J Am Vet Med Assoc.* 206(5):629-632.

Wynchank D and Berk M. (1998a). Fluoxetine treatment of acral lick dermatitis in dogs: A placebo-controlled randomized double blind trial. *Depression and Anxiety.* 8:21-23.

Wynchank D and Berk M. (1998b). Behavioral changes in dogs with acral lick dermatitis during a 2-month extension phase of fluoxetine treatment. *Hum. Psychopharmacol Clin Exp*. 13: 435-437.

B. Substantial Evidence:

1. Field Study (Study T8E420001):

Title: Efficacy Evaluation of Fluoxetine (fluoxetine hydrochloride) for the Control of Separation Anxiety in Dogs.

Type of Study: Field Study

Purpose: The primary objective was to confirm the clinical effectiveness of 1-2 mg/kg of RECONCILE chewable tablets administered once daily for the treatment of separation anxiety (SA) in client-owned dogs. Secondary objectives included the evaluation of adverse reactions of RECONCILE chewable tablets in dogs, the association between the frequency of SA signs and the subjective SA behavioral scores and evaluation of the palatability of the RECONCILE chewable tablets.

Investigators:

Brett A. Berryhill DVM Baton Rouge, LA	Hobson Fulmer DVM Eastpoint, FL	Melanie Kenzie DVM London, Ontario Canada
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Suzanne Petrillo DVM Orchard Park, NY	Casey Thomas DVM Junction City, KS	Samuel Geller DVM Quakertown, PA
Michelle Posage DVM Lexington, MA	Douglas Urban DVM Sunbury, OH	Lynn Erdman DVM Portland, OR

Animals: Two hundred and twenty nine (229) healthy, client-owned dogs were enrolled in the study. Of those 229, 112 dogs received the control tablets and 117 received RECONCILE chewable tablets. All dogs received behavior modification. Ninety-two dogs in the control group and 96 dogs in the RECONCILE chewable tablets group adequately completed the study to be evaluated for effectiveness. All dogs were at least 6 months of age and weighed between 2.7 kg and 58.4 kg. The population represented both male and female dogs as well as pure and mixed breeds.

Dosage Form: Fluoxetine hydrochloride in flavored 8 mg, 16 mg, 32 mg, and 64 mg chewable tablets. The control tablet contained the same inert excipients as the RECONCILE chewable tablets without fluoxetine.

Route of Administration: Oral

Dosage Groups:

Table 1: Dosing Table

Dog Weight (kg)	Tablet Size (mg)	Fluoxetine (mg)
4 – 8[a]	100	8
>8 – 16	200	16
>16 – 32	400	32
>32 – 64	800	64

[a] dogs weighing between 2 and less than 4 kg were administered ½ of an 8 mg scored tablet. The 8 mg tablet is not scored in the final market formulation, precluding administration to dogs less than 4 kg.

Study Duration: 70 days (14 days pre-treatment and 56 days of treatment).

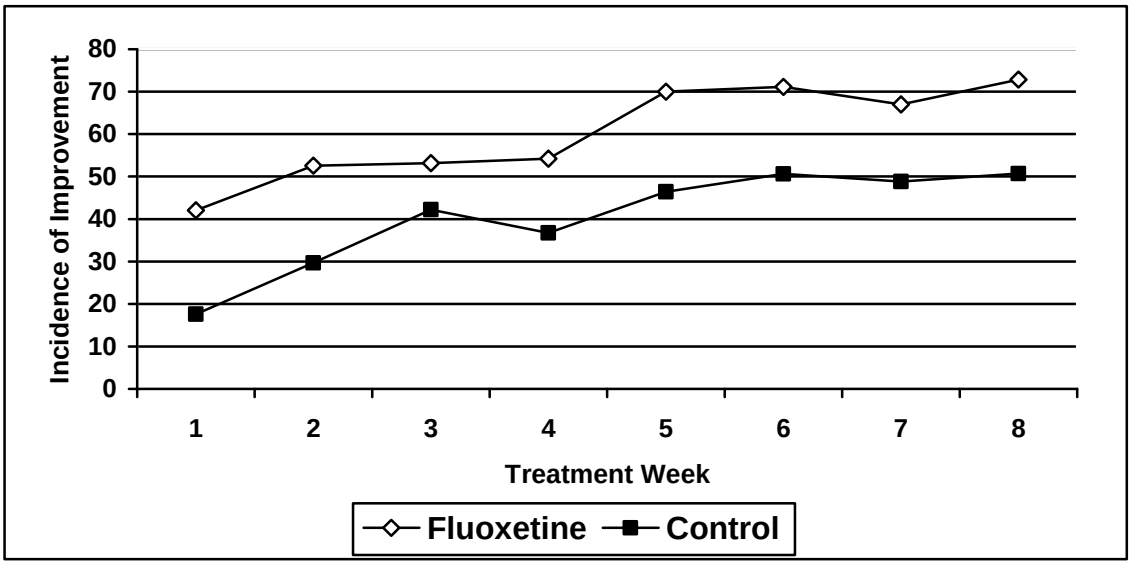
Parameters Measured: The primary effectiveness measure was the incidence of dogs demonstrating improvement in global separation anxiety (SA) severity score. Incidence of improvement of the individual SA behaviors and frequency of test article palatability were also assessed. The individual behaviors evaluated were destructive/rearranging behavior, excessive vocalization, inappropriate urination, inappropriate defecation, excessive salivation, excessive licking or grooming, shaking or shivering, restlessness, and depression. Body weight was measured prior to enrollment and at the end of treatment. A complete blood count, serum chemistry analysis, and urinalysis were performed pre-study and at the end of treatment.

Study Design: This was a multi-centered, double-masked, controlled, parallel-arm study comparing RECONCILE chewable tablets to control tablets with formal behavior modification in each arm. After initial consultation with the Investigator, owners evaluated their dogs for a 14-day pre-treatment period. Based on those observations, the Investigator made the initial diagnosis of SA, which was confirmed by a board-certified behaviorist. Dogs that met the inclusion criteria were allocated to a treatment group for a 56-day period. During the treatment period, owners were instructed to administer study medication once per day, execute the behavior modification plan, record daily observations, and complete a weekly questionnaire in a diary. The behavior modification plan consisted of desensitization and counter-conditioning exercises for the owner to conduct while at home, before leaving and after returning home. If an owner crated their dog prior to the study to control SA behavior, the owner continued to crate their dog during the study. The Investigator called the owner on Days 28 and 56 to check on general progress. The Investigator performed a physical examination on Days 42 (mid-study) and 70 (end of study). At the end of the treatment period, owners returned the daily diary and any remaining test article.

Statistical Methods: The statistical significance of treatment on owner assessed behavioral severity scores was assessed using a generalized linear mixed model analysis with the logit link function and the binomial error distribution in which the effect of treatment upon the binary response variable, improved or not improved relative to baseline, was modeled separately for each week. In the analysis, study center and study center by treatment interactions were employed as random effects.

Results: The primary measure of effectiveness was the incidence of improved global SA severity score (relative to pre-treatment). The percentage of dogs with improved global SA scores was statistically higher among dogs that received RECONCILE chewable tablets compared with dogs who received control tablets at each week, with the exception of treatment week 3 (Figure 1 and Table 2).

Figure 1: Study T8E420001 Incidence (%) of Improved Separation Anxiety Scores



The following table shows the level of statistical significance of the incidence of improvement between treatment groups at each treatment week.

Table 2: Statistical Significance at Each Treatment Week

Treatment Week	P-value
1	0.005
2	0.004
3	0.149
4	0.025
5	0.004
6	0.011

Treatment Week	P-value
7	0.024
8	0.010

Dogs treated with RECONCILE chewable tablets also showed improvement in destructive behavior, excessive vocalization, and restlessness over dogs that received the control tablets. In addition, dogs in both groups experienced improvement in inappropriate urination, inappropriate defecation, excessive salivation, excessive licking/grooming, shaking/shivering, and depression. Overall SA severity scores improved more rapidly for dogs taking RECONCILE chewable tablets than those receiving the control tablets, and the same effect was also noted for the individual scores for excessive vocalization and depression.

RECONCILE chewable tablets were palatable, as 70% of the dogs voluntarily accepted the tablets.

Conclusions: The oral administration of 1-2 mg/kg of RECONCILE chewable tablets once daily is effective for the treatment of separation anxiety when administered in conjunction with behavior modification in dogs. RECONCILE chewable tablets are palatable. To minimize the risk of adverse reactions, it is important not to exceed the recommended dose. Owners and veterinarians should assess the individual risks and benefits prior to initiating treatment with RECONCILE chewable tablets.

Adverse Reactions: The most common adverse reactions are as follows:

Table 3: Study T8E420001 Adverse Reactions

Adverse Reaction	Fluoxetine N=117		Control,[1] N=112	
	n	%	n	%
Calm /Lethargy/Depression	53	45.3	19	17.0
Anorexia/Decreased Appetite	34	29.1	12	10.7
Shaking/Shivering/Tremor	19	16.2	4	3.6
Vomiting	17	14.5	10	8.9
Restlessness/Hyperactivity	16	13.7	7	6.3
Excessive Vocalization (Includes Whining)	13	11.1	7	6.3
Anxiety	8	6.8	8	7.1
Diarrhea	7	6.0	7	6.3
Attachment to Owner	6	5.1	3	2.7
Disruptive/Destructive	6	5.1	8	7.1
Aggression	5	4.3	9	8.0
Excessive Licking	5	4.3	6	5.4
Otitis Externa	5	4.3	1	0.9
Tartar	5	4.3	5	4.5
Disorientation/Confusion	4	3.4	1	0.9
Submissive/Fearful	4	3.4	1	0.9
Disobedience	4	3.4	2	1.8

Adverse Reaction	Fluoxetine N=117		Control,[1] N=112	
Incoordination	4	3.4	0	0.0
Excessive Salivation	3	2.6	2	1.8
Hiding	3	2.6	0	0.0
Inappropriate Defecation	3	2.6	5	4.5
Panting	3	2.6	3	2.7
Seizures	3	2.6	1	0.9
Flatulence	2	1.7	1	0.9

[1] The control group received the tablet formulation without fluoxetine.

One of 112 dogs in the control group and three of 117 dogs that received RECONCILE chewable tablets experienced the serious adverse reaction of seizures in this study. One of the three dogs treated with RECONCILE chewable tablets experienced two seizures 10 days after the end of fluoxetine therapy. Despite escalating phenobarbital doses, the seizures continued and this dog died in status epilepticus approximately six months after the first seizure. The second of the three dogs treated with RECONCILE chewable tablets experienced one seizure approximately 1½ years prior to study enrollment immediately after experiencing head trauma. This dog did not experience any additional seizures until he experienced one seizure 45 days after the end of therapy with RECONCILE chewable tablets. During the 1½-year period since that second seizure, the dog's seizure activity increased from single seizures to cluster seizures despite increasing doses of phenobarbital and the addition of oral potassium bromide and rectal diazepam. The third dog treated with RECONCILE chewable tablets experienced one seizure 24 days after the start of therapy. No anticonvulsant therapy was initiated, and no further seizures were reported. The control dog experienced one seizure 35 days after the start of the administration of the control tablet. No anticonvulsant therapy was initiated, and no further seizures were reported.

Weight loss was a common adverse reaction, as 32.1% of the dogs treated with RECONCILE chewable tablets and 15.7% of the control dogs experienced weight loss greater than or equal to 5% of the initial body weight. The following table shows the number of dogs with weight change, with the dogs with weight loss stratified by percent loss relative to initial body weight. In Table 4, the total number (N) of dogs (112 and 102 in the RECONCILE chewable tablet and control group, respectively) are those dogs from the overall safety population (117 and 112 in the RECONCILE chewable tablet and control groups, respectively) with body weight measurements throughout the study. No dogs were withdrawn from the study because of weight loss alone.

Table 4: Dogs with Weight Change in Study T8E420001
(Weight loss stratified by percent loss relative to initial body weight)

Treatment Group (Number)	Weight Gain	Weight Loss			
		>0 to < 5.0% n (%)	≥ 5% to < 10% n (%)	≥ 10% to < 14%	≥ 15% n (%)

				n (%)	
RECONCILE chewable tablets N=112	46 (41.1%)	30 (26.8%)	26 (23.2%)	9 (8.0%)	1[a] (0.9%)
Control N=102	60 (58.8%)	26 (25.5%)	15 (14.7%)	1 (1.0%)	0 (0.0%)

[a] This dog lost 20% of its initial body weight and was the same dog that died in status epilepticus.

Eighteen dogs in the RECONCILE chewable tablet group and five dogs in the control group required a reduction in dose due to unacceptable adverse reactions, generally anorexia, shaking, vomiting, and depression. Reducing the dose decreased the severity of these adverse reactions in the RECONCILE chewable tablet group only. Although restarting the full dose of RECONCILE chewable tablets resulted in resumption of the original adverse reactions in approximately half of the dogs, they generally appeared less severe, with the exception of one dog who required a second dose reduction of RECONCILE chewable tablets due to unacceptable severity of adverse reactions.

III. TARGET ANIMAL SAFETY:

A. Toxicity Study (Study D3760):

Title: A One Year Chronic Toxicity Study with Two Month Recovery Phase of Fluoxetine Hydrochloride (LY110140) Administered Orally to Beagle Dogs

Investigators: Gregory T. Brophy, PhD
Stephen G. Lake, DVM, PhD

Location: Eli Lilly and Co
Indianapolis, IN

General Design:
Purpose: To determine the potential cumulative toxicity and reversibility of any toxicology of fluoxetine hydrochloride with chronic administration to Beagle dogs.

Animals: Test animals were adult laboratory Beagle dogs (4/gender in the control group, 5/gender in the treated group)

Dosage Form: Dry powder of the active pharmaceutical ingredient (API) in gelatin capsules was administered. This formulation was not the final market formulation. A pharmacokinetic bridging study (Study D00901) to RECONCILE chewable tablets indicated that this formulation is less bioavailable than RECONCILE chewable tablets.

Route of Administration: Oral

Dosage Groups: The following table shows the dosage groups used in this study and the dose equivalent to the RECONCILE chewable tablets. Due to toxicity at 20 mg/kg/day, the dose used in this dose group was reduced to 10 mg/kg/day (equivalent to 8.7 mg/kg/day or 4.4X the maximum dose of 2 mg/kg/day) starting on Day 180 and continuing through the end of the study.

Table 5: Dosage Groups

Treatment Group[1]	Study Dose (mg/kg/day)	RECONCILE Chewable Tablets Equivalent (mg/kg/day) Based Upon Mean AUC[2] Ratios (1.15)[3]	Actual Treatment Group (using RECONCILE Chewable Tablets dose)[4]
Control	0	0	Control
0.5 X	1.0	0.87	0.43 X
2.25 X	4.5	3.9	1.96 X
10 X	20	17.4	8.70 X

[1] X is defined as the maximum dose of 2 mg/kg/day.

[2] Area under the concentration versus time curve

[3] The tablet equivalents are estimated by dividing the fluoxetine-filled capsule doses by the mean (1.15) ratio of RECONCILE chewable tablet/capsule, as calculated from the relative bioavailability data, Study D00901 (the corresponding upper and lower 90% confidence limits about the ratio of treatment means = 1.28 and 1.08, respectively).

[4] Actual treatment group estimated as the fluoxetine-filled capsule treatment group divided by the average relative bioavailability of RECONCILE chewable tablet/capsule (1.15).

Study Duration: All dogs were dosed once daily for 1 year. Two dogs/sex/treatment group were removed from fluoxetine treatment during an additional two-month recovery phase.

Pertinent Measurements/Observations: Clinical observations, complete blood count (CBC) and blood chemistry, urinalysis, electrocardiogram, body weight, food consumption, fluoxetine and norfluoxetine plasma and tissue concentration, phospholipid tissue concentration, electron microscopy of buffy coat and lung, adrenal cortex and retina, organ weights, and pathology.

Results: Three of five female dogs in the 20 mg/kg group died or were euthanatized during the first six months of the study. The high dose was decreased to 10 mg/kg/day (equivalent to 8.7 mg/kg/day of RECONCILE chewable tablets) for the last six months of the treatment, and all remaining dogs completed the study. One dog in the 1 mg/kg group (equivalent to 0.87 mg/kg/day of RECONCILE chewable tablets) and two dogs in the 20 mg/kg group (equivalent to 17.4 mg/kg/day of RECONCILE chewable tablets) experienced a seizure. Aggressive behavior, ataxia, salivation at dosing, hyperesthesia, nystagmus, thin body condition, weakness, lethargy, diarrhea, and head tilt were also noted in the high dose group. Anorexia, tremors, decreased pupillary light response, mydriasis, vomiting, and decreased weight gain were observed in all treatment groups, but occurred more frequently in

the high dose group. With the exception of decreased weight gain, all abnormal observations resolved by the end of a two-month recovery period. Evidence of phospholipidosis was noted in the lung, liver, adrenal glands, lymph nodes, spleen, retina, and white blood cells of all groups, which resolved during the recovery period. Fluoxetine caused no marked or consistent effects on hematology, blood chemistries, or urinalysis. Bradycardia was absent on the electrocardiogram in the control and lowest dose groups, but was mildly present in a dose-dependent manner in the two higher dose groups. There were no effects noted on gross organ examination.

Conclusions: This study demonstrated that fluoxetine has a variable individual safety response and a narrow margin of safety, as one dog who received the equivalent of 0.87 mg/kg/day (0.43 times the maximum recommended RECONCILE chewable tablets dose of 2 mg/kg/day) experienced a seizure. Other adverse reactions may be observed at less than the minimum recommended dose of 1 mg/kg/day. Resolution of most of the adverse reactions, with the exception of decreased weight gain, was achieved by discontinuation of fluoxetine administration.

B. Pharmacokinetic Study (Study D00901):

Title: Pharmacokinetics of Fluoxetine and its Metabolite, Norfluoxetine in Beagle Dogs Given Two Formulations of Fluoxetine HCl in a Crossover Design

Investigators: N. A. Farid, PhD
R. C. Pohland, PhD

Location: Eli Lilly and Company
Indianapolis, IN

General Design:
Purpose: To determine and compare the pharmacokinetic parameters of fluoxetine and its major metabolite, norfluoxetine, in Beagle dogs after oral administration of a chewable tablet formulation and a dry powder capsule formulation.

Animals: Twelve (6 male, 6 female) Beagle dogs were randomly assigned to 2 groups of 6 dogs each.

Dosage Form:
Fluoxetine hydrochloride (LY110140) gelatin capsule (formulation used in the safety study D3760)
Fluoxetine hydrochloride (LY110140) chewable tablets (final market formulation)

Route of Administration: Oral

Dosage Groups:

Table 6: Dosage Groups

Group	Dosage Form	Study Day

01	Gelatin capsule	0
	Chewable tablet	21
02	Chewable tablet	0
	Gelatin capsule	21

Study Duration: Thirty-one total days. Dogs received a single dose of each formulation with a minimum 20-day washout period between dose administrations. Blood samples were collected at 0 (second dose only), 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, 144, and 240 hours after dosing.

Pertinent Measurements/Observations: Plasma concentration of fluoxetine and norfluoxetine, clinical observations, body weight, food consumption, and clinical pathology.

Results: No gender differences were observed in plasma concentrations or the pharmacokinetic parameters of fluoxetine and norfluoxetine. Concentrations of fluoxetine were <1 ng/mL in most of the plasma samples collected beyond 24 hours of dosing, whereas norfluoxetine was quantifiable up to 10 days after each dose. The plasma half-life ($T_{1/2}$) for fluoxetine in dogs ranged from 3 to 12.9 hours and the $T_{1/2}$ for norfluoxetine ranged from 33 to 64 hours. The type of formulation did not have an effect on maximum plasma concentration (C_{max}) or $T_{1/2}$ for fluoxetine, and C_{max}, AUC and $T_{1/2}$ for norfluoxetine. However, the bioavailability of fluoxetine in the RECONCILE chewable tablets was greater than that of the gelatin capsules, with the upper bound of the 90% confidence interval being > 1.25 for AUC_{last} (Table 7 and Table 8).

Table 7: Relative Concentrations of Fluoxetine

Fluoxetine						
Parameter	**Unit**	**RECONCILE Chewable Tablets**	**Capsule**	**Ratio**	**LCL**	**UCL**
$AUC_{0\text{-last}}$	ng*hr/mL	1340	1162	1.15	1.08	1.28
C_{max}	ng/mL	126.6	112.4	1.13	1.03	1.25
T_{max}	hr	1.7	1.8	0.94		
$T_{1/2}$	hr	6.2	6	1.03		

LCL=lower confidence limit
UCL=upper confidence limit
T_{max}=time to maximum plasma concentration (C_{max})

Table 8: Relative Concentrations of Norfluoxetine

Norfluoxetine						
Parameter	**Unit**	**RECONCILE**	**Capsule**	**Ratio**	**LCL**	**UCL**

		Chewable Tablets				
$AUC_{0\text{-last}}$	ng*hr/mL	10984	9758	1.13	1.06	1.19
C_{max}	ng/mL	138	126	1.10	1.03	1.14
T_{max}	hr	12.8	16.3	0.79		
$T_{1/2}$	hr	48	48	1.00		

Conclusions: Administration of fluoxetine hydrochloride as RECONCILE chewable tablets to dogs resulted in exposure to fluoxetine and norfluoxetine that is marginally higher than the levels of exposure observed when fluoxetine is administered as a capsule containing fluoxetine hydrochloride as a dry powder.

C. Field Study (Study T8E180101):

Title: Efficacy Evaluation of LY110140 for the Control of Separation Anxiety in Dogs without Behavior Modification

Type: Field Study

Purpose: The objective of this study was to evaluate the effectiveness of RECONCILE chewable tablets for the treatment of SA without behavior modification.

Investigators:

Mili Bass, DVM
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Bethlehem, PA

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Dean Rund, DVM
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Charles Schwirck, DVM
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Roger Sifferman, DVM
Springfield, MO

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Greg Tremoglie, DVM
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Melissa Wiest. DVM
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Cat Cross
Fort Collins, CO

Patrick Melese, DVM
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Jacqui Neilson, DVM
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Animals: One hundred and ninety eight (198) healthy, client-owned dogs were enrolled in the study. Of those 198 dogs, 99 dogs received the control tablets and 99 dogs received RECONCILE chewable tablets. Of the initial 198 dogs, 83 dogs in the control group and 85 dogs in the RECONCILE chewable tablets group adequately completed the study to be evaluated for effectiveness. All dogs were at least 6 months of age and weighed between 2.7 kg and 66.2 kg. The population represented both male and female dogs as well as pure and mixed breeds.

Dosage Form: Fluoxetine hydrochloride in flavored 8 mg, 16 mg, 32 mg, and 64 mg chewable tablets. The control tablet contained the same inert excipients as the RECONCILE chewable tablets without fluoxetine.

Route of Administration: Oral

Dosage Groups:

Table 9: Dosing Table

Dog Weight (kg)	Tablet Size (mg)	Fluoxetine (mg)
4 – 8[a]	100	8
>8 – 16	200	16
>16 – 32	400	32
>32 – 64	800	64

[a] dogs weighing between 2 and less than 4 kg were administered ½ of an 8 mg tablet

Study Duration: 56 days (14 days pre-treatment and 42 days of treatment).

Parameters Measured: Variables measured included the incidence of improved global SA severity score, the rate of change in overall SA scores, and the rate of change in individual behavior scores. The individual behaviors evaluated were destructive/rearranging behavior, inappropriate urination, inappropriate defecation, and excessive salivation. Body weight was measured prior to enrollment and at the end of treatment. A complete blood count and serum chemistry analysis were performed pre-study and at the end of treatment. A urinalysis was performed pre-study.

Study Design: This was a multi-centered, double-masked, controlled, parallel-arm study comparing fluoxetine to control without formal behavior modification in either arm. After the initial consultation with the investigator, dogs were evaluated by their owners for a 14-day pre-treatment period. Based on those observations, a diagnosis of SA was made by the Investigator. If the dog met the inclusion criteria, the patient was allocated to a treatment group and the owners were instructed to administer test article as well as record daily observations and a weekly overall severity score for a 42-day period. If an owner crated the dog prior to the study to control SA behavior, the owner continued to crate the dog during the study. At the end of the treatment period, owners returned the daily diary and any remaining test article. The Investigators performed a physical exam at the initial visit and final evaluation.

Results: The primary measure of effectiveness was the incidence of improved global SA severity score (relative to pre-treatment). There was no clinically significant improvement in global SA scores in the dogs that received RECONCILE chewable tablets compared with the dogs who received the control tablets throughout the treatment period. Both the treatment and control groups revealed the greatest change in global SA

severity scores between the pre-treatment period and week 1 with little additional improvement over the six-week treatment period. The rate of change in the weekly global SA severity score did not differ considerably between dogs treated with RECONCILE chewable tablets and control tablets.

Conclusions: Administration of RECONCILE chewable tablets did not result in considerable improvement in SA behaviors when administered without behavior modification. Therefore, because this study did not confirm the effectiveness of RECONCILE chewable tablets, this study will be used for safety purposes only.

Adverse Reactions: The most common adverse reactions are as follows:

Table 10: Study T8E180101 Adverse Reactions.

	Fluoxetine, N=99		**Control,[1] N=99**	
Adverse Reaction	**n**	**%**	**n**	**%**
Anorexia/Decreased Appetite	24	24.2	1	1.0
Vomiting	20	20.2	18	18.2
Calm/Lethargy/Depression	18	18.2	3	3.0
Diarrhea	14	14.1	10	10.1
Shaking/Shivering/Tremor	5	5.1	0	0.0
Aggression	4	4.0	4	4.0
Constipation	3	3.0	0	0.0
Submissive/Fearful	3	3.0	0	0.0
Weight Loss	3	3.0	0	0.0
Dietary Indiscretion	2	2.0	1	1.0
General Dermatitis	2	2.0	0	0.0
Anxiety	1	1.0	1	1.0
Pruritus/Itching	1	1.0	3	3.0
Cough	1	1.0	2	2.0
Cystitis	1	1.0	0	0.0
Disorientation/Confusion	1	1.0	0	0.0
Erythema	1	1.0	0	0.0
Exfoliation	1	1.0	0	0.0
Fecal Incontinence	1	1.0	0	0.0
Gastritis	1	1.0	0	0.0
Hematuria	1	1.0	0	0.0
Hyperesthesia	1	1.0	0	0.0
Inappropriate Urination	1	1.0	0	0.0
Incoordination	1	1.0	0	0.0
Nausea	1	1.0	0	0.0
Ocular Discharge	1	1.0	0	0.0
Otitis Externa	1	1.0	1	1.0
Pain	1	1.0	0	0.0
Pale Mucous Membranes	1	1.0	0	0.0
Panting	1	1.0	0	0.0
Seizure (Convulsion)	1	1.0	1	1.0
Stranguria	1	1.0	0	0.0
Urinary Incontinence	1	1.0	0	0.0

[1] The control group received the tablet formulation without fluoxetine.

One of 99 dogs treated with RECONCILE chewable tablets and one of 99 dogs treated with the control tablets experienced the serious adverse reaction of seizures in this study. The dog treated with RECONCILE chewable tablets experienced a seizure 9 days after initiation of drug therapy and 7 days after ingesting 8 ounces of milk chocolate and 14 ounces of dark chocolate. The dog had lost 11.2% of its initial body weight in that time. Magnetic resonance imaging (MRI) approximately one month after the seizure did not reveal an etiology. Approximately two months after the seizure, the veterinary neurologist diagnosed vestibular disease. No further seizures were reported. The control dog had a mild seizure 27 days after initiation of administration of the control tablets. The dog also had a previous history of recurrent weakness in the hind legs; the differential diagnosis for this weakness included seizures.

Weight loss was a common adverse reaction, as 26.2 % of dogs treated with RECONCILE chewable tablets and 9.6 % of control dogs experienced weight loss greater than or equal to 5% of the initial body weight. The following table shows the number of dogs with weight change, with the dogs with weight loss stratified by percent loss relative to initial body weight. In Table 11, the total number (N) of dogs (84 and 83 in the RECONCILE chewable tablet and the control group, respectively) are those dogs from the overall safety population (99 and 99 in the RECONCILE chewable tablet and the control groups, respectively) with body weight measurements throughout the study. No dogs were withdrawn from the study because of weight loss alone.

Table 11: Dogs with Weight Change in Study T8E180101
(Weight loss stratified by percent loss relative to initial body weight)

Treatment Group (Number)	**Weight Gain**	**Weight Loss**			
		>0 to < 5.0% n (%)	**≥ 5% to < 10% n (%)**	**≥ 10% to < 14% n (%)**	**≥ 15% n (%)**
RECONCILE chewable tablets N=84	28 (33.3%)	34 (40.5)	18 (21.4%)	4 (4.8%)	0 (0.0%)
Control N=83	47 (56.6%)	28 (33.7%)	5 (6.0%)	3 (3.6%)	0 (0.0%)

Two dogs in the RECONCILE chewable tablet group required a reduction in dose due to unacceptable side effects, generally anorexia, shaking, vomiting, and depression. Reducing the dose improved the severity of these side effects. Restarting the full dose resulted in resumption of the original side effects. In one dog, they appeared less severe, while the other dog was withdrawn from the study due to unacceptable severity of signs.

IV. 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.

V. USER SAFETY:

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

"Not for use in humans. **Keep out of reach of children.** In case of accidental ingestion seek medical attention immediately. In humans, the most common symptoms associated with overdosage include seizures, somnolence, nausea, tachycardia, and vomiting. In case of ingestion by a human, contact a physician immediately. For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Eli Lilly at 1-800-428-4441."

VI. 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 RECONCILE chewable tablets, when used according to the label, are safe and effective for the treatment of separation anxiety in conjunction with a behavior modification plan.

A. Marketing Status:

This drug is restricted to use by or on the order of a licensed veterinarian due to the expertise needed to diagnose and manage separation anxiety and to monitor for adverse reactions during treatment.

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 approval because no active ingredient (including any ester or salt of the active ingredient) of the drug has previously been approved.

C. Patent Information:

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

VII. ATTACHMENTS:

Facsimile Labeling:
Package Insert
Client Information Sheet

Carton and Vial Labeling