Date of Approval: April 29, 2026

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-613

AMODIP®

(amlodipine besylate tablets)

Chewable tablets

Cats

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

Sponsored by:

Ceva Sante Animale

Executive Summary

AMODIP® (amlodipine besylate tablets) chewable tablets is approved for the control of systemic hypertension based on indirect systolic blood pressure (SBP) measurement in cats and demonstrated safety and effectiveness through a field effectiveness study, published literature, and a target animal safety study. The approved dosing regimen consists of an initial dose of 0.125 to 0.25 mg/kg administered orally once daily, with the option to increase to a higher dose of 0.25 to 0.5 mg/kg once daily after 14 days if the cat has an inadequate clinical response based on indirect SBP measurements.

Safety and Effectiveness

Field Effectiveness Study
The field effectiveness study enrolled 77 client-owned cats diagnosed with systemic hypertension and randomized them to receive either AMODIP® or vehicle control in a double-masked, placebo-controlled design. The study demonstrated that the standard dose and the high dose controlled systemic hypertension in cats based on indirect SBP measurement as the primary effectiveness variable. AMODIP® was effective compared to a vehicle control tablet (no active ingredient) at Day 28, with 64.1% of AMODIP® treated cats meeting the effectiveness criteria of a lower indirect SBP measurement versus only 17.6% of control cats. The AMODIP® group achieved a mean SBP reduction of 28.2 mm Hg from baseline at Day 28, compared to only 9.9 mm Hg in the control group. After Day 28, control cats entered the open-label phase and started AMODIP® treatment for 90 days and had comparable SBP reductions to the original treatment group. The most common adverse reactions observed included vomiting, anorexia or inappetence, dehydration, and lethargy, and 11 cats discontinued AMODIP® treatment due to adverse reactions.

Published Literature
A publication described a prospective, unmasked, open-label study in 225 client-owned cats diagnosed with systemic hypertension where cats were administered AMODIP® once daily and ocular examinations were conducted at baseline then periodically for 1 year. Treatment of cats with systemic hypertension with AMODIP® at 0.625 to 1.25 mg once daily resulted in improvement in ophthalmic fundic lesions (target organ damage), and the severity of SBP and diastolic blood pressure was correlated with severity of fundic lesions. Cats with severe fundic lesions and severely decreased or absent vision at initiation of treatment were less likely to regain visual function despite retinal reattachment and improvement in retinal hemorrhages.

Target Animal Safety
The target animal safety study evaluated AMODIP® in 32 healthy cats administered 0X, 1X, 3X, or 5X the maximum initial starting dose (0.25 mg/kg) once daily for 6 months. The study demonstrated an adequate margin of safety at all dose levels. All cats receiving AMODIP® developed dose-dependent and time-dependent gingival hyperplasia beginning at weeks 10 to 12. AMODIP® treated cats showed expected pharmacologic effects including decreased blood pressure, decreased serum creatinine, and decreased serum potassium, though values remained within normal ranges and were not associated with clinical abnormalities. Additional findings included changes in urinalysis parameters secondary to AMODIP®'s mechanism of action, microscopic

changes in kidneys and gonads on histopathology, and one esophageal ulceration in a 5X group cat possibly related to tablet administration.

Conclusions

Based on the information submitted by the sponsor for AMODIP®, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-613

B. Sponsor

Ceva Sante Animale
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33500 Libourne
France

Drug Labeler Code: 013744

U.S. Agent Name and Address:

Alicia Henk
Ceva Animal Health LLC
8735 Rosehill Rd
Suite 300
Lenexa, KS 66215

C. Proprietary Name

AMODIP®

D. Drug Product Established Name

amlodipine besylate tablets

E. Pharmacological Category

Antihypertensive

F. Dosage Form

Chewable tablets

G. Amount of Active Ingredient

1.25 mg amlodipine per scored chewable tablet

H. 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).

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

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.

K. Route of Administration

Oral

L. Species

Cats

M. Indication

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

II. EFFECTIVENESS

Dosage characterization was based on published literature. Effectiveness was demonstrated in a masked, controlled field study in cats with systemic hypertension.

A. Dosage Characterization

An initial oral dose of 0.125 to 0.25 mg/kg once daily that may be doubled or increased up to 0.5 mg/kg once daily was selected based on the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement: Guidelines for Identification, Evaluation and Management of Systemic Hypertension in Dogs and Cats (2018)[1] and other published scientific literature that evaluated orally administered doses of amlodipine besylate within the same dose range for the control of systemic hypertension in cats.

[1] Acierno, M.J, Brown, S., Coleman, A.E., Jepson, R.E., Papich, M., Stepien, R.L., & Syme, H.M. (2018). ACVIM Consensus Statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *Journal of Veterinary Internal Medicine, 32*(6), 1803-1822.

B. Substantial Evidence

The effectiveness of AMODIP® (amlodipine besylate tablets) chewable tablets for the control of systemic hypertension in cats was evaluated in the field study in client-owned cats and a published article (Cirla, 2021).[2]

1. Field Effectiveness Study

Title: Efficacy and Clinical Safety of Amlodipine in Cats with Hypertension: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Pivotal Clinical Field Trial. (Study No. V2969001)

Study Dates: November 2011 to August 2013.

Study Locations: Twenty-three veterinary clinics in Finland, France, and Germany participated in the study.

Helsinki, Finland
Tampere, Finland
Pamier, France
St. Pourçain, France
Aix au Provence, France
Digne Les Bains, France
Freising, Germany
Erdweg, Germany
Neuwied, Germany
Erftstadt-Lechenich, Germany
Traunstein, Germany
Olching, Germany
Turku, Finland
Palokka, Finland
Marseille, France
Pau, France
Carpentras, France
Villefontaine, France
Bremen, Germany
Freilassing, Germany
Wassenberg, Germany
München, Germany
Freiberb, Germany

Study Design: This was a multicenter, double-masked, randomized, placebo-controlled field study.

Objective: To determine the effectiveness of AMODIP® in reducing SBP in cats diagnosed with systemic hypertension.

Study Animals: The study enrolled 77 client-owned cats (36 spayed females and 41 neutered males) diagnosed with systemic hypertension (SBP≥165 mm Hg). The cats ranged in age from 7 to 20 years old and weighed 3 to 8 kg. The cats represented both pure and mixed breeds. All 77 cats were evaluated for safety and 73 were evaluated for effectiveness.

Primary diseases associated with the hypertension included chronic kidney disease (33.8%), idiopathic hypertension (27.3%), hyperthyroidism (24.7%), early-stage heart disease (7.8%), diabetes mellitus (2.6%), and other (3.9%). On medical history, 34 cats (44.2%) had evidence of chronic kidney disease (CKD)

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[2] Cirla, A., Drigo, M., Andreani, V., & Barsotti, G. (2021). Ocular fundus abnormalities in cats affected by systemic hypertension: Prevalence, characterization, and outcome of treatment. *Veterinary Ophthalmology*, *24*(2), 185-194.

and 10 of those cats (29.4%) were on an angiotensin-converting enzyme (ACE) inhibitor for treatment of renal disease.

Experimental Design: The study was conducted according to Good Clinical Practices (GCP). The cats were randomized on Day 0 to receive AMODIP® or vehicle control at a 1:1 ratio (42 cats in the AMODIP® group and 35 cats in the control group). Cats in the AMODIP® group were treated for 90 days and cats in the control group received the vehicle control for 28 days (masked phase) and then AMODIP® for 90 days (open-label phase). All cats were evaluated twice during screening (Screening A and B Visits) and on Days 14 and 28 of the masked phase of the study. After Day 28, the AMODIP® group cats were evaluated on Day 90 before exiting the study and the control group cats were evaluated on Days 42 and 120. All cats completing the study received 90 days of AMODIP® treatment.

Table II.1. Treatment Groups Through Day 28 (Masked Phase)

Treatment Group	Dose mg/kg/day	Number of Cats
AMODIP®	0.125	42
Vehicle control[a]	0	35

[a] Tablet with inactive ingredients only

Inclusion Criteria:

- Weight between 2.5 to 10 kg
- Hypertension with SBP≥165 mm Hg (average of 5 measurements within 15 mm Hg) on 2 separate screening visit days within 2 weeks, provided the cat was not apparently excited based on clinical judgement (to rule out “white coat hypertension”).
- If a primary disease associated with hypertension was present, then the primary disease was stable with no need for immediate initiation of other medication or dose adjustment of current medication.

Exclusion Criteria:

- Use of systemic treatment with calcium-channel blockers, vasodilators (e.g., hydralazine), alpha-1 adrenergic antagonists (e.g., prazosin), angiotensin receptor blockers, beta-blockers, or aldosterone antagonists (e.g., spironolactone) within 30 days before the Screening B visit.
- Use of long-acting glucocorticoids or continuous use of short acting glucocorticoids within the last 3 months before the Screening B visit.
- Initiation or change in dosing of methimazole, carbimazole, phenylpropanolamine, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics (e.g., furosemide), short acting systemic glucocorticoids (single treatment), or any other medication for the primary disease associated with the hypertension within 14 days before the Screening B visit.

- Initiation or change in dosing of ACE inhibitors or renal diet within 30 days before the Screening B visit.
- Initiation or significant change in dosing of insulin treatment for diabetes mellitus within 30 days before the Screening B visit.
- Presence of ocular or neurological signs which were caused by hypertension and required immediate medical treatment.
- SBP>200 mm Hg.
- Clinically relevant liver failure or impaired hepatic function.
- Unstable chronic kidney disease that was expected to worsen significantly during the study. Cats at late stages of kidney disease (International Renal Interest Society (IRIS) stage 3 and 4) were not included.
- Cat was in severe acute pain.
- Cat was pregnant or lactating.
- Concurrent participation in any other clinical study or administration of any other investigational drug within the preceding 30 days.
- Any other condition or situation which, in the investigator's opinion, could disturb the conduct of the study.

Indirect blood pressure was measured with a commercially available high definition oscillometry (HDO) device that was intended for use in cats. The blood pressure of cats was measured twice on separate days (Screening A and Screening B) during a 14-day screening period to confirm the presence of systemic hypertension prior to enrollment in the study. On Day 0 (Visit 0), cats were randomized to treatment group (AMODIP® or control).

Drug Administration: AMODIP® was administered to AMODIP® group cats orally, once daily for 90 (±7) days by the cat owner at home. The vehicle control was administered to control group cats orally, once daily for 28 days using the same procedures; the vehicle control was a tablet of the same appearance as AMODIP® that did not include the active ingredient. The dose was offered to the cat by hand, given with food or pilled if the cat refused to consume it voluntarily. The dose was based on body weight of the cat at screening.

Table II.2. Dosing Table

Weight (kg)	Standard Dose	Double Dose
2.5 - 5	0.5 tablet (0.625 mg)	1 tablet (1.25 mg)
5.1 - 10	1 tablet (1.25 mg)	2 tablets (2.5 mg)

Cats in the AMODIP® group were dosed at an initial target dosage of 0.125 mg/kg/day for 14 days. At Day 14 (Visit 1), cats continued the 0.125 mg/kg/day dose to Day 28 (Visit 2) if SBP was <150 mm Hg or had decreased ≥15% from their baseline reading. In the event SBP was ≥150 mm Hg or had not decreased at least 15% from baseline, the cat's study treatment dosage was doubled to a target dosage of 0.25 mg/kg/day. Effectiveness was determined using the Day 28

SBP measurements. The AMODIP® group cats continued the same dose they were on at Day 28 through Day 90.

Cats in the control group were initially dosed with the vehicle control. After the Day 28 visit, the control group cats were started on AMODIP® at an initial target dose of 0.125 mg/kg/day. At Day 42 (Visit 3), these cats continued the 0.125 mg/kg/day dose if SBP was <150 mm Hg or had decreased ≥15% from their baseline reading, or the dose was doubled to a target dosage of 0.25 mg/kg/day if SBP was ≥150 mm Hg or had not decreased at least 15%. The control group cats continued the same dose they were on at Day 42 through Day 120.

Measurements and Observations: Demographic information, medical history, concomitant medications, baseline physical examination, body weight, SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) were collected at the Screening A visit. Physical examination, body weight, medical history, concomitant medications, bloodwork (hematology, serum chemistry), urinalysis, Quality of Life (QoL) assessment (appetite, drinking, urinating, mobility, and cat-owner interactions), SBP, DBP, and MAP were collected at the Screening B visit. Safety was evaluated through physical examinations, bloodwork, urinalyses, QoL assessments, documentation of adverse events, and monitoring for evidence of target organ damage (TOD). SBP, DBP, and MAP were measured on Days 14, 28, and 90 for the AMODIP® group cats and on Days 14, 28, 42, and 120 for the control group cats. The control group cats had the additional blood pressure measurement taken at Day 42, 2 weeks after starting AMODIP® to determine if an increase in dose was needed.

Statistical Methods:
Primary effectiveness analyses were performed based on the Per-Protocol (PP) population, which includes randomized cats that had no protocol violations and had SBP measurement data at baseline (Screening B) and at Day 28. The PP datasets included a total of 73 cats, including 39 in the AMODIP® group and 34 in the control group.

The experimental unit was the individual cat. A cat was considered a treatment responder if, on Day 28, it had a decrease of SBP to <150 mm Hg or an SBP decrease from Screening B of at least 15%.

To demonstrate superiority of AMODIP® compared to vehicle control, the following statistical hypotheses were applied on the primary effectiveness variable:

H0: $\pi_{amlodipine} = \pi_{control}$
H1: $\pi_{amlodipine} \neq \pi_{control}$

where π is the proportion of responders of the specific treatment group. The proportion of responders were analyzed with a logistic regression model, with the treatment group included as a fixed effect, and Screening B SBP, renal disease (yes/no), and concomitant ACE inhibitor use (yes/no) as covariates. The hypothesis was tested at two-sided $\alpha = 0.05$ significance level. A two-sided 95%

confidence interval (CI) for the Odds Ratio (OR) (AMODIP® vs. control) was also calculated.

Effectiveness was established if, on Day 28, the proportion of responders in the AMODIP® group was superior ($p<0.05$) to the proportion of responders the control group or the lower limit of the two-sided 95% CI for the OR is greater than 1.

Results:
Primary Effectiveness (Day 28):
On Day 28, the proportion of responder cats in the AMODIP® group was statistically superior ($p=0.0002$) to the proportion of responder cats in the control group. Additionally, the lower limit of the two-sided 95% CI for the OR was greater than 1 (2.79) (Table II.3).

Table II.3. Primary Effectiveness Analysis: Odds Ratio (95% Confidence Interval)

Effect	Study Day	OR (95% CI)	p-value
AMODIP® vs Control	14	3.22 (1.12, 9.32)	0.0306[a]
AMODIP® vs Control	28	8.56 (2.79, 26.25)	0.0002

[a] No multiplicity adjustment was made.

The number of cats that responded to treatment on Day 28 (Visit 2) was 25 (64.1%) and 6 (17.6%) in the AMODIP® and control group, respectively. The number of cats that did not respond to treatment on Day 28 was 14 (35.9%) and 28 (82.4%) in the AMODIP® and control group, respectively (Table II.4). Cats that discontinued treatment due to adverse reactions during the masked phase of the study were considered “non-responders”. There was no effect of primary disease or concomitant use of ACE inhibitors on response to treatment, and non-response to treatment was not associated with a particular type of adverse reaction.

Table II.4. Proportion of Cats that Responded to Treatment

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

[a] Evaluation of effectiveness on Day 28 and the start of the second (open label) phase where control group cats were switched to AMODIP®
[b] Open label phase
[c] Number of cats and percentage of total cats

The AMODIP® group mean change in absolute SBP on Days 14 and 28 compared to baseline (Screening B) was -21.7 mm Hg and -28.2 mm Hg, respectively (Table II.5). The control group mean change in absolute SBP on Days 14 and 28 compared to baseline was -11.7 mm Hg and -15.2 mm Hg, respectively (Table II.6). The mean change in SBP was significantly greater in the AMODIP® group compared to the control group from baseline to Day 14 ($p=0.005$) and Day 28 ($p<0.001$).

After the control group switched to treatment with AMODIP® on Day 28, the control group mean change in absolute SBP on Days 42 and 120 was -24.1 mm Hg and -21.0 mm Hg, respectively. After treatment with AMODIP®, the control group had a decrease in mean absolute SBP comparable to that of the AMODIP® group during the masked phase of the study.

Table II.5. AMODIP® Group Mean SBP and Change from Screening B Visit by Study Day

Day	Number of Cats	Mean SBP in mm Hg (SD)[a]	Mean Absolute Change in SBP in mm Hg (SD)	Mean % Change in SBP in mm Hg (SD)
Screening A	N = 39	181.4 (12.2)	NA	NA
Screening B	N = 39	181.5 (12.9)	NA	NA
Day 14	N = 39	159.8 (16.9)	-21.7 (18.8)	-11.7 (9.9)
Day 28	N = 39	153.3 (17.1)	-28.2 (19.6)	-15.2 (10.3)
End of Study (Day 90)	N = 35	158.9 (15.0)	-22.3 (16.4)	-12.0 (8.7)

[a] SD = Standard deviation

Table II.6. Control Group Mean SBP and Change from Screening B Study Visit

Day	Number of Cats	Mean SBP in mm Hg (SD)[a]	Mean Absolute Change in SBP in mm Hg (SD)	Mean % Change in SBP in mm Hg (SD)
Screening A	N = 34	180.4 (12.8)	NA	NA
Screening B	N = 34	179.6 (10.7)	NA	NA
Day 14	N = 34	170.4 (18.1)	-9.3 (15.4)	-5.1 (8.7)
Day 28	N = 34	169.7 (20.5)	-9.9 (14.6)	-5.7 (8.2)
Day 42[b]	N = 31	155.8 (19.1)	-24.1 (19.5)	-13.2 (10.6)
End of Study (Day 120)[b]	N = 30	157.9 (18.8)	-21.0 (17.5)	-11.7 (9.6)

[a] SD = Standard deviation
[b] Control group treatment changed to AMODIP® after Day 28 study visit was complete. Control group Days 42 and 120 reflect SBP values while treated with amlodipine.

Changes in DBP and MAP mirrored the changes in SBP for both treatment groups. There were no clinically relevant effects of treatment with AMODIP® on physical examination, body weight, bloodwork, and urinalysis.

For QoL assessments, at Day 28, owners reported a trend towards cats administered AMODIP® (35%) feeling better than the cats in the control group (14.7%).

Symptoms of TOD were low at the screening visits and throughout the study. The TOD assessment for vocalization was decreased in the AMODIP® group compared to the control group and was decreased in the control group after Day 28 compared to the screening visits and Day 14 and 28 visits.

During the field study the voluntary consumption of AMODIP® was assessed by the cat owners and recorded by the investigator at each visit. The percentage of AMODIP® cats voluntarily taking the tablet at Day 28 was 17.5%, 62.5% accepted the tablet with food, and 20% required pilling.

Dose and Treatment Effect:
The AMODIP® dose was increased (doubled) after 14 days of treatment in 22 cats (53.7%) in the AMODIP® group and in 12 (38.7%) of the control cats after starting amlodipine treatment. There was no difference in response to treatment at Day 28 for cats that remained on the initial AMODIP® dose compared to cats that had a doubled dose, indicating that doubling the dose based on response to treatment within 14 days of starting treatment was appropriate for control of systemic hypertension based on SBP measurements.

Concomitant Treatments:
The most commonly administered concomitant treatments were anti-infective drugs, drugs to treat gastrointestinal disorders, anti-inflammatory drugs,

vaccinations, and sedatives/anesthesia drugs. Drugs acting on the renin-angiotensin system (ACE inhibitors) were administered to 12 cats during the study (AMODIP® n=7 (16.7%), control n=5 (14.3%)); no change in dose or initiation of ACE inhibitor treatment was allowed after study enrollment.

Adverse Reactions:
During the masked phase of the study (through Day 28) a total of 23 adverse reactions were reported in 28.6% of the cats (12 of 42) in the AMODIP® treatment group, while 17 adverse reactions were reported in 28.6% of the cats (10 of 35) in the control group. Adverse reactions that were clearly secondary to a concurrent disease are not included in Table II.7.

Table II.7. Adverse Reactions by Treatment Group from Day 0 to 28 (Masked Phase)[a]

Adverse Reaction	AMODIP® N=42[b] n (%)[c]	Control N=35[b] n (%)[c]
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)

[a] Recurrent adverse reactions for the same cat are only counted once
[b] N = total number of cats enrolled
[c] n (%) = number of cats per adverse reaction and percentage of the total population per treatment group.

Table II.8. Adverse Reactions Reported After Day 28 (Open Label Phase)[a]

Adverse Reaction	AMODIP® N=77[b] n (%)[c]
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 (2.3)
Hematemesis	2 (2.3)

[a] Recurrent adverse reactions for the same cat are only counted once
[b] N = total number of cats enrolled
[c] n (%) = number of cats per adverse reaction and percentage of the total population per treatment group.

During the entire study, serious adverse reactions were noted in five AMODIP® group cats and two control group cats. Six of the serious adverse reactions were determined to be unrelated to treatment, except for one AMODIP® group cat where the determination was deemed possibly related. One AMODIP® group cat was being treated for hyperthyroidism with methimazole. The cat received both a steroid and an NSAID one month after starting AMODIP® treatment and developed anorexia and hepatopathy and was euthanized. The causality was considered possibly related based on the hepatic metabolism of amlodipine and development of hepatopathy when administered concurrently with the NSAID and steroid.

There were 11 cats that discontinued AMODIP® treatment due to an adverse reaction, and 1 that temporarily discontinued treatment. Five of the 12 cats that discontinued treatment due to an adverse reaction had a causality of possibly or probably related to treatment and included anorexia, lethargy, worsening pre-existing heart murmur, hematemesis, and development of icterus. The other adverse reactions that led to discontinuation of treatment were likely due to underlying concurrent diseases.

Conclusions: AMODIP® was safe and effective for the control of systemic hypertension in cats when administered at an initial dose of 0.125 to 0.25 mg/kg once daily, with an increase to 0.25 to 0.5 mg/kg once daily if there was an inadequate response based on SBP measurement 14 days after starting treatment. The most common adverse reactions were vomiting, anorexia or inappetence, dehydration, and lethargy.

2. Published literature

Cirla, A., Drigo, M., Andreani, V., & Barsotti, G. (2021). Ocular fundus abnormalities in cats affected by systemic hypertension: Prevalence, characterization, and outcome of treatment. *Veterinary Ophthalmology*. *24*(2):185-194.

This publication describes a prospective, unmasked, open-label study in 225 cats that had been diagnosed with systemic hypertension based on measurement of indirect SBP. There were 133 neutered male and 92 spayed female cats that were between 1 to 20 years old; the cats included a variety of pure and mixed

breeds. Concurrent diseases included CKD, hyperthyroidism, and hypertrophic cardiomyopathy. The primary assessment included SBP measurement and complete ophthalmic examinations, including documentation of ocular fundic lesions using a scoring system (Grade 0 to 4) and fundus photographic documentation. Fundic lesions were scored as Grade 0 = no lesions, Grade 1 = increased arterial vascular tortuosity with minimal to moderate narrowing of the retinal arteries, Grade 2 = Grade 1 abnormalities observed as well as mild retinal hemorrhages and/or subretinal exudation (bullous retinal detachment), Grade 3 = Grade 1 and 2 abnormalities observed with partial retinal detachment and moderate/severe retinal and/or vitreous hemorrhages, and Grade 4 = Grade 1 to 3 abnormalities observed as well as subtotal/total retinal detachment. Cats were considered to have systemic hypertension if they had an SBP≥160 mm Hg and DBP≥100 mm Hg. Enrolled cats were administered AMODIP® tablets at a dose of 0.625 to 1.25 mg per cat once daily. Cats were followed and reexamined for up to 1 year on Days 7, 14, 21, 28, 45, 90, 180, and 365 after starting AMODIP®. Cats whose owners failed to keep follow up appointments were excluded from the study. Therapeutic effect and clinical improvement were evaluated by: 1) the average time for improvement in fundus abnormalities compared to the initial fundus score, 2) the number of hypertensive cats with improved fundus abnormalities at each follow up time, 3) the number of hypertensive cats with no ocular lesions from baseline to the last follow up (day 365), 4) the number of hypertensive cats with minor improvements in fundus abnormalities, and 5) the number of hypertensive cats with no improvement and/or deteriorated fundus abnormality.

Two-hundred eleven cats completed the study and were included in the analyses. Ocular fundus lesions were documented in 132 cats (58.6%) with 28 cats (21.2%) with Grade 1 lesions, 24 cats (18.2%) with Grade 2, 48 cats (36.4%) with Grade 3, and 32 cats (24.2%) with Grade 4. SBP and DBP were correlated with the severity of fundus abnormalities based on the fundus score. At the first follow-up (Day 7) 117 cats (88.6%) had improved fundus examinations, 14 cats (10.6%) had no change, and 1 cat (0.8%) was worse. At the last follow-up (Day 365), of the 132 cats that had fundus abnormalities at enrollment, 121 cats (91.6%) showed a significant improvement in the fundus appearance with retinal reattachment and resolution of hemorrhages if they had been present previously. Based on the visual assessments in the 132 cats that had fundus abnormalities initially, by the end of the study 71 cats (53.8%) had maintained visual function (normal menace response, normal dazzle reflex, normal pupillary light reflexes), 31 cats (23.5%) had visual function that was judged as uncertain, and 30 cats (22.7%) were considered blind. Cats scored with Grades 3 to 4 fundic lesions at the start of treatment showed severely affected or absent visual function at Day 365. In these cats, severe or diffuse secondary retinal degeneration was observed, despite most of them showing retinal reattachment and/or resolution of the hemorrhages during the study period. There was only one reported adverse reaction during the study. One cat (female spayed, 10 years old) developed gingival hyperplasia after 6 months of treatment.

Conclusion: The published article demonstrated that treatment of cats with systemic hypertension with AMODIP® at 0.625 to 1.25 mg per cat once daily

resulted in improvement in ophthalmic fundic lesions (target organ damage), and that the severity of SBP and DBP was correlated with severity of fundic lesions. Cats with severe fundic lesions and severely decreased or absent vision at initiation of treatment were less likely to regain visual function despite retinal reattachment and improvement in retinal hemorrhages.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Amlodipine: A Target Animal Safety Study in Cats. (Study No. 498143)

Study Dates: May 24, 2012 to March 29, 2013

Study Location: 's-Hertogenbosch, The Netherlands

Study Design:

Objective: To evaluate the margin of safety of amlodipine besylate tablets when administered orally once daily to adult cats at 0X, 1X, 3X, and 5X of the maximum initial starting dose for 6 months.

Study Animals: Thirty-two healthy cats (16 male, 16 female) were assigned to 1 of 4 treatment groups. At the start of the study, cats were approximately 11 to 12 months old and weighed 3.7 to 5 kg for males and 2.8 to 4.7 kg for females.

Experimental Design: Cats were weighed upon arrival prior to allocation and were allocated to one of four treatment groups (0X, 1X, 3X, and 5X) of eight cats per group (four per sex) so that each group had comparable weights and ages. No littermates were assigned to the same group. All cats were dosed once daily with either the vehicle control tablets (no active ingredient) or AMODIP® at 0.25 mg/kg (1X group), 0.75 mg/kg (3X group) or 1.25 mg/kg (5X group). The laboratory study was conducted in accordance with Good Laboratory Practice (GLP) regulations (Organisation for Economic Co-Development (OECD) Principles).

Table III.1. Treatment Groups and Drug Administration

Group	Dose Multiple	Dose mg/kg/day	Number and Sex of Animals
1	0X	0	4 females, 4 males
2	1X	0.25	4 females, 4 males
3	3X	0.75	4 females, 4 males
4	5X	1.25	4 females, 4 males

Drug Administration: After overnight fasting, cats were dosed once daily in the morning using a combination of whole and/or half tablets according to body weight and assigned treatment group. The dosing administration methods (listed in order of preference) were: (1) spontaneous uptake from hand or empty bowl, (2) facilitated

uptake with tablet(s) administered with small amount of canned food, or (3) forced intake with tablet(s) placed into the mouth, swallow reflex induced, and flushed with a small amount of water. The amlodipine tablets were 1.25 mg, scored tablets. The

control tablets were a vehicle only tablet (inactive ingredients only). Control group cats were dosed based on body weight with the same number of tablets as the 5X group cats.

Measurements and Observations: The evaluations and observations schedule included clinical observations (at least once daily during pretest and twice-daily during treatment before and after dosing), physical examinations (pre-test, monthly, and at study termination), body weight (weekly), food consumption (daily), direct ophthalmic examinations (pre-test, week 4, week 13, and end of treatment), electrocardiogram (ECG) examinations (pre-test, and on weeks 4, 13, and 26), indirect blood pressure measurements (pre-test, and on weeks 4, 13, and 26 prior to dose administration and 2h and 6h post dose), hematology, serum chemistry, and urinalysis (pre-test, week 4, week 13, and end of treatment).

Statistical Methods: The experimental unit was the individual cat. For continuous outcomes measured only once during the study, Analysis of Variance (ANOVA, Mixed procedure in SAS, SAS Institute, Cary NC; version 9.4) was used to evaluate a model containing treatment, sex, and treatment-by-sex interaction as fixed effects. If the treatment-by-sex effects interaction was not significant, the main effect of treatment was evaluated at alpha=0.10. If the treatment-by-sex effects were significant at the 10% level, within-sex treatment effects were evaluated using pair-wise comparisons of each treatment group against the control using linear contrasts at an unadjusted alpha=0.10. Organ weight data were expressed as a percentage of the final body weight and as absolute weights.

Continuous variables measured at multiple times during the study (ECG, blood pressure, body weight, clinical pathology, and weekly food consumption) were analyzed by repeated measures analysis of covariance with treatment, sex, time, treatment-by-sex, sex-by-time, treatment-by-time, and treatment-by-sex-by-time terms in the model as fixed effects, and animal identified as the subject in the repeated statement (the Mixed procedure in SAS, Repeated Measures Analysis of Covariance (RMANCOVA)). Pre-treatment values (prior to the first dose) were used as a covariate and remained in the model regardless of statistical significance. The treatment-by-sex-by-time interaction was evaluated at the 5% level. If the treatment-by-sex-by-time interaction was significant (alpha=0.05), no further hypothesis testing was conducted; summary statistics for each treatment group at each time point within each sex are provided. If the treatment-by-sex-by-time interaction was not significant, then the two-way interactions of treatment-by-sex and treatment-by-time were evaluated. If the treatment-by-sex interaction was significant at the 10% level, within-sex treatment effects were evaluated using pair-wise comparisons of each treatment group against control using linear contrasts at an unadjusted alpha=0.10. If the treatment-by-time interaction was significant at the 10% level (regardless of the significance of the treatment-by-sex term), then pair-wise comparisons of each treatment group against control for each time using linear contrasts at an unadjusted alpha=0.10 was performed.

If neither of the two-way interactions involving treatment were significant, then the main effect of treatment group was evaluated at the 10% level. If the treatment effect was significant, then pair-wise comparisons of each treatment group against control using linear contrasts at an unadjusted alpha=0.10 were performed.

Results from urinalysis were summarized, but no hypothesis testing was conducted. Daily clinical observations and gross observations were not subjected to statistical analysis.

Results:
Physical Examinations: There was no effect of amlodipine administration on physical and ophthalmoscopic examinations.

Clinical Observations: All cats in the 1X, 3X, and 5X groups developed gingival hyperplasia. Gingival hyperplasia started at week 12 in the 1X and 3X groups and at week 10 in the 5X group. Severity of the gingival hyperplasia was time and dose dependent with the lesions in all groups worsening over time.

Diarrhea occurred in one 1X cat and two 3X cats on a few occasions during the study. One 1X cat had mucous in stool and hematochezia once.

Body Weight and Food Consumption: There was no effect of amlodipine administration on body weight for the 1X, 3X, and 5X group mean body weights compared to the control group mean body weight. One control group cat, two 3X group cats, and one 5X group cat had decreased appetite that led to decreased body weight for 2 to 3 weeks duration. The inappetence resolved when canned food or soaked kibble were offered, indicating discomfort from the gingival hyperplasia was the cause of the inappetence.

Blood Pressure: Indirect SBP and DBP were measured using a high definition oscillometric. Measurements were obtained using a tail specific cuff. The average of five measurements, within 20 mm Hg systolic blood pressure, were used. SBP was significantly different and lower in the 1X, 3X, and 5X groups compared to the control group ($p=0.0153$, 0.0640, and 0.0016, respectively). DBP was significantly different and lower in the 1X and 5X groups compared to the control group ($p=0.0146$ and 0.0040, respectively). The SBP and DBP of cats in the control and amlodipine groups remained within the normal range.

Electrocardiogram (ECG): No abnormalities in heart rhythm were noted for any cat. There were no clinically detectable changes in heart rate between groups and compared to baseline. Mean ST segment was higher (longer) in the 5X dose group compared to the control group ($p=0.0149$). The 5X group cats had a longer ST segment secondary to the mechanism of action of amlodipine, although there were no clinically detectable findings associated with the ST segment changes.

Clinical Pathology: 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. The effect of amlodipine administration on serum creatinine was significant at Week 4 in the 1X, 3X, and 5X groups (decreased) compared to the control group ($p=0.0125$, 0.233, and 0.0146, respectively).

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. For values that were below the reference range (3.4 to 5.2 mmol/L, 3.4 to 5.2 mEq/L), none of the decreased

potassium values were of clinical significance. The effect of amlodipine administration on serum potassium was statistically significant in the 3X and 5X groups (decreased) compared to the control group (p=0.023 and 0.0046, respectively).

There were no clinically relevant changes for the hematology, coagulation, and other serum chemistry variables compared to baseline or the control group.

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. Mean USG was lower compared to baseline for the 1X, 3X, and 5X males and for the 3X and 5X females. The mean USG for the 1X males and females remained within the normal range for all timepoints. Urine volume varied week to week for individual cats in all groups. Group mean urine volume was larger in the 3X and 5X groups at week 13 and week 26 compared to the control group and to acclimation volumes. The urinalysis findings are secondary to the mechanism of action of amlodipine.

Pathology: All 1X, 3X, and 5X group cats had gingival hyperplasia and secondary enlargement of mandibular lymph nodes with reactive hyperplasia. One male cat in the 5X group had a focal esophageal ulceration which may have been secondary to administration of the large number of tablets. There was microscopic hyperplasia of the gingival connective tissue and epithelium with varying degrees of inflammation in the 1X, 3X, and 5X groups. Microscopic findings in the kidneys in the 3X and 5X groups included tubular basophilia, interstitial inflammation, tubular dilation, and degeneration of the tubular epithelium, although these findings were not associated with clinical findings or serum chemistry results. Microscopic degenerative changes in the testes were noted in the 1X, 3X, and 5X group cats more frequently than the control group cats. Two 5X female cats had microscopic evidence of uterine atrophy with absence of corpora lutea and developing follicles in the ovaries. There were no findings aside from gingival hyperplasia and the esophageal ulceration in one male 5X group cat on gross necropsy or histopathology that could be associated with the decreased appetites, supporting the cause of decreased appetite as secondary to discomfort from the gingival hyperplasia.

Organ Weights: Adrenal gland weights were significantly different and higher in the 3X and 5X groups compared to the control group (p=0.0259 and 0.0051, respectively). Ovary weights and relative ovary weights compared to body weight were significantly different and lower in the 5X group compared to the control group (p=0.0189 and 0.0159, respectively). The decreased ovary weight and relative ovary weight is consistent with signs of atrophy noted on histopathology.

Conclusions:
The study supports the safe use of AMODIP® (amlodipine besylate tablets) chewable tablets in cats when used at the labeled dose. AMODIP® demonstrated an adequate margin of safety when administered at 0.25, 0.75, or 1.25 mg/kg once daily in normal, normotensive cats for 6 months.

Treatment with AMODIP® was associated with gingival hyperplasia, intermittent hyporexia, decrease in blood pressure, hypokalemia, decreased creatinine,

increased fibrinogen, elevated ST interval, abnormal urinalysis findings, and changes in gonads on histopathology. Cats with systemic diseases or concurrent treatments that predispose them to hypokalemia may require additional monitoring.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to AMODIP®:

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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that AMODIP®, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose hypertension and monitor the response to treatment, and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

AMODIP®, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.