CLOMICALM- clomipramine hydrochloride tablet
Virbac AH, Inc.

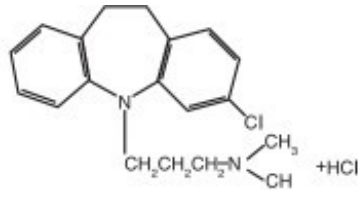
CLOMICALM® (clomipramine hydrochloride)

Caution

Federal 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]-10,11dihydro-5H dibenz[b,f]azepine monohydrochloride. CLOMICALM tablets are oblong, light brown in color and contain clomipramine hydrochloride formulated together with meat components. 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 ±SD):

	$AUC_{0\text{-inf}}$ (nmol hr/L)	Cmax (nmol/L)	Tmax (hr)	Absolute Bioavailability (F)
Fed	1670±575	601±286	1.18±0.32	0.21±0.07
Fasted	1350±447	379±154	1.31±0.32	0.17±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±0.8 L/kg) suggests that the drug is widely distributed throughout

the body. **Clomipramine is primarily metabolized in the liver.**

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. Periodic reassessment of hematological and serum biochemical data during the administration of this medication is advised. 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 levels of tricyclic antidepressants have been reported to be decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin); therefore plasma concentrations of clomipramine may be decreased 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). Tricyclic antidepressants themselves may exhibit hepatic enzyme inhibition and possibly increase plasma levels of barbiturates (phenobarbital). 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. Because clomipramine is principally metabolized in the liver, caution is advised in using this medication in the presence of preexisting liver disease.

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® (clomipramine hydrochloride) 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.

Post-Approval Experience: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting: lethargy/depression, anorexia, elevation in liver enzymes, vomiting and diarrhea. Hepatobiliary disease has occurred, especially in the presence of pre-existing conditions or with concurrent administration of drugs metabolized via the hepatic system. Additionally, in an overdose situation, the following signs have been reported: ataxia, convulsion(s), anticholinergic effects (e.g., mydriasis, bradycardia, tachycardia, and arrhythmia) and vocalization. To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

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
2.75-5.5	5 mg	1	5 mg
5.6-10.9	10 mg	2	5 mg
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

Store in a dry place at controlled room temperature, between 59° and 77°F (15-25°C). Store unused tablets in the original closed container.

How Supplied

CLOMICALM tablets are available in 5, 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs.

Keep this and all drugs out of reach of children.

Manufactured by: Virbac AH, Inc.
P.O. Box 162059, Fort Worth, TX 76161, USA
Approved by FDA under NADA # 141-120
04/24 - 03
302304

Information for Dog Owners

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

Introduction:
Virbac AH, Inc. 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 tablets belong to the dibenzazepine class of tricyclic antidepressants. Clomipramine hydro-chloride 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.

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 separaton 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 illnesses 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.

It is important to inform your veterinarian of any perceived changes in your dog's behavior, appetite, or overall health while administering any medication. Some dogs display a temporary lethargy with the first few days of CLOMICALM® (clomipramine hydrochloride) tablets treatment. In some cases, signs of separation anxiety, such as vocalization, may temporarily increase at the initiation of treatment. In an overdose situation, seek veterinary attention for your pet as soon as possible.

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:
The following adverse reactions have been reported associated with administration of CLOMICALM tablets: lethargy/depression, vomiting, diarrhea, elevation in liver enzymes, convulsion(s), increased heart rate, decreased heart rate, increased thirst and confusion. Liver disease has occurred, especially in the presence of pre-existing conditions or with concurrent administration of drugs metabolized by the liver. In overdoses, signs such as vomiting, lethargy or depression, weakness and incoordination, dilated pupils, and vocalization may occur. Consult with your veterinarian if your dog experiences these or any other conditions.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

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
2.75-5.5	5 mg	1	5 mg
5.6-10.9	10 mg	2	5 mg
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:
Store in a dry place at controlled room temperature, between 59° and 77°F (15-25°C). Store unused tablets in the original closed container.

How Supplied:
CLOMICALM tablets are available in 5, 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Manufactured by: Virbac AH, Inc.
P.O. Box 162059 Fort Worth, TX 76161, USA
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CLOMICALM

clomipramine hydrochloride tablet

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:51311-140
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	5 mg

Product Characteristics

Color	brown	**Score**	2 pieces
Shape	OVAL	**Size**	9mm
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51311-140-05	1 in 1 CARTON		
1		30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141120	02/23/2022	

CLOMICALM

clomipramine hydrochloride tablet

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:51311-141
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	20 mg

Product Characteristics

Color	brown	**Score**	2 pieces
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51311-141-20	1 in 1 CARTON		
1		30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141120	02/23/2022	

CLOMICALM

clomipramine hydrochloride tablet

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:51311-142
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	80 mg

Product Characteristics

Color	brown	**Score**	2 pieces
Shape	OVAL	**Size**	13mm
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51311-142-80	1 in 1 CARTON		
1		30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141120	02/23/2022	

Labeler - Virbac AH, Inc. (131568396)

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