AMODIP®
(amlodipine besylate tablets) chewable tablets
1.25 mg amlodipine

Calcium channel blocker
For oral use in cats only

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

Description: AMODIP® (amlodipine besylate tablets) is supplied as an oblong, single scored chewable tablet containing amlodipine besylate equivalent to 1.25 mg of amlodipine. Amlodipine besylate is a synthetic calcium channel blocker.

Indication: AMODIP® is indicated for the control of systemic hypertension in cats.

Dosage and Administration: AMODIP® should be administered initially at the standard dose of 0.125-0.25 mg/kg per day according to the dosing table below. After 2 weeks, if there is an inadequate clinical response to treatment, the dose may be increased to the high dose of 0.25-0.5 mg/kg per day according to the dosing table. Cats less than 2.5 kg cannot be accurately dosed with AMODIP®.

Weight (kg)	Standard dose	High dose
2.5 - 5.0	0.5 tablet (0.625 mg)	1 tablet (1.25 mg)
5.1 - 10	1 tablet (1.25 mg)	2 tablets (2.5 mg)

Only remove tablets from the blister card just before dosing. After a half tablet is administered, return the remaining half tablet to the blister card and administer the next day.

Contraindications: Do not use in cats with a hypersensitivity to amlodipine.

Warnings:

User Safety Warnings: Not for use in humans. Keep out of reach of children.

Wash hands after handling. If accidentally ingested, seek medical attention immediately and show the package insert or the label to the physician.

Animal Safety Warnings: Keep AMODIP® in a secure location out of reach of dogs, cats and other animals to prevent accidental ingestion or overdose.

Precautions:

AMODIP® has not been evaluated in cats with systolic blood pressure > 200 mm Hg.

Cats at risk for hypokalemia should be monitored regularly during treatment with AMODIP®. Serum potassium may decrease in some cats after starting treatment (see **Animal Safety**).

The safe use of AMODIP® in cats with hepatic disease has not been evaluated. AMODIP® is metabolized by the liver and has a plasma elimination half-life ($t_{1/2}$) of 53.3 hours following oral administration (see **Clinical Pharmacology**).

AMODIP® may cause an increase in urine volume and decrease in urine specific gravity secondary to the mechanism of action that causes dilation of afferent renal arterioles (see **Animal Safety**).

The safe use of AMODIP® has not been evaluated in cats less than 11 months of age.

The safe use of AMODIP® has not been evaluated in cats that are pregnant, lactating, or intended for breeding.

Adverse Reactions:

Seventy-seven client-owned cats were enrolled in the field study that evaluated the safety and effectiveness of AMODIP® compared to a vehicle control tablet (no active ingredients) for a 28-day masked phase, followed by an unmasked open label phase. During the unmasked, open label phase, cats in the AMODIP® group continued on AMODIP® for an additional 62 days (total of 90 days), and the control group cats were administered AMODIP® from Days 28 to 120 (92 days total). In the masked phase a total of 23 adverse reactions were reported in 12 cats (28.6%) in the AMODIP® group, and 17 adverse reactions were reported in 10 cats (28.6%) in the control group. The adverse reactions that occurred during the field study are presented in Tables 1 and 2.

Table 1. Adverse Reactions by Treatment Group from Day 0-28 (Masked Phase)*

Adverse Reaction	AMODIP® N=42 n (%)	Vehicle Control N=35 n (%)
Vomiting	2 (4.8)	3 (8.6)
Alopecia	1 (2.4)	1 (2.9)
Conjunctivitis	1 (2.4)	0
Cystitis	1 (2.4)	2 (5.7)
Diarrhea	1 (2.4)	0
Gingivitis	1 (2.4)	0
Hypertrophic Cardiomyopathy	1 (2.4)	0
Glomerulonephritis	1 (2.4)	0
Renal Insufficiency	1 (2.4)	1 (2.9)
Weight loss	1 (2.4)	0
Arrhythmia	0	1 (2.9)
Hyperactivity	0	1 (2.9)
Anorexia	0	1 (2.9)
Lethargy	0	1 (2.9)

*Recurrent adverse reactions for the same cat are only counted once

Table 2. Adverse Reactions Reported After Day 28 (Unmasked, Open Label Phase)*

Adverse Reaction	AMODIP® N=77 n (%)
Vomiting	8 (10.4)
Anorexia and Inappetence	6 (7.8)
Dehydration	4 (5.2)
Lethargy	4 (5.2)
Worsening Renal Disease	4 (5.2)
Cystitis/UTI	3 (3.9)
Diarrhea	2 (2.6)
Hematemesis	2 (2.6)

*Recurrent adverse reactions for the same cat are only counted once

During the entire study, seven serious adverse reactions occurred (5 AMODIP® group cats, 2 control group cats). Six of the serious adverse reactions were determined to be unrelated to treatment, and one was deemed possibly related. One cat started AMODIP® while receiving methimazole for hyperthyroidism. The cat received a steroid and an NSAID 40 days after starting AMODIP®, developed anorexia and a hepatopathy and was euthanized.

Foreign Market Experience:

The following adverse events were reported voluntarily during post approval use of AMODIP® in foreign markets: gingival hyperplasia, lethargy, diarrhea, vomiting, weight loss, hypotension, ataxia, and anorexia.

Contact Information:

For a copy of the Safety Data Sheet (SDS) or to report a suspected adverse reaction contact Ceva Animal Health, LLC at 1-800-999-0297.

For additional information about adverse drug experience reporting for animal drugs contact FDA at 1-888-FDA-VETS or at http://www.fda.gov/reportanimalae

Clinical Pharmacology:

Mechanism of Action: Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), that binds selectively to L-type calcium channels and inhibits the transmembrane influx of calcium ions into vascular smooth muscle, cardiac muscle, and cardiac nodal tissue. As a class, dihydropyridines are arterial/arteriolar dilators that reduce arterial blood pressure but have little effect on the venous side of the circulation. Through selective peripheral arterial/arteriolar vasodilation, amlodipine has antihypertensive effects by reducing blood pressure through a decrease in peripheral vascular resistance.

Pharmacokinetics: The pharmacokinetics of amlodipine were evaluated in healthy adult cats (6 male and 6 female) following oral (0.25 mg/kg) and intravenous (0.125 mg/kg) administration. The geometric mean oral bioavailability based on area under the curve from dosing extrapolated to infinity (AUC_{inf}) was 68%. Following oral administration, the mean maximum plasma concentration (C_{max}) was 24.6 ng/mL with a median time to C_{max} of 4 hours (range 3-24 hours) and an area under the curve from dosing to the last quantifiable concentration (AUC_{last}) of 1291 ng/mL*hr. The elimination half-life ($t_{1/2}$) following oral and intravenous administration were 53.3 and 51.5 hours, respectively. After multiple daily doses with either the oral or intravenous administration, the projected mean time to 97% of steady state is approximately 11 days.

Following intravenous administration, the mean systemic clearance is 0.15 L/hr/kg, and the mean volume of distribution is 10.2 L/kg. Plasma protein binding of amlodipine in cats is approximately 96.4%.

Target Animal Safety: A six-month target animal laboratory safety study was performed in 32 healthy, normotensive cats aged 11-12 months old and weighing 2.8-5.0 kg at the start of the study. The cats were placed into four treatment groups with 8 cats each (4 males, 4 females). Cats were orally dosed once daily in the morning at 0, 0.25, 0.75 or 1.25 mg/kg body weight of AMODIP®, which corresponded to 0, 1X, 3X or 5X the maximum labeled dose of 0.25 mg/kg/day. Control group cats received the same number of vehicle control tablets (inactive ingredients only) based on body weight as the 1.25 mg/kg (5X) group cats.

All cats survived and completed the study. There were no amlodipine-related effects on ophthalmology examinations, group mean food consumption and group mean body weight. Gingival hyperplasia and erythema developed in cats in the AMODIP® groups at 10-12 weeks after the start of the study. The gingival hyperplasia incidence and severity were dose and time-related, and eventually all cats that received AMODIP® were affected. Several cats had self-limiting periods of decreased food consumption, thought to be secondary to the gingival hyperplasia.

Systolic blood pressure (SBP) was significantly different and lower in the 1X, 3X and 5X groups compared to the control group. Diastolic blood pressure (DBP) was significantly different and lower in the 1X and 5X groups compared to the control group. The SBP and DBP of cats in the control and amlodipine groups remained within the normal range.

On electrocardiogram (ECG), the ST segment was significantly different and longer in the 5X group compared to the control group and is an expected effect of the mechanism of action of amlodipine. There were no clinically relevant effects on heart rate between groups compared to baseline.

There was a trend for lower serum creatinine in individual cats in the 1X, 3X and 5X groups compared to the control group and to baseline. There was a trend for lower serum potassium in individual cats in the 1X, 3X and 5X groups compared to the control group and to baseline. On urinalysis, there was a trend for decreased urine specific gravity (USG), urine total protein and urine creatinine levels and a trend for increased urine volume in the 3X and 5X groups.

On pathology, all cats in the 1X, 3X and 5X groups had gingival hyperplasia and secondary enlargement of the mandibular lymph nodes. Microscopic findings in the kidneys in the 3X and 5X groups included tubular basophilia, interstitial inflammation, tubular dilation, and degeneration of the tubular epithelium. There was an amlodipine-related effect on microscopic degeneration of testes in cats in the 1X, 3X and 5X groups, uterine atrophy with absence of corpora lutea and developing follicles in the ovaries and decreased ovarian weight at necropsy in two 5X female cats.

Effectiveness:

Field Study

Seventy-seven client-owned cats were enrolled in an international, multi-centered, double-masked, randomized field study that evaluated the effectiveness and safety of AMODIP® chewable tablets compared to a vehicle control tablet (no active ingredients) for a 28-day masked phase, followed by an unmasked open label phase. During the unmasked, open label phase, cats in the AMODIP® group continued on AMODIP® for an additional 62 days (total of 90 days), and the control group cats were administered AMODIP® from Days 28 to 120 (92 days total). Enrolled cats had demonstrated a persistent systolic blood pressure (SBP) >165 mm Hg (average of 5 measurements) as measured with high definition oscillometry (HDO) on two separate visits within a two-week period. Cats with a primary disease associated with hypertension (e.g., chronic kidney disease, hyperthyroidism, diabetes mellitus) were in stable condition with no need for immediate initiation of other medication or dose adjustment of current medication.

A total of 42 were randomized to receive AMODIP® (n=42 cats) at an initial dose of 0.125 – 0.25 mg/kg once daily (standard dose), and 35 cats received vehicle control tablets. Blood pressure was measured at treatment Days 14 and 28. If the SBP response was not satisfactory after 14 days, the veterinarian could double the dose to 0.25-0.5 mg/kg (high dose). On study Day 28 the treatment for an individual cat was considered successful if SBP was reduced by ≥15% compared to pre-treatment baseline SBP or below 150 mm Hg. At Day 28, twenty-five cats (62.5%) in the AMODIP® and six cats (17.6%) in the control group met the criteria for success for individual cats. At Day 28 there was a statistically significant change in mean SBP from baseline in the AMODIP® group (-28.2 mm Hg, -15.2%) compared to the control group (-9.9 mm Hg, -5.7%), therefore AMODIP® met the criteria for success for the effectiveness endpoint for the study.

After the Day 28 visit, the study was unmasked for the open label phase. During the open label phase of the study, the AMODIP® group continued on AMODIP® treatment until Day 90 (90 days total), and the control group switched from vehicle control to AMODIP® treatment for 90 days (until Day 120).

Table 3 summarizes the proportion of responders in the first blinded phase of the study by study day as well as responders in the second (open) follow-up phase.

Table 3. Descriptive Statistics for Proportion of Cats That Responded to Treatment

Group	Visit	N	Responder n (%)	Non-Responder n (%)
AMODIP®	Day 14	39	18 (46.2)	21 (53.8)
	Day 28[a]	39	25 (64.1)	14 (35.9)
	Day 90[b]	35	15 (42.9)	20 (57.1)
Control	Day 14	34	7 (20.6)	27 (79.4)
	Day 28[a]	34	6 (17.6)	28 (82.4)
	Day 42[b]	31	19 (61.3)	12 (38.7)
	Day 120[b]	30	17 (56.7)	13 (43.3)

[a] Evaluation of effectiveness on Day 28 and the start of the second (open) phase where control group cats were switched to AMODIP®

[b] Unmasked, open label phase where all cats were administered AMODIP®

There were no clinically relevant findings on physical examination, hematology, serum chemistry, urinalysis and quality of life assessments associated with AMODIP® treatment. A significant difference in DBP was observed at Day 28 between the AMODIP® group (78.6 mm Hg) and the control group (90.1 mm Hg). A significant difference in mean arterial pressure (MAP) was observed at Day 28 between the AMODIP® group (104.9 mm Hg) and the control group (116.5 mm Hg).

Palatability during the field study was documented by the cat owner that administered each dose. For AMODIP® group cats at Day 28, 17.5% consumed the tablet voluntarily, 62.5% consumed the tablet with food, and 20% required pilling.

Evaluation of Target Organ Damage

A published article described a prospective, open-label field study in 225 cats with systemic hypertension (SBP ≥160 mm Hg) that were treated with AMODIP® at

0.625-1.25 mg/cat/day. Ocular fundic lesions were evaluated and scored prior to starting treatment and periodically for one year. Fundic lesion scores improved in cats treated with AMODIP® and the improvement of fundic lesions was correlated with the decrease in SBP. One cat developed gingival hyperplasia after 6 months of treatment.

How Supplied: AMODIP® (amlodipine besylate tablets) Chewable Tablets are supplied in the following package sizes: 3 blister cards of 10 tablets (30 tablets per carton), and 10 blister cards of 10 tablets (100 tablets per carton).

Storage Conditions: Store at or below 25˚C (77˚F), excursions permitted to 30˚C.

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Manufactured for: Ceva Animal Health, LLC, Lenexa, KS 66215

Made in France

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