

Does your dog exhibit any of these problematic behaviors when left home alone?

- ✓ Destroying household items
- ✓ Urinating or defecating indoors
- ✓ Barking, howling and/or whining
- ✓ Excessive drooling
- ✓ Frequent pacing
- ✓ Attempt to escape / signs of damage around doors or windows

**Your dog may be suffering from Separation Anxiety.**



Navigating through a pandemic has been challenging for everyone—except perhaps for our dogs—who have been living a more socially active life than usual because so many pet owners have been working from home.

However, a change back to normal work week routines will leave our dogs with less companionship during the day. Many dogs adopted during the pandemic have no idea what “normal” is for their families. When life resumes some sense of normalcy, the sudden lack of constant contact with people may cause some pets to experience separation anxiety.

## What is Separation Anxiety?

Separation anxiety is a condition in which affected dogs may exhibit certain problematic behaviors when left alone, such as when owners leave for work or to run an errand. Whether a particular dog is going to develop separation anxiety depends on several factors:

- Specific factors about the individual dog—their emotional resiliency, level of attachment to the owner, underlying predisposition to anxiety and panic disorders, etc.
- Environmental factors—Will owners be allowed to work from home part-time or will they be going back to the office full time?
- Prior learning and experiences—
  - Has there been appropriate reinforcement for independent behavior?
  - Has excessive attention seeking been rewarded in the past?
  - Did the pet have separation anxiety prior to relinquishment by a former owner?

## How Can I Prevent Separation Anxiety?

You may not be able to prevent this disorder from developing in your dog; however, leaving your dog home alone on occasion so he gets used to being there without you may decrease the chances of him developing separation anxiety.

## How Is Separation Anxiety Diagnosed?

You should discuss any signs of separation anxiety such as those listed on page 1, including signs that may be suggestive of other disorders, with your veterinarian.<sup>1,2</sup> Your veterinarian can rule out any medical causes with a physical exam and possibly other diagnostic tests. A video of your dog when home alone may help your veterinarian confirm that these signs are indeed behavioral.

## Can My Dog's Separation Anxiety Be Treated?

Once your dog has been diagnosed with separation anxiety, your veterinarian will develop a comprehensive treatment plan that includes behavior modification to help develop your dog's independence and possibly medication.

### Behavior Modification

Treatment for separation anxiety involves behavior modification, including the following:

- Try leaving your dog with a delicious snack like a frozen Kong or puzzle toy to not only keep them occupied but also to help associate your departure with something wonderful.
- Remain calm and ignore your dog for 20 to 30 minutes prior to leaving so as not to create a heightened state of arousal just prior to your departure.

- Never punish your dog for house soiling or destruction as it will only serve to increase the anxiety associated with anticipation of your return.

For more information on the initial training steps for separation anxiety, please visit [reconcile.com/bond-training-information](http://reconcile.com/bond-training-information).

### Medication

Depending on the severity, medication, such as Reconcile® (fluoxetine hydrochloride) from PRN® Pharmacal, may be needed to help decrease anxiety. Reconcile is an FDA-approved medication that is commonly used to treat separation anxiety in dogs in conjunction with behavior modification training.<sup>3,4</sup> Reconcile is a once-a-day flavored, chewable tablet prescribed by your veterinarian.



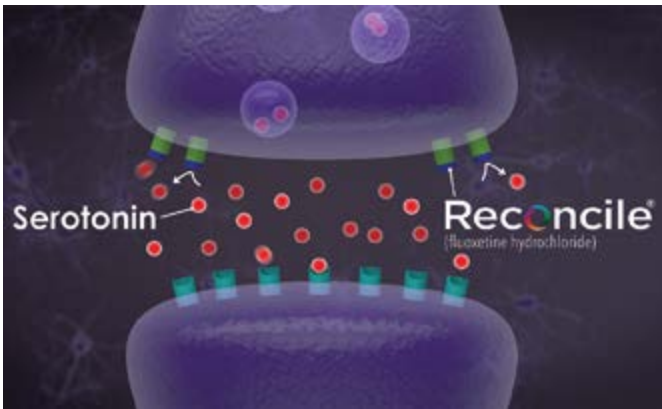
### Reconcile® Product Facts

- Reconcile is a flavored, chewable, once-a-day tablet, making administration easier for both the pet owner and their dog.
- Reconcile, developed specifically for dogs with separation anxiety, has been clinically tested and FDA approved for use in dogs.
- Convenient strengths (8 mg, 16 mg, 32 mg and 64 mg); this is unlike generic human formulations.
- Reconcile has an exclusive behavior modification plan; the BOND™ program was designed to help you train your dog using simple, easy-to-understand steps.



## How Does Reconcile Work?

Reconcile is a selective serotonin reuptake inhibitor (SSRI). Chemical messengers known as neurotransmitters communicate information between nerve cells. Neurotransmitters are released into the space between two cells and are then reabsorbed back into the nerve cell that released them. Serotonin is a neurotransmitter that is responsible for many functions within the brain, including the control of anxiety. Low levels of serotonin may result in impaired communication between nerves, producing an increased level of anxiety. Reconcile can help correct this chemical imbalance by blocking the reuptake of serotonin and temporarily increasing its level in the brain.

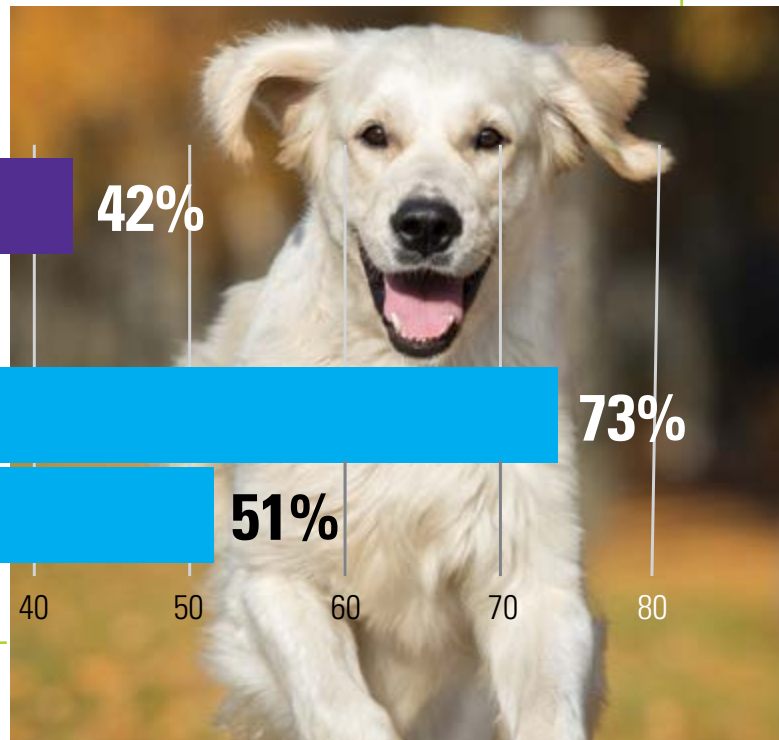
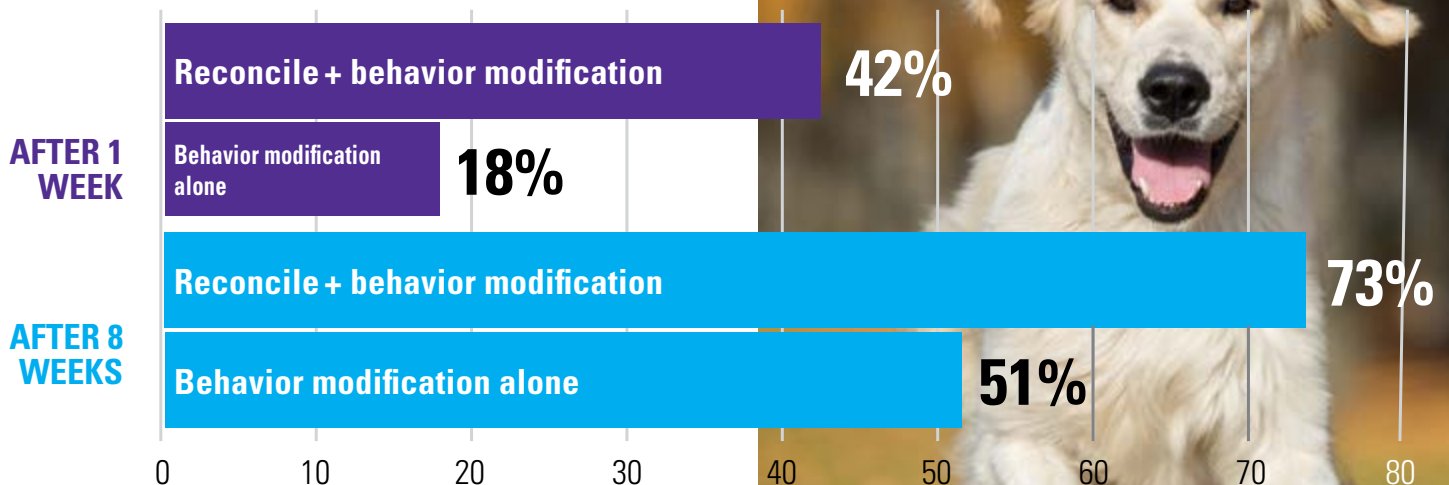


Reconcile works by making your dog more receptive to your training program. A study of 229 dogs receiving behavior modification training showed that a significantly higher number of dogs treated with Reconcile had measurable improvement compared with those receiving a placebo (see study results below).

As a pet owner, it's important to be aware of the typical signs of separation anxiety and discuss them with your veterinarian. It's also important to remember that your dog is not bad but is suffering from a readily treatable medical condition.

## Important Safety Information

The most common adverse events in decreasing order of reported frequency are: decreased appetite, depression/ lethargy, shaking/ shivering/tremor, vomiting, restlessness and anxiety, seizures, aggression, diarrhea, mydriasis, vocalization, weight loss, panting, confusion, incoordination, and hypersalivation. Reconcile chewable tablets are contraindicated for dogs with a history of seizures or when used with MAOIs. For product label, including complete safety information, see package insert.



# Reconcile<sup>®</sup>

(fluoxetine hydrochloride)

Affordable. Reliable. Chewable.

PRESCRIBING INFORMATION FOR VETERINARIAN  
07-2021

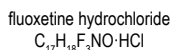
RECONCILE<sup>®</sup> (fluoxetine hydrochloride) Chewable Tablets

## Caution:

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

## Description:

RECONCILE is a chewable, flavored tablet that contains fluoxetine hydrochloride. RECONCILE chewable tablets are available in 8, 16, 32, and 64 mg tablet strengths for oral administration to dogs. The active ingredient in RECONCILE chewable tablets is fluoxetine hydrochloride, a selective serotonin reuptake inhibitor (SSRI). The molecular weight of fluoxetine is 345.79. The structural formula is depicted below.



## Indications:

RECONCILE chewable tablets are indicated for the treatment of canine separation anxiety in conjunction with a behavior modification plan.

## Dosage and Administration:

The recommended dose of RECONCILE chewable tablets is 1–2 mg/kg (0.5–0.9 mg/lb) administered once daily, in conjunction with a behavior modification plan. A typical behavior modification plan consists of the pet owner implementing standard training techniques based on principles such as rewarding appropriate behavior; coming and going in a manner that does not elicit inappropriate responses from the dog; and teaching the dog to be content while alone.

Table 1: Recommended Dose of RECONCILE Chewable Tablets

(lb)	Dog Weight (kg)	No. of Tablets/Day	Tablet Strength
8.8 – 17.6	4.0 – 8.0	1	8
17.7 – 35.2	8.1 – 16.0	1	16
35.3 – 70.4	16.1 – 32.0	1	32
70.5 – 140.8	32.1 – 64.0	1	64

The effectiveness and safety of RECONCILE chewable tablets was demonstrated in a field study in client-owned dogs (see **EFFECTIVENESS** and **ADVERSE REACTIONS**). At the end of the 8-week study, 73% of dogs treated with RECONCILE chewable tablets showed significant improvement ( $p=0.010$ ), as compared to behavior modification alone (51%). During the course of therapy, 42% of dogs showed improvement within the first week, which was significantly greater ( $p=0.005$ ) than with behavior modification alone (18%). The patient's response to therapy should be monitored. If no improvement is noted within 8 weeks, case management should be reevaluated.

The effectiveness and clinical safety of RECONCILE chewable tablets for long-term use (i.e., for more than 8 weeks) has not been evaluated. RECONCILE chewable tablets were evaluated at the recommended label dose for one year in a laboratory safety study in dogs (see **ANIMAL SAFETY**).

Professional judgment should be used in monitoring the patient's response to therapy to determine the need to continue treatment with RECONCILE chewable tablets beyond 8 weeks. To discontinue therapy, it is not necessary to taper or reduce doses because of the long half-life of this product. Continued behavioral modification is recommended to prevent recurrence of the clinical signs.

RECONCILE chewable tablets are readily consumed by dogs or can be administered like other tablet medications, and can be given with or without food.

Professional discretion should be used in determining the need for dose reduction in the event of a possible adverse reaction. Approximately half of patients tolerate a return to the previous dose after 1–2 weeks on a reduced schedule (see **ADVERSE REACTIONS**).

If a dose is missed, the next scheduled dose should be administered as prescribed. Do not increase or double the dose.

## Contraindications:

RECONCILE chewable tablets are contraindicated for use in dogs with epilepsy or a history of seizures. RECONCILE chewable tablets should not be given concomitantly with drugs that lower the seizure threshold (e.g., phenothiazines such as acepromazine or chlorpromazine).

RECONCILE chewable tablets should not be given in combination with a monoamine oxidase inhibitor (MAOI) [e.g., selegiline hydrochloride (L-deprenyl) or amitraz], or within a minimum of 14 days of discontinuing therapy with an MAOI.

RECONCILE chewable tablets are contraindicated in dogs with a known hypersensitivity to fluoxetine HCl or other SSRIs.

Because fluoxetine and its major metabolite, norfluoxetine, have long half-lives, a 6-week washout interval should be observed following discontinuation of therapy with RECONCILE chewable tablets prior to the administration of any drug that may adversely interact with fluoxetine or norfluoxetine.

## Warnings:

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 over dosage include seizures, somnolence, nausea, tachycardia, and vomiting. In case of ingestion by a human, contact a physician immediately. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call 1-800-874-9764.

## Precautions:

RECONCILE chewable tablets are not recommended for the treatment of aggression. RECONCILE chewable tablets have not been clinically tested for the treatment of other behavioral disorders. Studies to determine the effects of RECONCILE chewable tablets in breeding, pregnant, or lactating dogs and in patients less than 6 months of age have not been conducted.

Seizures may occur in dogs treated with RECONCILE chewable tablets, even in dogs without a history of epilepsy or seizures (see **ADVERSE REACTIONS**).

Before prescribing RECONCILE chewable tablets, a comprehensive physical examination should be conducted to rule out causes of inappropriate behavior unrelated to separation anxiety. The examination should include a thorough history and assessment of the patient's household environment and standard practice laboratory tests as appropriate for the patient's age and health status. Veterinarians should be familiar with the risks and benefits of the treatment of behavioral disorders in dogs before initiating therapy. Inappropriate use of RECONCILE chewable tablets, i.e., in the absence of a diagnosis or without concurrent behavior modification, may expose the animal to unnecessary adverse reactions and may not provide any lasting benefit of therapy.

RECONCILE chewable tablets have not been evaluated with drugs that affect the cytochrome P450 enzyme system. RECONCILE chewable tablets should be used with caution when co-administered with any drug that affects the cytochrome P450 enzyme system (for example, ketoconazole). Studies to assess the interaction of RECONCILE chewable tablets with tricyclic antidepressants (TCAs) (for example, amitriptyline and clomipramine) have not been conducted. The minimum washout period to transition dogs from TCAs to RECONCILE chewable tablets has not been evaluated. Published pharmacokinetic data demonstrates that TCAs are cleared 4 days following discontinuation.<sup>1,2</sup>

## Adverse Reactions:

In two North American multi-site field studies, which included a total of 427 dogs, the following adverse reactions were observed:

### Seizures:

In one study, 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. One of the three dogs treated with RECONCILE chewable tablets experienced two seizures 10 days after the end of therapy. Despite escalating phenobarbital doses, the seizures continued and this dog died in status epilepticus approximately six months after the first seizure. Another of the three dogs treated with RECONCILE chewable tablets had experienced one seizure approximately 1½ years prior to study enrollment immediately after receiving head trauma. No additional seizures were reported to have occurred until 45 days after concluding treatment with RECONCILE chewable tablets. During the 1½-year period since the second seizure, this 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 and the control dog experienced one seizure 24 days and 35 days, respectively, after the start of therapy; no anticonvulsant therapy was initiated and no further seizures were reported in either dog.

In the second study, one of 99 dogs treated with RECONCILE chewable tablets and one of 99 dogs treated with the control tablet experienced the serious adverse reaction of seizures 9 and 27 days, respectively, after initiation of therapy. The dog treated with RECONCILE chewable tablets was subsequently diagnosed with vestibular disease and the control dog had a history of recurrent hind leg weakness.

In a European multi-site study, 234 dogs were treated with daily doses of fluoxetine chewable tablets ranging from 0.25 mg/kg to 4 mg/kg. One dog treated with a daily dose of 0.4 mg/kg for one month experienced one seizure one week after discontinuing therapy. No anticonvulsant therapy was initiated and no further seizures were reported.

### Weight loss:

Of the dogs in the two North American field studies with body weight measurements throughout the study ( $n=196$  and  $n=185$  in the RECONCILE chewable tablets and control group, respectively), a 5% or greater weight loss (when compared to initial, pre-study body weight) was observed in 58 (29.6%) of dogs treated with RECONCILE chewable tablets and 24 (13.0%) of dogs in the control group. No dogs were withdrawn from clinical studies due to weight loss alone. The following table shows the number of dogs with weight loss, stratified by percent weight loss relative to initial body weight.

Table 2: Dogs with Weight Loss (stratified by percent loss relative to initial body weight)

Treatment Group	≥ 5% to < 10%	≥ 10 to < 15%	≥ 15%
	Number (%)	Number (%)	Number (%)
RECONCILE chewable tablets	44 (22.5%)	13 (6.6%)	1 <sup>a</sup> (0.5%)
Control	20 (10.8%)	4 (2.2%)	0 (0%)

<sup>a</sup> This dog lost 20% of its initial body weight and was the same dog that died in status epilepticus.

## Other adverse reactions:

Additional adverse reactions observed in dogs treated with RECONCILE chewable tablets at a rate of 1% or greater were:

Table 3: Adverse Reactions Reported in the North American Field Studies

Adverse Reaction	RECONCILE Chewable Tablets, n=216		Control,* n=211	
	n	%	n	%
Calm/Lethargy/Depression	71	32.9	22	10.4
Decreased Appetite	58	26.9	13	6.2
Vomiting	37	17.1	28	13.3
Shaking/Shivering/Tremor	24	11.1	4	1.9
Diarrhea	21	9.7	17	8.1
Restlessness	16	7.4	8	3.8

Excessive Vocalization (Including Whining)	13	6.0	7	3.3
Aggression	9	4.2	13	6.2
Otitis Externa	6	2.8	2	0.9
Disorientation	5	2.3	1	0.5
Incoordination	5	2.3	0	0.0
Constipation	3	1.4	0	0.0
Excessive Salivation	3	1.4	4	1.9

\* The control group received the tablet formulation without fluoxetine.

#### Dose Reduction:

Twenty 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, vomiting, shaking and depression. Lowering the dose eliminated or reduced the severity of these adverse reactions in the RECONCILE chewable tablet group only. Resumption of the full dose of RECONCILE chewable tablets resulted in a return of the initial adverse reactions in approximately half of the affected dogs. The majority of these adverse reactions were intermittent and mild. However, one dog experienced recurrence of severe adverse reactions, which necessitated withdrawal from the study for that dog. Additionally, two dogs required a second dose reduction of RECONCILE chewable tablets. Effectiveness was maintained in a majority of those dogs in which a dose reduction was necessary.

#### Post Approval Experience (Rev. 2010):

The following adverse events are based on post-approval adverse drug experience reporting with RECONCILE chewable tablets. Not all adverse reactions are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data.

The following adverse events are listed in decreasing order of reported frequency: decreased appetite, depression/lethargy, shaking/shivering/tremor, vomiting, restlessness and anxiety, seizures, aggression, diarrhea, mydriasis, vocalization, weight loss, panting, confusion, incoordination, and hypersalivation.

For a copy of the SDS or to report suspected adverse drug events, contact Pegasus Laboratories at 1-800-874-9764. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

#### Clinical Pharmacology:

Fluoxetine exerts its effect by inhibiting the reuptake of serotonin at the pre-synaptic neuron. Fluoxetine does not act as a sedative. Fluoxetine is well absorbed after oral administration (~72%). It is largely metabolized in the liver by cytochrome P-450 enzyme system to norfluoxetine, an equipotent SSRI that contributes to the efficacy of RECONCILE chewable tablets.

After a single dose, and also at steady state, calculations were made as follows:

**Table 4: Single Dose\* Pharmacokinetic Parameters of Fluoxetine Hydrochloride (mean ± standard error).**

	AUC <sub>0-∞</sub> (µg·hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	T <sub>1/2</sub> Range (hr)
Fluoxetine	1.388 (±0.137)	126.6 (±12.3)	1.8 (±0.2)	6.2 (±0.8)	3.0 – 12.9
Norfluoxetine	11.44 (±0.74)	138.3 (±9.6)	12.8 (±1.7)	49 (±3)	33.0 – 64.0

In a 21-day study, fluoxetine was administered daily at a dose of 0.75, 1.5 and 3.0 mg/kg to laboratory Beagles. The maximum plasma concentration (C<sub>max</sub>) and area under the plasma concentration time curve (AUC) for fluoxetine were approximately dose proportional between 0.75 and 1.5 mg/kg, with a greater than dose proportional increase at 3 mg/kg. Norfluoxetine C<sub>max</sub> and AUC were generally dose proportional.

Although steady state appeared to be reached within 10 days in the 21-day study, a continuous increase in trough concentrations was observed in a one year, multiple-dose laboratory safety study. In this study, dogs administered a 1 mg/kg dose of fluoxetine had plasma fluoxetine concentrations that continued to increase over the one-year dosing period. A similar increase in concentrations was observed with norfluoxetine. This phenomenon was not observed at higher doses. During the one-year dosing interval and the subsequent two-month recovery period, there were no changes in the nature and frequency of adverse reactions observed as compared to those seen by Day 28 of fluoxetine administration.

#### Effectiveness:

In one randomized multi-centered, double-blinded, vehicle-controlled study of 8 weeks duration, 229 dogs were evaluated at 34 investigative sites in the United States and Canada. One hundred seventeen dogs were randomized to 1–2 mg/kg/day of RECONCILE chewable tablets and 112 dogs were randomized to the control group. Both groups underwent concurrent behavior modification. In seven of the eight weeks, the percentage of dogs with improved overall separation anxiety scores was significantly higher (p < 0.05) among dogs treated with RECONCILE chewable tablets compared to dogs that received the control tablet. At the end of the study, 73% of dogs treated with RECONCILE chewable tablets showed significant improvement (p=0.010) as compared to 51% of dogs treated with behavior modification alone.

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

#### Animal Safety:

In a one-year laboratory safety study, dogs were dosed daily at 1, 4.5, and 20 mg/kg/day of a gelatin capsule filled with fluoxetine powder. Based upon the results of a relative bioavailability study comparing the fluoxetine-filled capsule versus the RECONCILE chewable tablets, the corresponding equivalent doses were 0.87, 3.9, and 17.4 mg/kg/day of RECONCILE chewable tablets (where the average ratio of fluoxetine AUC values for RECONCILE chewable tablets/fluoxetine-filled capsule = 1.15).

Three of five female dogs in the 20 mg/kg group died or were euthanized 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.

#### Storage Information:

Store at 20–25°C (68–77°F). Excursions permitted between 15–30°C (59–86°F). Do not remove desiccant from the bottle. Completely close bottle between uses.

#### How Supplied:

RECONCILE is supplied in 8mg, 16mg, 32mg and 64mg strengths; as 30 tablets per bottle, with a child-resistant cap. NADA #141-272, Approved by FDA

#### Manufactured by:

Pegasus Laboratories, Inc. • Employee-Owned • Pensacola, FL 32514



## References

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