1. General Information

NADA Number: 141-120

Sponsor: Novartis Animal Health US, Inc.
Post Office Box 18300
Greensboro, NC 227419-8300

Generic Name of Drugs: Clomipramine Hydrochloride

Trade Name: Clomicalm™ Tablets

Marketing Status: Rx: Federal (USA) law restricts this drug to use by on the order of a licensed veterinarian

2. Indications and Usage

Clomicalm Tablets are to be used as part of a comprehensive behavioral management program to treat separation anxiety in dogs greater than 6 months of age.

3. Dosage Form, Route of Administration and Recommended Dosage

The recommended daily dose of Clomicalm Tablets is 2 to 4 mg/kg/day (0.9 - 1.8 mg/lb/day). It can be administered as a single daily dose or divided twice daily based on patient response and/or tolerance of side effects. Clomicalm Tablets may be given with a small amount of food in an attempt to reduce the incidence of vomiting that may be experienced by some dogs.

Clomicalm Tablets are available in 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs. Each tablet strength is formulated to be dosed by animal weight at 2 to 4 mg/kg/day (0.9 - 1.8 mg/lb/day) *(see dosage schedule below)*.

Dog Weight (lbs.)	CLOMICALM per Day	No. Tablets per Day	Tablet Strength
11- 22	20 mg	1	20 mg
22.1- 44	40 mg	1	40 mg
44.1- 88	80 mg	1	80 mg
88.1-176	160 mg	2	80 mg

Once the desired clinical effect is achieved and the owners have successfully instituted the appropriate behavioral modification, the dose of Clomicalm Tablets may be reduced to maintain the desired effect or discontinued. Withdrawal side effects were not reported in studies with Clomicalm Tablets in dogs. However, in

clinical practice, it is recommended to taper the individual patient dose while continuing to monitor the dog's behavior and clinical status through the dose reduction or withdrawal period. Continued behavioral modification is recommended to prevent recurrence of the clinical signs.

4. Effectiveness

A. Dose Establishment

Purpose: To compare the efficacy of two doses of clomipramine hydrochloride versus a placebo, in combination with behavioral therapy, for the treatment of separation anxiety in dogs. The tolerability of the test treatments was also evaluated.

Type of Study: Multi-centered, double-blinded, placebo-controlled

Animals: One hundred and fifteen (115) client-owned dogs exhibiting at least one of the following signs of separation anxiety (vocalization, destruction, urination, defecation) were enrolled in this study. A total of 93 of these dogs were included in the safety evaluation and a total of 89 dogs completed the trial and were included in the efficacy evaluation.

Dosages: High dose 1.0 - 2.0 mg/kg
Low dose 0.5 - <1.0 mg/kg
Placebo

All dogs received behavior modification (desensitization and counterconditioning) in addition to clomipramine hydrochloride or placebo.

Route of administration: Oral

Frequency of treatment: Twice Daily

Controls: Placebo

Duration of study: The dogs were dosed for 84 days with evaluations pre-treatment and then on Days 28, 56 and 84.

Investigators/Study Locations:

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Results: The primary efficacy endpoint was the number of animals in each treatment group that showed improvement in the 4 signs of separation anxiety used as entrance criteria (vocalization, destruction, urination, defecation) compared to the initial visit.

Table 1: The total number (%) of dogs in which each sign was present at visit 1 (Day 0) but had disappeared or improved by visit 4 (Day 84).

Destruction

DOSE	VISIT 1	VISIT 4
High	15	13 (87%)
Low	29	17 (59%)
Placebo	25	14 (56%)

Defecation

DOSE	VISIT 1	VISIT 4
High	11	10 (91%)
Low	8	6 (75%)
Placebo	12	6 (50%)

Urination

DOSE	VISIT 1	VISIT 4
High	16	13 (81%)
Low	12	8 (67%)
Placebo	12	7 (58%)

Vocalization

DOSE	VISIT 1	VISIT 4
High	19	15 (79%)
Low	25	15 (60%)
Placebo	25	16 (64%)

Conclusions: The dose of 1-2 mg/kg twice daily in combination with behavior modification was more effective than behavior modification alone for the control of the signs of separation anxiety. The data support further investigation of 1-2 mg/kg twice daily over the low dose of 0.5-<1 mg/kg.

Adverse Events: Table 2 compares the adverse events seen in dogs treated with clomipramine hydrochloride (high and low doses combined) to the adverse events reported in dogs treated with the placebo.

Table 2: Adverse Events

	Clomipramine hydrochloride n = 63	**Placebo n = 30**

Vomiting	16 (25%)	1 (3%)
Diarrhea	7 (11%)	2 (7%)
Lethargy	6 (10 %)	2 (7%)
Weight Gain	3 (5%)	2 (7%)
Weight Loss/Anorexia	3 (5%)	0
Aggression*	3 (5%)	1 (3%)
Seizures	2 (3%)	0
Hyperthermia	1 (2%)	0

*Growling

B. Clinical Trial

Purpose: To demonstrate the efficacy and safety of clomipramine hydrochloride tablets in the treatment of separation anxiety in dogs, in combination with behavioral therapy, and to compare the efficacy of once daily to twice daily dosing.

Type of Study: Multi-centered, double-blinded, placebo-controlled

Animals: One hundred eighty-one (181) client-owned dogs exhibiting at least one of the following signs of separation anxiety (salivation, destruction, urination, defecation) were enrolled in this study. A total of 176 of these dogs were included in the safety analysis. A total of 159 dogs were included in the efficacy analysis.

Dosages: 2-4 mg/kg divided twice daily
2-4 mg/kg once daily
placebo

All dogs received behavior modification (desensitization and counterconditioning) in addition to clomipramine hydrochloride or placebo.

Route of administration: Oral

Frequency of Treatment: Once or Twice Daily

Controls: Placebo

Duration of study: The dogs were dosed for 56 days with evaluations by the veterinarians pre-treatment and then on Days 28 and 56. The owners maintained a daily diary of the number of times they left the house and whether or not (YES or NO) the dogs displayed any of the signs of separation anxiety (salivation, destruction, urination, defecation). These were tabulated into a weekly score for each of the 8 weeks of the study.

Investigator/Study Location:

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Results: The primary efficacy endpoint was the number of animals in each treatment group which showed improvement in the four signs of separation anxiety used as entrance criteria (salivation, destruction, urination, defecation) compared to the initial visit. The most prevalent signs observed at the initial visit were destruction (seen in 83% of the dogs) and salivation (51% of dogs).

There were no significant differences between the once daily and twice daily dosing regimens. These regimens were thus combined for analysis.

Table 3: Percentage of Dogs Considered Improved

Week of Study	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
Clomipramine Hydrochloride	47%	60%	63%	75%	63%	68%	69%	65%
Placebo	29%	45%	47%	56%	53%	44%	55%	55%
Fisher's Exact Test p-values	0.020	0.062	0.036	0.014	0.143	0.00	0.075	0.214

Results from Fisher's Exact Test on behavioral scores indicate significant differences between the placebo group and the clomipramine hydrochloride treatment groups as early as the first week of treatment.

The rate of improvement in the signs of separation anxiety was tested using regression analysis. The results from the repeated measures regression analyses are presented in Table 4.

Table 4: Regression Slopes for Improvement Scores

Treatment Group	**Slope**
Twice Daily	-0.074
Once Daily	-0.064
Placebo	-0.036

No significant differences existed between the slopes (improvement in signs of separation anxiety) of the once daily and twice daily treatment groups. The slope of the twice daily and once daily groups were significantly different from the placebo ($p=0.0537$ and 0.0988, respectively). When the two groups were combined the slope was -0.074 and the combined comparison to placebo was more significant ($p \leq 0.0220$).

Conclusions: Administration of clomipramine hydrochloride at a dose of 2-4 mg/kg either once a day or divided twice a day was effective in controlling the clinical signs associated with separation anxiety when used in conjunction with behavior modification. By the end of the trial, improvement was seen in both treated and control groups but the rate and extent of improvement was greater when clomipramine hydrochloride was used with the behavior modification compared to behavior modification alone.

Adverse Reactions: Table 5 compares the adverse events seen in dogs treated with clomipramine hydrochloride (once and twice daily combined) to the adverse events reported in dogs treated with the placebo.

Table 5: Adverse Events

	Clomipramine Hydrochloride N = 118	**Placebo N = 58**
Vomiting	20 (17%)	7 (12%)
Lethargy	20 (17%)	5 (9%)
Diarrhea	10 (9%)	2 (3%)
Polydipsia	6 (5%)	0

Decreased Appetite	3 (3%)	3 (5%)
Dry Mouth	1 (0.9%)	1 (2%)
Tremors	1 (0.9%)	0
Constipation	1 (0.9%)	0
Anisocoria	1 (0.9%)	0
Polyuria	1 (0.9%)	0

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5. Target Animal Safety

A. Six-Month Oral Toxicity Study in Beagle Dogs with Clomipramine Hydrochloride Tablets.

Purpose: To determine the potential cumulative toxicity and dose-response relationships of clomipramine hydrochloride tablets when administered as high as 5 times the daily use rate.

Investigator: Edwin I. Goldenthal

Study Location: MPI Research
Mattawan, MI

Type of Study: Laboratory Safety Study

Animals: Forty-eight (24M, 24F) Beagle dogs, 5 months of age, were randomly assigned to 4 groups of 12 dogs each.

Dosage Groups: Placebo
4 mg/kg/day
12 mg/kg/day
20 mg/kg/day

Route of administration: Oral

Controls: Placebo tablets
Duration of Study: The dogs were dosed daily for 6 months. During the last 6 days of the study, dosages were tapered off such that half of the dogs/sex/dose were not dosed and the other half were dosed at half the assigned dose for 3 days, then a quarter of the assigned dose for the last 3 days.

Results: All animals survived to the scheduled necropsy. Vomiting was seen in all groups including controls, but occurred more frequently in dogs receiving 12 and 20 mg/kg/day during the study. The drug was given with a small amount of food in order to decrease the incidence of vomiting. One dog from the 4 mg/kg/day group and 4 dogs from the 20 mg/kg/day group showed decreased activity levels during weeks 1-13.

Body weights and body weight changes were unaffected by the treatment. Average food and water consumption was similar for control and treated groups. There were no clinically significant findings on ophthalmoscopic, physical or electrocardiograph examinations. There were no test article-related alterations in the hematology or biochemistry parameters evaluated or the macroscopic, organ weights or microscopic observations at necropsy.

Conclusions: Clomipramine is safe for use in dogs at the recommended dose of 2-4 mg/kg/day. The co-administration of a small amount of food may help reduce the incidence of vomiting.

B. Oral Toxicity in Dogs

Purpose: To assess the chronic toxicity of clomipramine.

Investigators: P. Noel, L.E. Mawdesley-Thomas, D. Cozens, H. Vaughan, A. Street

Study Location: Huntingdon Research Centre
Huntingdon, England

Type of Study: Laboratory Safety Study

Animals: Thirty-two (16M, 16F) Pembrokeshire Corgis were randomly assigned to 4 groups of 8 dogs each.

Dosage Groups: Untreated Control
12.5 mg/kg/day
50 mg/kg/day
100 mg/kg/day

Route of administration: Oral (clomipramine in gelatin capsules)

Controls: Untreated

Duration of Study: The dogs were dosed daily for 12 months.

Results: Five dogs from the high dose group died between weeks 8 and 21. Death was preceded by a period of weight loss and the clinical signs seen included convulsions, lethargy and pupil dilation. No dogs from the control, low or mid dose groups died during the study.

Muscular weakness and generalized body tremors occurred in the high dose groups and infrequently in the mid dose dogs during the first few weeks. Lethargy was seen starting approximately 1 hour after dosing in the mid and high

dose groups. Pupil dilation was seen in all groups dosed with clomipramine, occurring within 15 minutes to 1 hour after dosing. Vomiting was seen in all groups but increased in incidence in a dose-dependent manner.

Testicular hypoplasia was seen in 2 of 4 male dogs in the mid dose group and the 1 remaining dog from the high dose group. The testes of the low dose and control dogs were within normal limits.

Conclusions: This study demonstrated the toxicity of clomipramine when administered at overdoses up to 25X the recommended maximum dose of 4 mg/kg/day. Vomiting, pupil dilation and lethargy were all seen within 1 hour of administration in a dose related manner. At the low dose of 12.5 mg/kg/day (3X the recommended maximum dose), pupil dilation was the primary clinical observation. Muscle weakness and tremors were seen which progressed to convulsions at a dose of 100 mg/kg/day (25X the recommended maximum dose). Death was also associated with a dose of 100 mg/kg/day. Testicular hypoplasia was associated with doses ≥ 50 mg/kg/day (12.5X the recommended maximum dose).

C. Clomicalm™ Tablets: Evaluation of an Arrhythmogenic Effect in Conscious Dogs During a 7-Day Period of Treatment by the Oral Route

Purpose: To assess any possible effects of Clomicalm Tablets on the electrocardiogram, heart rate, intra-ocular pressure, body weight, hematologic and clinical chemistry parameters.

Investigators: S. Richard, P. Champeroux, E. Martel

Study Location: Centre De Recherches Biologiques
Baugy, France

Type of Study: Laboratory Safety Study

Animals: Eight (4M, 4F) Beagle dogs, weighing between 11.6 and 15.4 kg

Dosage Groups: Cross-over design: placebo (microcrystalline cellulose in capsules) and Clomicalm Tablets at 20 mg/kg.

Route of administration: Oral

Duration of Study: Each dog was dosed once daily for 7 days with the placebo and Clomicalm Tablets according to a cross-over design. A washout period of not less than 1 week was allowed. The electrocardiogram was recorded by surgically implanted telemetric monitoring for 30 seconds every 15 minutes over each 7 day treatment period. Intraocular pressure was measured before and 2 hours following

dosing on days 1 and 7. Blood parameters were evaluated before treatment on days 1 and 7.

Results: At 20 mg/kg (5X the maximum recommended dose), Clomicalm Tablets induced reproducible bradycardia. Sino-atrial block, atrio-ventricular block and ventricular extrasystole were also observed sporadically in 3 of 8 dogs when dosed with Clomicalm Tablets. No drug-related effects were noted on body weight, blood parameters, or intra-ocular pressure.

Conclusions: The product label should indicate that Clomicalm Tablets should be used with caution in dogs with cardiovascular disease because of the drug's potential to produce bradycardia, sino-atrial block, atrio-ventricular block and ventricular extrasystole at 5X the maximum recommended dose.

6. Human Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs which are non-food animals.

Human Warnings are provided on the product label as follows: **"**Not for use in humans. Keep out of reach of children. In case of accidental ingestion seek medical attention immediately. In children, accidental ingestion should be regarded as serious. There is no specific antidote for clomipramine. Overdose in humans causes anticholinergic effects including effects on the central nervous (e.g. convulsions) and cardiovascular (e.g. arrhythmias, tachycardia) systems. People with known hypersensitivity to clomipramine should administer the product with caution."

7. Agency Conclusions

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that Clomicalm (clomipramine hydrochloride) Tablets for dogs, when used under labeled conditions of use, are safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the diagnosis of separation anxiety, management of the condition and monitoring of possible adverse effects of the drug.

Under section 512(c)(2)(F)(i) of the FFDCA, 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) has been approved in any other application.

Novartis Animal Health US, Inc. holds no patents on this product.

8. Labeling (Attached)

A. Veterinarian's Insert
B. Client’s Insert
C. Bottle label
D. Carton