

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Amodip 1.25 mg chewable tablets for cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains :

Active substance:

Amlodipine 1.25 mg
(Equivalent to 1.73 mg of amlodipine besilate)

Excipients:

Qualitative composition of excipients and other constituents
Artificial chicken flavour
Malted yeast
Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Magnesium stearate
Silica colloidal anhydrous

Oblong in shape, score line on one side, beige to light brown tablets.
Tablets can be divided into two equal parts.

3. CLINICAL INFORMATION

3.1 Target species

Cats

3.2 Indications for use for each target species

For the treatment of systemic hypertension in cats.

3.3 Contraindications

Do not use in the case of cardiogenic shock and severe aortic stenosis.

Do not use in cases of severe hepatic failure.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

The primary cause and/or co-morbidities of hypertension, such as hyperthyroidism, chronic kidney disease and diabetes, should be identified and treated.

In cats situational hypertension (also called white coat hypertension) occurs as a consequence of the in-clinic measurement process in an otherwise normotensive animal. In case of high stress levels measurement of systolic blood pressure may lead to incorrect diagnosis of hypertension. It is recommended that stable hypertension is confirmed by repeated measurement of systolic blood pressure on different days before commencing therapy.

Continued administration of the veterinary medicinal product over an extended period of time should be in accordance with an ongoing benefit/risk evaluation, performed by the prescribing veterinarian that includes measurement of systolic blood pressure routinely during treatment (e.g. every 6 to 8 weeks).

3.5 Special precautions for use

Special precautions for safe use in the target species:

Special caution is required in patients with hepatic disease as amlodipine is highly metabolised by the liver. As no studies have been conducted in animals with liver disease, use of the veterinary medicinal product in these animals should be based on a benefit-risk assessment by the attending veterinarian.

Administration of amlodipine may sometimes result in a decrease in serum potassium and chloride levels. Monitoring of those levels is recommended during treatment. Older cats with hypertension and chronic kidney disease (CKD) may also suffer from hypokalaemia as a result of their underlying disease.

The safety of amlodipine has not been established in cats weighing less than 2.5 kg.

Safety has not been tested in cats with cardiac failure. Use in these cases should be based on a benefit risk assessment by the veterinarian.

The chewable tablets are flavoured. In order to avoid any accidental ingestion, store tablets out of reach of the animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

This veterinary medicinal product may decrease blood pressure. In order to reduce the risk of accidental ingestion by children, do not take the tablets out of blisters until ready to administer to the animal. Return part-used tablets into the blister and carton. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to amlodipine should avoid contact with the veterinary medicinal product. Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cats:

Very common (>1 animal / 10 animals treated):	Emesis ¹ , Gingival hyperplasia ² Enlarged lymph node (localised) ^{2,3}
Common (1 to 10 animals / 100 animals treated):	Digestive tract disorder (e.g , diarrhoea, anorexia) ¹ Lethargy ¹ , Dehydration ¹

¹Mild and transient

²Mild, observed at the dose of 0.25 mg/kg in healthy young adult cats, and doesn't usually require stopping treatment. In older cats these signs are very rare.

³Submandibular

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

Laboratory studies in rodents have not produced any evidence of teratogenicity or reproductive toxicity. The safety of veterinary medicinal product has not been established during pregnancy and lactation in cats. Use only in accordance with the risk-benefit assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Concomitant use of amlodipine with other agents that may reduce blood pressure may cause hypotension. These agents include: diuretics, beta-blockers, other calcium channel blockers, inhibitors of the renin angiotensin aldosterone system (renin inhibitors, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors (ACEI), and aldosterone antagonists), other vasodilators and alpha-2 agonists. It is advised to measure blood pressure before administering amlodipine with these agents and to ensure cats are adequately hydrated.

However, in clinical cases of feline hypertension, no evidence of hypotension occurring as a result of combining amlodipine with the ACEI benazepril was observed.

Concomitant use of amlodipine with negative chronotropes and inotropes (such as beta-blockers, cardioselective calcium channel blockers and antifungal azoles (e.g itraconazole) may reduce force and rate of contraction of the heart muscle. Particular attention must be paid before administering amlodipine with these drugs in cats with ventricular dysfunction.

The safety of concomitant use of amlodipine and the anti-emetic agents dolasetron and ondansetron has not been evaluated in cats.

3.9 Administration routes and dosage

Oral use

Amlodipine tablets should be administered orally at a recommended starting dose of 0.125 - 0.25 mg/kg/day.

After 14 days of treatment, the dose may subsequently be doubled or increased up to 0.5 mg/kg once daily if adequate clinical response has not been achieved (e.g. systolic blood pressure remaining over 150 mmHg or a decrease of less than 15 % from the pre-treatment measurement).

Weight of cat (kg)	Starting dose (number of tablets)
2.5 - 5.0	0.5
5.1 - 10.0	1
10.1 and above	2

To ensure a correct dosage, body weight should be determined as accurately as possible.

The tablets can be given directly to the animals or administered with a small quantity of food.

3.10 Symptoms of overdose (and where applicable, emergency procedures, and antidotes)

Reversible hypotension may occur in cases of accidental overdose. Therapy is symptomatic.

After administration of 0.75 mg/kg and 1.25 mg/kg once daily for 6 months to healthy young adult cats, hyperplastic gingivitis, reactive lymphoid hyperplasia in mandibular lymph nodes, and increased Leydig cell vacuolisation and hyperplasia were seen. At the same dose levels plasma potassium and chloride levels were decreased and an increase in urinary volume associated with decreased urinary specific gravity was observed. These effects are unlikely to be observed under clinical conditions with short term accidental overdosing.

In a small two-week tolerance study of healthy cats (n=4), doses between 1.75 mg/kg and 2.5 mg/kg were administered, and mortality (n=1) and severe morbidity (n=1) occurred.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QC08CA01

4.2 Pharmacodynamics

Amlodipine is a voltage dependent calcium channel blocker, member of the dihydropyridine group, binding selectively to the L-type of channels found in vascular smooth muscle, cardiac muscle and cardiac nodal tissue.

Amlodipine favours the L-type calcium channels found in vascular smooth muscle acting hence predominantly by decreasing vascular resistance. The major blood pressure lowering effect of amlodipine is related to its dilatory action on arteries and arterioles, while amlodipine has little effect on the venous circulation. The duration and waning of anti-hypertensive effects are dose-dependent.

Although amlodipine has a greater affinity for the vascular L-type calcium channels, it can also act on those found in the cardiac muscle and cardiac nodal tissue. A decrease in heart rate and a negative inotropic effect on the heart have been observed in vitro in guinea-pig isolated hearts. In a 26-week target animal safety study conducted in cats, amlodipine, at a dose of 0.25 to 1.25 mg/kg administered orally, did not affect heart rate and no electrocardiogram (ECG) abnormalities were observed.

Binding of amlodipine to the L-type calcium channels is slow, avoiding hence rapid reductions in blood pressure which lead to reflex tachycardia as a result of activation of baroreceptors. In cats with hypertension, once daily dosing with amlodipine tablets provided clinically significant reductions in blood pressure and due to the slow onset of action of amlodipine, acute hypotension and reflex tachycardia tend not to occur.

In vitro data showed amlodipine improves endothelial cell function by increasing the generation of nitric oxide and through anti-oxidant and anti-inflammatory actions. In humans, this is an important effect as endothelial dysfunction accompanies hypertension, coronary heart disease and diabetes, all conditions in which amlodipine is used as part of the treatment regimen. In cats, the importance of these additional effects remains to be determined since the role of endothelial dysfunction in the pathophysiology of feline hypertension has, so far, not been studied.

The kidney is, along with the heart, the eye and the CNS, a major target organ of hypertension receiving 20 to 25% of the cardiac output and having a high pressure first capillary bed (the glomerular capillary bed) to facilitate the formation of glomerular filtrate. Calcium channel blockers such as amlodipine are thought to preferentially dilate the afferent arteriole over the efferent arteriole. Since ACEI preferentially dilate the efferent arteriole, they lower the intraglomerular pressure and frequently decrease the magnitude of proteinuria. For this reason, combination of ACEI and calcium channel blockers may be especially beneficial in hypertensive cats with proteinuria.

In a clinical study, a field-representative sample of client-owned cats with persistent hypertension (systolic blood pressure (SBP) >165 mmHg) were randomised to receive amlodipine (initial dose of 0.125-0.25 mg/kg, rising to 0.25 - 0.50 mg/kg if response was not satisfactory after 14 days) or placebo, once daily. SBP was measured after 28 days and treatment was considered successful if SBP

was reduced by 15% or more of pre-treatment SBP or to below 150 mmHg. 25 out of 40 cats (62.5%) given amlodipine were successfully treated compared with 6 out of 34 (17.6%) given placebo. It was estimated that amlodipine treated animals have 8 times greater odds of treatment success than placebo treated cats (OR 7.94, 95% confidence interval 2.62 - 24.09).

4.3 Pharmacokinetics

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak plasma levels between 3 to 6 hours post dose. After a single dose of 0.25 mg/kg, absolute bioavailability is estimated to be 74% and the peak plasma level is 25 ng/ml, in fasted state. Absorption of amlodipine is not influenced by concomitant food intake in humans. Amlodipine tablet may be given with or without food to cats in clinical use.

Distribution

The pKa of amlodipine is 8.6. Amlodipine is highly bound to plasma proteins. In vitro protein binding in cat plasma is 97%. The volume of distribution is approximately 10 l/kg.

Biotransformation

Amlodipine is extensively metabolised by the liver in laboratory animals and humans. All known metabolites lack pharmacological activity. All amlodipine metabolites found in vitro in cat hepatocytes have been earlier identified in incubations of rat, dog and human hepatocytes. Thus, none of them are unique to the cat.

Elimination

The mean plasma elimination half-life of amlodipine is 53 hours in healthy cats. At 0.125 mg/kg/day, plasma level of amlodipine was approaching steady-state by 2 weeks in healthy cats. Total plasma clearance in healthy cats is estimated to be 2.3 ml/min/kg.

Excretion balance has been characterised in humans and several animal species, but not in the cat. In dogs, equal distribution of radioactivity was found in the urine and faeces.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life of halved tablets: 24 hours.

5.3 Special precautions for storage

Do not store above 30°C.
Any unused half tablets should be returned to the blister pack.

5.4 Nature and composition of immediate packaging

Polyamide/Aluminium/PVC-Aluminium heat-sealed blister with 10 tablets per blister.

Cardboard box with 30, 100 and 200 tablets.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{mm/yyyy}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database.
(<https://medicines.health.europa.eu/veterinary>).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box containing 3 blisters of 30 tablets
Cardboard box containing 10 blisters of 100 tablets
Cardboard box containing 20 blisters of 200 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Amodip 1.25 mg chewable tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Amlodipine 1.25 mg (Equivalent to 1.73 mg of amlodipine besilate)

3. PACKAGE SIZE

30 tablets
100 tablets
200 tablets

4. TARGET SPECIES

Cats

5. INDICATIONS**6. ROUTES OF ADMINISTRATION**

Oral use

7. WITHDRAWAL PERIODS**8. EXPIRY DATE**

Exp {mm/yyyy}
Once divided use within 24 hours.
Shelf life of halved tablets: 24 hours.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 30°C.
Any unused half tablets should be returned to the blister pack.

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER



14. MARKETING AUTHORISATION NUMBER(S)

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Amodip 

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

1.25 mg of amlodipine

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

1. Name of the veterinary medicinal product

Amodip 1.25 mg chewable tablets for cats

2. Composition

Each tablet contains:

Active substance:

Amlodipine 1.25 mg
(Equivalent to 1.73 mg of amlodipine besilate)

Oblong in shape, score line on one side, beige to light brown tablets.
Tablets can be divided into two equal parts.

3. Target species

Cats

4. Indications for use

Amodip is intended for the treatment of systemic hypertension in cats.

5. Contraindications

Do not use in the case of cardiogenic shock and severe aortic stenosis.

Do not use in cases of severe hepatic failure.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

6. Special warnings

Special warnings:

The primary cause and/or co-morbidities of hypertension, such as hyperthyroidism, chronic kidney disease and diabetes, should be identified and treated.

In cats situational hypertension (also called white coat hypertension) occurs as a consequence of the in-clinic measurement process in an otherwise normotensive animal. In case of high stress levels measurement of systolic blood pressure may lead to incorrect diagnosis of hypertension. It is recommended that stable hypertension is confirmed by repeated measurement of systolic blood pressure on different days before commencing therapy.

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Special precautions for safe use in the target species:

Special caution is required in patients with hepatic disease as amlodipine is highly metabolised by the liver. As no studies have been conducted in animals with liver disease, use of the veterinary medicinal product in these animals should be based on a benefit-risk assessment by the attending veterinarian.

Administration of amlodipine may sometimes result in a decrease in serum potassium and chloride levels. Monitoring of those levels is recommended during treatment. Older cats with hypertension and chronic kidney disease (CKD) may also suffer from hypokalaemia as a result of their underlying disease.

The safety of amlodipine has not been established in cats weighing less than 2.5 kg.

Safety has not been tested in cats with cardiac failure. Use in these cases should be based on a benefit risk assessment by the veterinarian.

The chewable tablets are flavoured. In order to avoid any accidental ingestion, store tablets out of reach of the animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

This veterinary medicinal product may decrease blood pressure. In order to reduce the risk of accidental ingestion by children, do not take the tablets out of blisters until ready to administer to the animal. Return part-used tablets into the blister and carton. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to amlodipine should avoid contact with the veterinary medicinal product. Wash hands after use.

Pregnancy and lactation:

Laboratory studies in rodents have not produced any evidence of teratogenicity or reproductive toxicity. The safety of veterinary medicinal product has not been established during pregnancy and lactation in cats. Use only in accordance with the risk-benefit assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:

Concomitant use of amlodipine with other agents that may reduce blood pressure may cause hypotension. These agents include: diuretics, beta-blockers, other calcium channel blockers, inhibitors of the renin angiotensin aldosterone system (renin inhibitors, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors (ACEI), and aldosterone antagonists), other vasodilators and alpha-2 agonists. It is advised to measure blood pressure before administering amlodipine with these agents and to ensure cats are adequately hydrated.

However, in clinical cases of feline hypertension, no evidence of hypotension occurring as a result of combining amlodipine with the ACEI benazepril was observed.

Concomitant use of amlodipine with negative chronotropes and inotropes (such as beta-blockers, cardioselective calcium channel blockers and antifungal azoles (eg. itraconazole)) may reduce force and rate of contraction of the heart muscle. Particular attention must be paid before administering amlodipine with these drugs in cats with ventricular dysfunction.

The safety of concomitant use of amlodipine and the anti-emetic agents dolasetron and ondansetron has not been evaluated in cats.

Overdose:

Reversible hypotension may occur in cases of accidental overdose. Therapy is symptomatic.

After administration of 0.75 mg/kg and 1.25 mg/kg once daily for 6 months to healthy young adult cats, hyperplastic gingivitis, reactive lymphoid hyperplasia in mandibular lymph nodes, and increased Leydig cell vacuolisation and hyperplasia were seen. At the same dose levels plasma potassium and chloride levels were decreased and an increase in urinary volume associated with decreased urinary specific gravity was observed. These effects are unlikely to be observed under clinical conditions with short term accidental overdosing.

In a small two-week tolerance study of healthy cats (n=4), doses between 1.75 mg/kg and 2.5 mg/kg were administered, and mortality (n=1) and severe morbidity (n=1) occurred.

7. Adverse events

Cats:

Very common (>1 animal / 10 animals treated):
Emesis ¹ , Gingival hyperplasia ²
Enlarged lymph node (localised) ^{2,3}
Common (1 to 10 animals / 100 animals treated):
Digestive tract disorder (e.g diarrhoea, anorexia) ¹
Lethargy ¹ , Dehydration ¹

¹Mild and transient

²At the dose of 0.25 mg/kg, observed in healthy young adult cats but not in the clinical trial with older hypertensive cats. This does not usually require stopping the treatment.

³Submandibular

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

Oral use

Amlodipine tablets should be administered orally at a recommended starting dose of 0.125 -0.25 mg/kg/day.

After 14 days of treatment, the dose may subsequently be doubled or increased up to 0.5 mg/kg once daily if adequate clinical response has not been achieved (e.g. systolic blood pressure remaining over 150 mmHg or a decrease of less than 15 % from the pre-treatment measurement).

Weight of cat (kg)	Starting dose (number of tablets)
2.5 - 5.0	0.5
5.1 - 10.0	1
10.1 and above	2

To ensure a correct dosage, body weight should be determined as accurately as possible.

9. Advice on correct administration

Tablets can be broken in halves to adapt the dosage to the weight of the cat most accurately. The tablets can be given directly to the animals or administered with a small quantity of food.

10. Withdrawal periods

Not applicable

11. Special storage precautions

Keep out of the sight and reach of children.
Any unused half tablets should be returned to the blister pack.

Do not store above 30°C.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton and on the blister after Exp. The expiry date refers to the last day of that month.

Shelf life of halved tablets: 24 hours
Any half tablets remaining after 24 hours should be discarded.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.
Ask your veterinary surgeon how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorization numbers and pack sizes

(MA)

Cardboard box of 30 tablets
Cardboard box of 100 tablets
Cardboard box of 200 tablets

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{mm/yyyy}

Detailed information on this veterinary medicinal product is available in the Union Product Database.
(<https://medicines.health.europa.eu/veterinary>)

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
(*Name and address to be completed nationally*)

Tel: +800 35 22 11 51

Email: pharmacovigilance@ceva.com

Manufacturer responsible for batch release:

Ceva Santé Animale

Boulevard de la Communication

Zone Autoroutière
53950 Louverné
France

17. Other information

In a clinical study, a field-representative sample of client-owned cats with persistent hypertension (systolic blood pressure (SBP) >165 mmHg) were randomised to receive amlodipine (initial dose of 0.125-0.25 mg/kg, rising to 0.25 - 0.50 mg/kg if response was not satisfactory after 14 days) or placebo, once daily. SBP was measured after 28 days and treatment was considered successful if SBP was reduced by 15% or more of pre-treatment SBP or to below 150 mmHg. 25 out of 40 cats (62.5%) given amlodipine were successfully treated compared with 6 out of 34 (17.6%) given placebo. It was estimated that amlodipine treated animals have 8 times greater odds of treatment success than placebo treated cats (OR 7.94, 95% confidence interval 2.62 - 24.09).

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