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CLOMICALM™ TABLETS
(clomipramine hydrochloride)

NADA 141-120

Novartis Animal Health US, Inc
Greensboro, NC 27419-8300

NADA 141-120

FOIS 1

Freedom of Information Summary
CLOMICALM™ (clomipramine hydrochloride) Tablets

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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	0.003	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

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) Pembroke-shire 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 \geq 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

Vet insert

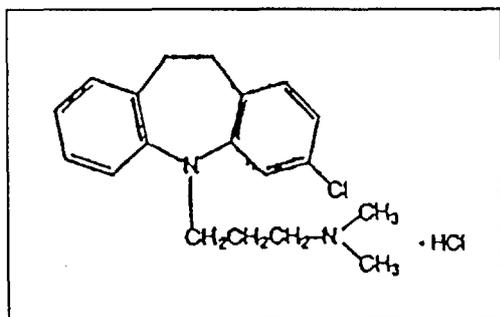
CLOMICALM™ Tablets (clomipramine hydrochloride)

Caution:

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

Description:

CLOMICALM (clomipramine hydrochloride) Tablets belong to the dibenzazepine class of tricyclic antidepressants. Clomipramine hydrochloride is 3-chloro-5[3-(dimethyl-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride. CLOMICALM Tablets are oblong, light brown in color and contain clomipramine hydrochloride formulated together with meat components. CLOMICALM Tablets are available in 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs. The molecular weight of clomipramine hydrochloride is 351.3. The structural formula is:



Clinical Pharmacology:

Clomipramine hydrochloride reduces the clinical signs of separation anxiety by affecting serotonergic and noradrenergic neuronal transmission in the central nervous system. While clomipramine hydrochloride can cause lethargy in dogs (see Adverse Reactions) its mode of action is not as a sedative. Clomipramine hydrochloride's capacity to inhibit re-uptake of serotonin in the central nervous system is believed to be the primary mechanism of action.

Clomipramine hydrochloride is rapidly absorbed when administered orally. A single-dose crossover study involving 12 dogs evaluated clomipramine hydrochloride bioavailability after IV (2 mg/kg) and oral (4 mg/kg) administration in either a fed or fasted state. The administration of clomipramine hydrochloride in the presence of food resulted in an increase in the rate and extent of drug absorption as shown in the following table (mean \pm SD):

	AUC _{0-inf} (nmol hr/L)	C _{max} (nmol/L)	T _{max} (hr)	Absolute Bioavailability (F)
Fed	1670 \pm 575	601 \pm 286	1.18 \pm 0.32	0.21 \pm 0.07
Fasted	1350 \pm 447	379 \pm 154	1.31 \pm 0.32	0.17 \pm 0.05

The absolute bioavailability is approximately 25% greater in fed dogs. The apparent terminal plasma half-life ranges from approximately 2 to 9 hours in fed and 3 to 21 hours in fasted dogs. The difference and variability in apparent half-life estimates may be attributable to prolonged drug absorption in the fasted state. The relatively large volume of distribution (3.8 \pm 0.8 L/kg) suggests that the drug is widely distributed throughout the body.

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. Inappropriate barking or destructive behavior, as well as inappropriate elimination (urination or defecation) may be alleviated by the use of CLOMICALM Tablets in conjunction with behavior modification.

Separation anxiety is a complex behavior disorder displayed when the owner (or other attachment figure) leaves the dog. The signs of separation anxiety evaluated in controlled trials were vocalization, destructive behavior, excessive salivation, and inappropriate elimination. In the absence of the owner or attachment figure, dogs with separation anxiety may exhibit one or more of these clinical signs. Although the owner (attachment figure) may inadvertently misinterpret this behavior, which only happens in their absence, as spiteful, it is thought to be the result of anxiety experienced by the dog. Punishment is not considered appropriate for a dog with separation anxiety.

Proper recognition of clinical signs, including a complete patient history and assessment of the patient's household environment, is essential to accurately diagnose and treat separation anxiety.

The use of CLOMICALM Tablets should not replace appropriate behavioral and environmental management but should be used to facilitate a comprehensive behavior management program.

Contraindications:

CLOMICALM Tablets are contraindicated in dogs with known hypersensitivity to clomipramine or other tricyclic antidepressants.

CLOMICALM Tablets should not be used in male breeding dogs. Testicular hypoplasia was seen in dogs treated for 1 year at 12.5 times the maximum daily dose.

CLOMICALM Tablets should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor [e.g. selegiline hydrochloride (L-deprenyl), amitraz].

CLOMICALM Tablets are contraindicated for use in dogs with a history of seizures or concomitantly with drugs which lower the seizure threshold.

Human Warnings:

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., arrhythmia, tachycardia) systems. People with known hypersensitivity to clomipramine should administer the product with caution.

Precautions:

General: CLOMICALM Tablets are not recommended for other behavior problems, such as aggression (see Adverse Reactions). Studies to establish the safety and efficacy of CLOMICALM Tablets in dogs less than 6 months of age have not been conducted.

Diagnosis: It is critical to conduct a comprehensive physical examination, including appropriate laboratory tests, and to obtain a thorough history and assessment of the patient's household environment, to rule-out causes of inappropriate behavior unrelated to separation anxiety before prescribing CLOMICALM Tablets.

Veterinarians should be familiar with the risks and benefits of the treatment of behavioral disorders in dogs before initiating therapy. Inappropriate use of CLOMICALM Tablets, i.e., in the absence of a diagnosis or without concurrent behavioral modification, may expose the animal to unnecessary adverse effects and may not provide any lasting benefit of therapy.

Drug Interactions: Recommendations on the interaction between clomipramine and other medications are extrapolated from data generated in humans. Plasma concentrations of clomipramine have been reported to be increased by the concomitant administration of phenobarbital. Plasma levels of closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine). Plasma levels of closely related tricyclic antidepressants have been reported to be decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin). Caution is advised in using clomipramine with anticholinergic or sympathomimetic drugs or with other CNS-active drugs, including general anesthetics and neuroleptics.

Prior to elective surgery with general anesthetics, clomipramine should be discontinued for as long as clinically feasible.

Use in Concomitant Illness: Use with caution in dogs with cardiovascular disease. At 20 mg/kg/day (5X the maximum recommended dose), bradycardia and arrhythmias (atrioventricular node block and ventricular extrasystole) were observed in dogs. Because of its anticholinergic properties, clomipramine should be used with caution in patients with increased intraocular

pressure, a history of narrow angle glaucoma, urinary retention or reduced gastrointestinal motility.

Reproductive Safety: Safety studies to determine the effects of CLOMICALM Tablets in pregnant or lactating female dogs have not been conducted. CLOMICALM Tablets should not be used in breeding males (See Contraindications).

Efficacy:

Dose Establishment: A 12 week, placebo-controlled, multi-site clinical trial was conducted in the US and Europe to establish an effective dose of CLOMICALM Tablets in dogs. Treatment with CLOMICALM Tablets, at 2 - 4 mg/kg/day divided twice daily, in conjunction with behavioral modification (desensitization and counterconditioning) was more effective than behavior modification alone in reducing the signs of separation anxiety in dogs.

Dose Confirmation: In another placebo-controlled, multi-site clinical trial, CLOMICALM Tablets at 2 - 4 mg/kg/day given either once daily or divided twice daily showed significant improvement in resolving signs of separation anxiety when tested against behavioral modification alone (desensitization and counterconditioning). In this 8 week study, the rate of improvement of the dogs receiving CLOMICALM Tablets with behavioral modification was significantly faster than the rate of improvement of the dogs receiving behavioral modification alone. After one week on trial, 47% of the dogs receiving CLOMICALM Tablets once or twice (divided dose) daily in conjunction with behavioral modification showed clinical improvement compared to improvement in 29% of the dogs receiving behavioral modification alone.

Safety:

CLOMICALM Tablets were demonstrated to be well-tolerated in dogs at the recommended label dose of 2-4 mg/kg/day. In a six month target animal safety study, beagle dogs were dosed daily at 4 (1X), 12 (3X), and 20 (5X) mg/kg/day. Emesis was seen in all groups including the dogs receiving placebo, but occurred more frequently in dogs receiving 12 and 20 mg/kg. Decreased activity was also seen in dogs receiving the 12 and 20 mg/kg. There were no apparent treatment-related alterations in the following: body weights, physical examination findings, electrocardiograph examinations, hematology or biochemistry parameters, ophthalmoscopic examinations, macroscopic or microscopic organ examinations and organ weights. Average food and water consumption over the 26 week period was similar for control and treated groups.

In a one year study, pure bred dogs were dosed daily at 12.5 (3X), 50 (12.5X), and 100 (25X) mg/kg/day. Emesis and mydriasis were observed within 15 minutes to one hour after dosing in dogs receiving 12.5, 50, and 100 mg/kg/day and lethargy was observed within 1 hour of dosing in dogs receiving 50 and 100 mg/kg. Testicular hypoplasia was seen in dogs receiving 50

mg/kg. At 100 mg/kg/day (25X) convulsions and eventual death occurred in five out of the eight dogs.

Adverse Reactions:

Frequency and category of adverse reactions observed in dogs dosed with CLOMICALM Tablets or placebo were observed in multisite clinical studies as follows.

Adverse Reactions Reported in Placebo-Controlled Clinical Field Trials		
	CLOMICALM N=180	Placebo N=88
Emesis	36 (20%)	8 (9%)
Lethargy	26 (14%)	7 (8%)
Diarrhea	17 (9%)	4 (5%)
Polydipsia	6 (3%)	0
Decreased Appetite	6 (3%)	3 (3%)
Aggression*	3 (2%)	1 (1%)
Seizure	2 (1%)	0
Dry Mouth	1 (0.5%)	1 (1%)
Tremors	1 (0.5%)	0
Constipation	1 (0.5%)	0
Anisocoria	1 (0.5%)	0
Polyuria	1 (0.5%)	0
Hyperthermia	1 (0.5%)	0

*These dogs displayed growling behavior towards either humans or other dogs.

Dosage and Administration:

The recommended daily dose of CLOMICALM Tablets is 2 to 4 mg/kg/day (0.9-1.8 mg/lb/day) (see dosing table below). It can be administered as a single daily dose or divided twice daily based on patient response and/or tolerance of the side effects. It may be prudent to initiate treatment in divided doses to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop. To reduce the incidence of vomiting that may be experienced by some dogs, CLOMICALM Tablets may be given with a small amount of food.

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

The specific methods of behavioral modification used in clinical trials involved desensitization and counterconditioning techniques. Since the manifestation of separation anxiety can vary according to the individual dog, it is advised that a specific behavior modification plan be developed based on a professional assessment of each individual case.

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.

The effectiveness and clinical safety of CLOMICALM Tablets for long-term use (i.e., for more than 12 weeks) has not been evaluated.

Professional judgment should be used in monitoring the patient's clinical status, response to therapy and tolerance to side effects to determine the need to continue treatment with CLOMICALM Tablets and to continue to rule-out physiological disorders which may complicate the diagnosis and treatment of separation anxiety.

Storage Conditions:

CLOMICALM Tablets should be stored at room temperature between 59° and 86°F (15-30°C).

Keep this and all drugs out of reach of children.

To report suspected adverse reactions or in case of accidental human ingestion, call 1-800-637-0281.

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27404, USA

NADA # 141-120, Approved by FDA

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CLOMICALM™ Tablets

(clomipramine hydrochloride)

Caution:

Federal (USA) Law restricts this drug to use by or on the order of a licensed veterinarian.

Introduction

Novartis Animal Health encourages you to take the time to read this package insert which describes the use of CLOMICALM Tablets for the treatment of separation anxiety in conjunction with behavior modification (training) in dogs. CLOMICALM Tablets do not act as a sedative. Instead, CLOMICALM Tablets help to reduce the anxiety associated with this condition, thus allowing your dog to more effectively benefit from behavior training. After reading this insert, if you have any questions about the use of CLOMICALM Tablets, please consult your veterinarian.

Description:

CLOMICALM (clomipramine hydrochloride) Tablets belong to the dibenzazepine class of tricyclic antidepressants. Clomipramine hydrochloride is 3-chloro-5[3-(dimethyl-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride. CLOMICALM Tablets are oblong, light brown in color and contain clomipramine hydrochloride formulated together with meat components. CLOMICALM Tablets are available in 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs.

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. Inappropriate barking or destructive behavior, as well as inappropriate elimination (urination or defecation) may be alleviated by the use of CLOMICALM Tablets in conjunction with behavior modification.

Separation anxiety is a complex behavior disorder displayed when the owner (or other attachment figure) leaves the dog. In the absence of the owner or attachment figure, dogs with separation anxiety may exhibit one or more clinical signs. The signs of separation anxiety evaluated in controlled trials were vocalization, destructive behavior, excessive salivation, and inappropriate elimination. Although it may appear that this behavior, which only happens in the dog owner's absence, is a spiteful action, this behavior is thought to be a result of anxiety experienced by the dog. Therefore, punishment would not be appropriate for the dog with this behavior.

Behavior Modification (Training)

Behavior training is a necessary component of therapy with CLOMICALM Tablets. In clinical trials, specific behavior training techniques were used at the following times:

- when the owner interacted with the dog while at home
- when the owner was preparing to leave the home
- when the owner returned home and greeted the dog

Since the methods used for behavior training can vary according to patient needs, it is important that you follow the instructions provided by your veterinarian regarding the specific techniques recommended for modifying your dog's behavior.

Contraindications:

CLOMICALM Tablets are contraindicated in dogs with known hypersensitivity to clomipramine or related tricyclic antidepressants

CLOMICALM Tablets should not be used in male breeding dogs. Testicular hypoplasia was seen in dogs treated for 1 year at 12.5 times the maximum daily dose.

CLOMICALM Tablets should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor [e.g. selegiline hydrochloride (L-deprenyl), amitraz].

CLOMICALM Tablets are contraindicated for use in dogs with a history of seizures or concomitantly with drugs which lower the seizure threshold.

Human Warnings:

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., arrhythmia, tachycardia) systems. People with known hypersensitivity to clomipramine should administer the product with caution.

Precautions:

It is important that your dog be closely monitored by your veterinarian while on a treatment plan with CLOMICALM Tablets and behavior training. You must inform your veterinarian of any current or future medications you are administering to your dog. The use of CLOMICALM Tablets in conjunction with certain other drugs or when your dog has other illness may be contraindicated or increase the risks of adverse reactions.

It is important that you inform your veterinarian of any changes in your dog's environment including, but not limited to, a new family member, a new pet, a move to a new location, or a change in your existing daily

schedule. Some changes may result in an altered response to therapy.

The safety and efficacy of CLOMICALM Tablets have not been established in dogs less than 6 months of age or in pregnant or lactating female dogs. CLOMICALM Tablets should not be used in breeding male dogs (see Contraindications). CLOMICALM Tablets are not recommended for other behavior problems, such as aggression.

Efficacy:

CLOMICALM Tablets were tested in clinical trials involving client-owned dogs to determine effectiveness. CLOMICALM Tablets, at 2 - 4 mg/kg/day (0.9 - 1.8 mg/pound/day) when used in conjunction with behavior training accelerated both the time to improvement and the final result of separation anxiety therapy compared to behavioral training alone.

Adverse Reactions:

In clinical trials the following were associated with administration of CLOMICALM Tablets: vomiting, lethargy, diarrhea, increased thirst and appetite fluctuations. Consult with your veterinarian if your dog experiences any of these or any other conditions.

Dosage and Administration:

The recommended daily dose of CLOMICALM Tablets is 2 to 4 mg/kg/day (0.9 - 1.8 mg/lb/day) (see dosing table below). Your veterinarian will instruct you to give the drug either once a day or divide the daily dose into 2 separate doses depending on your dog's response to the drug or tolerance to any 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. If a dose is missed, the next dose should be administered (without doubling) at the next scheduled dosing time.

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

Your veterinarian may decrease the dose or discontinue treatment with CLOMICALM Tablets depending on your dog's response to treatment. Continued behavior training is recommended, even after cessation of drug therapy.

Storage Conditions:

CLOMICALM Tablets should be stored at room temperature between 59° and 86°F (15-30°C).

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

In case of accidental human ingestion or accidental overdose in dogs, call 1-800-637-0281.

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27404, USA

NADA # 141-120,

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Manufactured for:
Novartis Animal
Health US, Inc.
Greensboro, NC
27404
NADA# 141-122
Approved by FDA

CLOMICALM
(clomipramine hydrochloride)

20 mg (11-22 lb body weight)

FOR USE IN DOGS ONLY

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Net contents: 30 tablets
20 mg each

Product # 40322

 **NOVARTIS**



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.

DOSAGE AND ADMINISTRATION:
See enclosed insert for details.

STORAGE CONDITIONS: CLOMICALM Tablets should be stored at room temperature between 59° and 86°F (15-30°C). Store unused tablets in the original closed container.

Keep this and all drugs out of the reach of children. In case of accidental human ingestion call 1-800-437-0281. In case of accidental overdose in dogs call 1-800-437-0281.

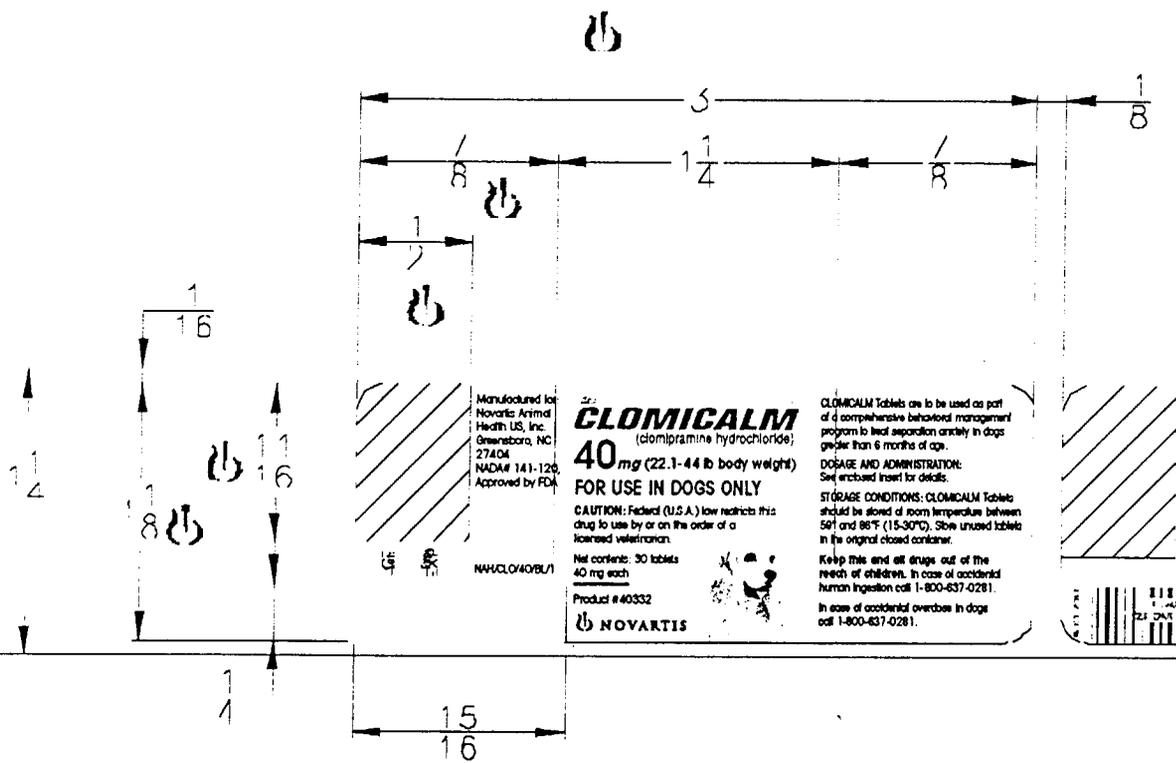
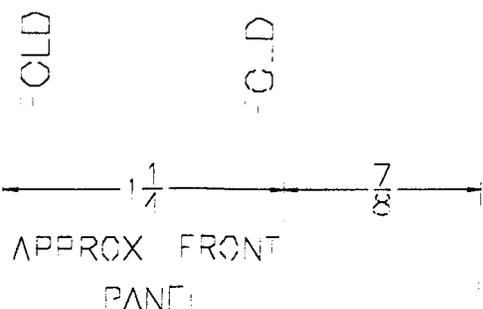


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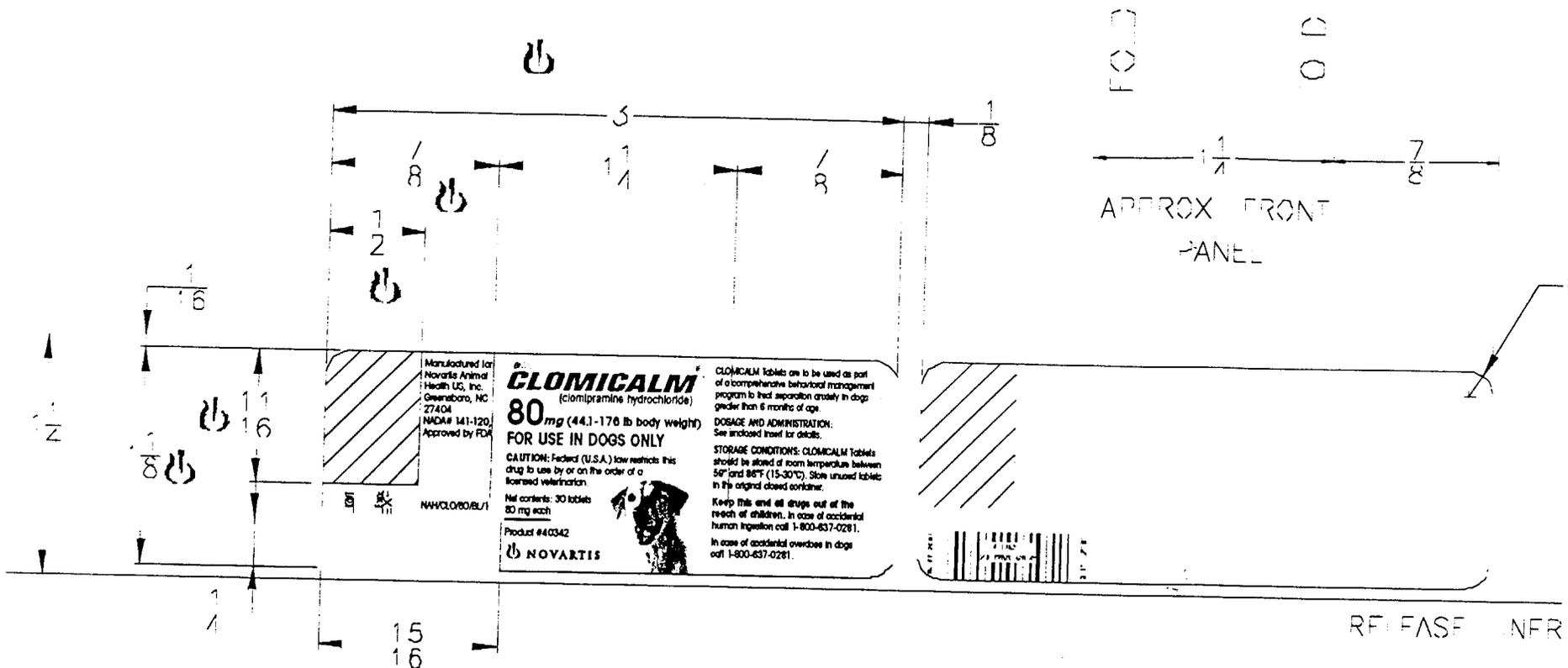
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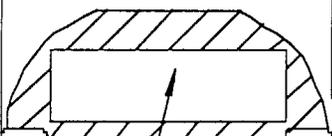
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FOR USE IN DOGS ONLY

CLOMICALM
40 mg
(clomipramine hydrochloride)

CLOMICALM
(clomipramine hydrochloride)
40 mg

NOVARTIS

FOR USE IN DOGS ONLY

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.

CAUTION:
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Recommended for dogs
22.1 to 44 lb
in body weight.



ADMINISTRATION:
CLOMICALM Tablets are administered on an animal weight basis of a dose of 2-4 mg/kg per day (0.9-1.8 mg/lb/day). See enclosed insert for details.

STORAGE CONDITIONS:
CLOMICALM Tablets should be stored at room temperature between 59° and 86°F (15-30°C). Store unused tablets in the original closed container.

Manufactured for:
Novartis Animal Health US, Inc.
Greensboro, NC 27404
NADA# 141-120, Approved by FDA

Net contents:
30 tablets
40 mg each
Product #40332

CLOMICALM
(clomipramine hydrochloride)
40 mg

NOVARTIS

FOR USE IN DOGS ONLY

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.

CAUTION:
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Recommended for dogs
22.1 to 44 lb
in body weight.



Keep this and all drugs out of the reach of children.
In case of accidental human ingestion call 1-800-637-0281.

In case of accidental overdose in dogs call 1-800-637-0281.

Manufactured for:
Novartis Animal Health US, Inc.
Greensboro, NC 27404
NADA# 141-120, Approved by FDA

Net contents:
30 tablets
40 mg each
Product #40332

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FOR USE IN DOGS ONLY

80 mg
CLOMICALM
(clomipramine hydrochloride)

CLOMICALM
(clomipramine hydrochloride)
80 mg

NOVARTIS

FOR USE IN DOGS ONLY
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.

CAUTION:
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Recommended for dogs 44.1 to 176 lb in body weight.

ADMINISTRATION:
CLOMICALM Tablets are administered on an animal weight basis of a dose of 2-4 mg/kg per day (0.9-1.8 mg/lb/day). See enclosed insert for details.

STORAGE CONDITIONS:
CLOMICALM Tablets should be stored at room temperature between 69° and 86°F (15-30°C). Store unused tablets in the original closed container.

Manufactured for:
Novartis Animal Health US, Inc.
Greensboro, NC 27404
NADA# 141-120, Approved by FDA

Net contents:
30 tablets
80 mg each
Product #40342

80 mg
CLOMICALM
(clomipramine hydrochloride)

NOVARTIS

FOR USE IN DOGS ONLY
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.

CAUTION:
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Recommended for dogs 44.1 to 176 lb in body weight.

Keep this and all drugs out of the reach of children.

In case of accidental human ingestion call 1-800-637-0281.

In case of accidental overdose in dogs call 1-800-637-0281.

Manufactured for:
Novartis Animal Health US, Inc.
Greensboro, NC 27404
NADA# 141-120, Approved by FDA

Net contents:
30 tablets
80 mg each
Product #40342

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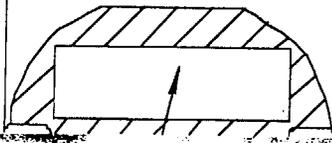
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FOR USE IN DOGS ONLY
30 Tablets

GLOMICALM
(clomipramine hydrochloride)
20 mg

GLOMICALM
(clomipramine hydrochloride)
20 mg

NOVARTIS

GLOMICALM
(clomipramine hydrochloride)
20 mg

NOVARTIS

FOR USE IN DOGS ONLY:
GLOMICALM 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.

CAUTION:
Federal (U.S.A) law restricts this drug to use by or on the order of a licensed veterinarian.

Recommended for dogs 11 to 22 lb in body weight.



ADMINISTRATION:
GLOMICALM Tablets are administered on an animal weight basis of a dose of 2-4 mg/kg per day (0.9-1.8 mg/lb/day). See enclosed insert for details.

STORAGE CONDITIONS:
GLOMICALM Tablets should be stored at room temperature between 68° and 86°F (15-30°C). Store these tablets in the original closed container.

Manufactured for
Novartis Animal Health Inc.
Greensboro, NC 27404
NADA# 141-20-Approved by FDA

Recommended for dogs 11 to 22 lb in body weight.
Net contents:
30 Tablets
20 mg each
Product #40322

FOR USE IN DOGS ONLY:
GLOMICALM 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.

CAUTION:
Federal (U.S.A) law restricts this drug to use by or on the order of a licensed veterinarian.

Recommended for dogs 11 to 22 lb in body weight.



FOR USE IN DOGS ONLY:
GLOMICALM 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.

CAUTION:
Federal (U.S.A) law restricts this drug to use by or on the order of a licensed veterinarian.

Recommended for dogs 11 to 22 lb in body weight.

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