Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amodip 1.25 mg Chewable Tablets for Cats

Amodip vet 1.25 mg Chewable Tablets for Cats
(DK, FI, SE, IS, NO, LT only)

Amlodipine Ceva 1.25 mg Chewable Tablets for Cats
(EE only)

Date Created: 25th March 2019.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0524/001/DC
Name, strength and pharmaceutical form	Amodip 1.25 mg Chewable Tablets for Cats
Applicant	Ceva Animal Health Ltd Unit 3 Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance(s)	Amlodipine 1.25 mg (equivalent to 1.73 mg of amlodipine besilate)
ATC Vetcode	QC08CA01
Target species	Cats
Indication for use	For the treatment of systemic hypertension in cats.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the current mutual recognition procedure	12th March 2019 Date of original decentralised procedure 28th April 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden. Repeat Use Bulgaria, France, Germany, Italy, Luxembourg, The Netherlands

I. SCIENTIFIC OVERVIEW

Amodip 1.25 mg Chewable Tablets for Cats has been developed as a new product for the treatment of hypertension in cats. The application was a MUMS procedure, based on a new active substance which is not yet authorised for veterinary use within the Community.

The product contains 1.25 mg amlodipine (as amlodipine besilate) to be administered orally at a dose of 0.125 – 0.25 mg/kg with or without food.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1]

The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 1.25 mg amlodipine (as amlodipine besilate) as the active substance. The excipients that are used for the tablet are artificial chicken flavour, malted yeast, microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate and silica colloidal anhydrous. Tablets can be divided into two equal parts to provide flexibility of dosing.

The container/closure system consists of a polyamide/aluminium/PVC-aluminium heat sealed blister with 10 tablets per blister. The blisters are packaged in an outer carton containing 30, 100 or 200 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Although a veterinary dosage form of amlodipine is not currently available, amlodipine tablets approved for use in humans have been used off-label for many years.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the active substance with malted yeast, chicken flavour, mannitol and croscarmellose sodium. Magnesium stearate silica colloidal anhydrous are sieved and mixed in. The powder is blended and compressed into tablets which are subsequently packaged into blisters. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is amlodipine besilate, an established active substance described in the European Pharmacopoeia and Ph. Eur. Certificates of Suitability have been supplied for manufacturers of this active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline, present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for loss on drying, uniformity of dosage units, characters, breakability into halves, dissolution, identification of active, assays of active and impurities and microbiological quality.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The active substance is manufactured in accordance with the Ph. Eur. Certificates of Suitability and the retest period for each manufacturer is 60 months and 36 months respectively.

Stability data on the finished product have been provided in accordance with the applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data provided for batches stored at 25°C/60%RH for 18 months and 30°C/65%RH for 12 months, whilst in an accelerated study batches were stored 6 months at 40°C/75%RH.

In-use stability studies were also submitted. Tablets were halved, with one half returned to the open blister for testing 48 hours later. The blisters were stored at 25°C/60%RH. An in-use shelf life of 24 hours has been established.

G. Other Information

Shelf life

- Shelf life of the veterinary medicinal product as packaged for sale: 36 months
- Shelf life of halved tablets: 24 hours

Special precautions for storage

- Do not store above 30°C.

- Any unused half tablets should be returned to the blister pack.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

The active substance is amlodipine. Amlodipine is a voltage dependant calcium channel blocker, which binds selectively to the L-type of channels found in vascular smooth muscle, cardiac muscle and cardiac nodal tissue. Amlodipine favours L-type calcium channels found in vascular smooth muscle acting hence predominantly by decreasing vascular resistance. The major blood pressure lowering effect of the active is related to its dilatory action on arteries and arterioles, while it has little effect on the venous circulation. The duration and waning of anti-hypertensive effects are dose dependent.

Binding of amlodipine to the L-type calcium channels is slow, avoiding 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.

Pharmacokinetics

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 in a fast state is 25ng/ml. 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. 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.

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. 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.

Toxicological Studies

The applicant provided a number of references and study reports based on product monograph for the human authorised product Norvasc. This information was supportive data. In addition the applicant provided bibliographic data and commissioned two *in vitro* mutagenicity studies.

Single Dose Toxicity
The active substance was administered orally to an equal number of male and female 6 week old rats. Rats were fasted 16-20 hours prior to administration of the active. After dosing rats were observed for 14 days. The LD_{50}[3] values for male and female rats were 393 mg/kg and 686 mg/kg respectively. The main symptom observed after oral administration were salivation, decrease in locomotor activity, dropping eyelid and a decrease in respiratory rate. The recovery time was approximately 10 days.

Repeated Dose Toxicity
A group of equal numbers of male and female rats were administered amlodipine besilate orally for a period of 3 months at a dose rate of 0, 3, 10 and 30 mg/kg once daily. Approximately 60% of the rats were autopsied at the end of the treatment period and the remaining rats were autopsied after a one month treatment free period. Examinations carried out included for example clinical signs, body weight, food and water consumption, blood and urine analysis, organ weight and pathology. No treatment related findings were seen at 3 mg/kg. At 10 mg/kg a slight decrease in heart rate was observed in females. A slight increase in haemoglobin, haemocrit and red blood cell values were observed in males in addition to a slight increase in blood urea nitrogen. Increased excretion of sodium and chloride was observed in both male and female rats. These findings were considered to be related to the pharmacological effects of amlodipine. At 30 mg/kg in addition an inhibition of body weight gain was observed. The NOAEL[4] is considered to be 10 mg/kg and the NOEL[5] 3 mg/kg.

In a second study amlodipine besilate was administered orally to a group of male and female rats for a period of 12 months. Dose levels were 0, 2, 10 and 25 mg/kg daily. After a 6 month period approximately 15% of rats per group were autopsied. Examinations included for example clinical signs, body weight, food and water consumption, blood and urine analysis, organ weight and pathology. No treatment related findings were observed at 2 mg/kg. At 10 mg/kg increased urinary volume and increased excretion of sodium and chloride were seen in males. Adrenal weight was increased in females and heart weight in males and females. In the adrenal gland morphological changes were noted. Inhibition of body weight gain was observed in male rats. These findings were considered to be related to the pharmacological effects of amlodipine. At 25 mg/kg the pharmacological effects of amlodipine were more exaggerated and mortality occurred. The NOAEL and NOEL was considered to be 2 mg/kg.

[3] LD_{50} – The dose that kills half the population
[4] NOAEL – No observed adverse effect level
[5] NOEL – No observed effect level

Reproductive Toxicity, including Teratogenicity

The active substance was administered orally to rats at daily dose of 0, 2, 10 and 25 mg/kg from 14 days before mating to day 7 of gestation. Males were dosed for 71 days prior to and during mating and females were dosed for 14 days prior to and during mating and up to 7 days of gestation. At 25 mg/kg growth inhibition was noted in both sexes. Food consumption was slightly inhibited in males at 25 mg/kg and in females at 25 mg/kg and 10 mg/kg. No significant difference was observed between treated and control groups regarding copulation or pregnancy index. At all dose levels no teratogenic or embryolethal effects were noted. The NOAEL of 10 mg/kg/day was determined.

A study investigating teratogenicity was discussed. Rats were administered dose of 0, 4, 10 and 25 mg/kg/day of amlodipine besilate orally on days 7 to 17 of pregnancy. Body weight gain and food consumption were slightly reduced in dams at 25 mg/kg/day. Teratogenic effects or adverse effects on foetal development were not noted. Neither adverse effects on the viability, postnatal development, behaviour or reproductive performance of the first generation offspring were noted nor abnormalities of the second generation foetuses. The NOAEL was considered 10 mg/kg/day and a NOEL of 4 mg/kg in rats. The same doses were administered to rabbits from day 6 to day 18 of gestation. Gain in weight was reduced in dams at 25 mg/kg/day. Neither teratogenic effects nor foetotoxicity were noted. The NOEL of 4 mg/kg/day was determined in rabbits.

In a peri- and post-natal study doses of 0, 2, 4 and 10 mg/kg/day were administered to female rats from day 17 of gestation to day 21 post-partum. Rats were allowed to deliver naturally and delivery conditions were observed, pregnancy period and birth rate were measured. There was no treatment related findings in dams or in pups and the fertility of the first generation offspring was unaffected in those receiving 2 and 4 mg/kg/day. At 10 mg/kg/day weakness and mortality was observed in parent dams. Prolonged gestation period, an increase in stillborn pups and a decrease in litter size of pups on day 4 were observed. A NOAEL for postnatal development was determined to be 10 mg/kg. The overall NOEL was 4 mg/kg/day.

Genotoxicity, Carcinogenicity

Two *in vitro* mutagenicity studies were conducted. A bacterial reverse mutation assay and a chromosome aberration test. Based on the studies submitted and the supportive data provided amlodipine is not considered to be genotoxic in the systems used. Additional supportive data provided supported the conclusion that amlodipine is not carcinogenic in humans.

Studies of Other Effects

No changes in the immune system were reported in the single and repeated dose toxicity studies.

Observations in Humans

Amlodipine is indicated for the treatment of hypertension and coronary heart disease in humans. In has been available on the market for 20 years. Clinical use in humans is extensive. Both short and long term studies indicate that amlodipine effectively lowers mild to moderately elevated blood pressure during a 24 hour period. Amlodipine exerts a blood pressure lowering effect through peripheral vasodilation.

After oral administration, absorption occurs gradually with peak plasma concentrations reached between 6 and 12 hours with a terminal half-life of about 35-50 hours. Absolute bioavailability has been estimated between 64 and 90%. The long plasma half-life of amlodipine permits once-daily administration of the drug. The recommended dose in adults is 5-10 mg once daily. In clinical use amlodipine is generally well tolerated. Most commonly reported side effects are dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue, which were reported with a frequency of 1-10%.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure could be the result of accidental ingestions, dermal contact with the product, accidental ingestion by a child and during / post dosing potential contact with product and saliva on the persons skin. The product is provided in blister packs which are considered to be child-resistant, in addition warning and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- This 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 oral ingestion, seek medical advice and show the label or the package leaflet to the physician.
- People with known hypersensitivity to amlodipine should avoid contact with the veterinary medicinal product.
- Wash hands after use.

Environmental Safety

The applicant has provided a Phase I environmental risk assessment in compliance with the relevant guidelines which showed that no further assessment is required. The product will only be used in non-food companion animals and as a result environmental exposure will be low. A Phase II ERA was not required. No environmental warnings or information are therefore required as the product is safe for the environment when used as directed.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
A literature review was provided. Amlodipine is a 1, 4-dihydropyridine, member of the group of calcium channel antagonists, which dilates arteries / arterioles thus reducing arterial blood pressure but has minimal effect on venous circulation. Arterial blood pressure is the product of cardiac output and total peripheral resistance, and because peripheral resistance is mainly in the arterioles amlodipine lowers blood pressure in situations where arteriolar tone is abnormally raised. This effect has been observed clinically.

Amlodipine binds selectively to voltage dependent calcium channels of the L-type, favouring the L-type calcium channels found in vascular smooth muscle over those found in cardiac muscle and cardiac nodal tissue. Thus amlodipine predominantly has vascular effects.
Amlodipine binds slowly to the calcium channels. In an experiment using rat aortas, amlodipine inhibited contraction, reaching maximal effects after three hours.

Although the effects of amlodipine on smooth muscle are greater than on cardiac muscle and node tissue, a negative inotropic and chronotropic effect of amlodipine has been observed in *in vitro* tests on guinea pig hearts. In conscious and unconscious dogs the only electrocardiographic changes noted was a slight shortening of the P-R interval. 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.

In the kidney, amlodipine predominantly vasodilates the preglomerular resistance vessels. During *in vitro* studies in rat kidneys, amlodipine fully reversed the effect of angiotensin II, which itself decreases glomerular filtration, suggesting that amlodipine may increase glomerular filtration. Amlodipine also improves the function of endothelial cells through increase in the generation of nitric oxide. It may also improve endothelial cell function through anti-inflammatory and anti-oxidant effects. In humans, endothelial cell dysfunction accompanies hypertension, coronary heart disease and diabetes and amlodipine had been shown to improve endothelial cell function through anti-oxidant and anti-inflammatory actions.

Pharmacokinetics
Studies were conducted to examine pharmacokinetics. In one non-GLP study the plasma levels of amlodipine were assessed in cats receiving a human formulation in current clinical use in cats. An equal number of male and female cats received 1.25 mg amlodipine of the human product Norvasc without food on Day 1. Mortality and viability was measured at least twice daily and clinical signs

were recorded at least once daily. Blood samples were collected prior to administration of the test products and at various time points up to 168 hours after administration and pharmacokinetic parameters were measured. The cats included in the study responded similarly. Samples were taken frequently enough to document the peak plasma levels. There was a slow absorption followed by a long elimination. The terminal plasma half-life ranged from 39.5 to 88.5 hours. The study was useful in providing approximate estimates of the pharmacokinetic profile of amlodipine in the Norvasc formulation when administered as a single dose to cats.

Another study conducted assessed the plasma levels of amlodipine at steady state in cats receiving a human formulation in current clinical use in cats. The aim of the study was to compare the pharmacokinetic data from this study with the pharmacokinetic data gathered at a different dose in the previous study and to examine the effect of amlodipine on blood pressure in cats. An equal number of male and female cats were included in the study. Each cat received a quarter of a tablet (containing 0.625 mg of amlodipine) without food each day for 14 consecutive days. Mortality and viability were observed at least twice daily and clinical signs observed at least once daily. Blood samples were collected prior to administration of the test products and at various time points up to 24 hours after administration on Day 1, 7 and 14. Pharmacokinetic parameters were measured. Blood pressure and heart rate measurement were taken on days 1, 7 and 14, 15 – 30 minutes before each pharmacokinetic blood sample was taken. Samples were taken frequently enough to document the peak plasma levels. The data provided useful information on the pharmacokinetics of once daily dosing of amlodipine in cats and suggest a plateauing to steady state after around 14 days.

The plasma levels of amlodipine in cats receiving the final tablet formulation were assessed in another study to estimate oral bioavailability through comparison with pharmacokinetics following intravenous administration. An equal number of male and female cats each received one tablet (1.25 mg amlodipine, target dose 0.25 mg/kg) or 0.125 mg/kg amlodipine intravenously without food. Food was provided two hours after administration of the dose. The doses selected (0.125 mg/kg and 0.25 mg/kg) were based on those currently used clinically in cats. Blood samples were collected one day prior to administration and at various time points up to 168 hours after administration. Pharmacokinetic parameters were measured. Animal observations and blood sampling were frequent enough to map profiles. The pharmacokinetic profiles broadly concur with those from the product examining the human product Norvasc. A comparison of the profiles of the oral and IV dose enabled the calculation of bioavailability (74%), clearance (2.3 ml/min/kg) and volume distribution. The values were calculated on the assumption that the dose-concentration relationship is linear between doses of 0.125 mg/kg and 0.25 mg/kg. The study provided information on the pharmacokinetics of the final tablet formulation, including expected bioavailability. As the product is indicated for a minor use and that the consequence of not treating hypertension can be severe, the estimations provided support their inclusion in the SPC.

Two metabolism studies were conducted which provided information on the metabolic routes for amlodipine in cats. Bibliographic pharmacokinetic data was provided. During an *in vivo* study using radiolabelled amlodipine, none of the metabolites found in rat, dog or human has any significant calcium antagonist activity relative to amlodipine.

Elimination
No studies have been conducted regarding elimination in the cats. However this is acceptable based upon scientific advice from the CVMP which states that elimination has been characterised in humans and several animals species and does not need to be characterised in cats. In dogs equal distribution of radioactivity was found in urine and faeces, and in humans elimination mainly occurs in urine. In all species there are two major paths of elimination, urine and faeces.

Pharmacodynamic and pharmacokinetic interactions
There are no peer-reviewed studies to examine interactions between amlodipine and other anti-hypertensive drugs with different mechanisms of action. In a study conducted in cats, there was no evidence of interaction, for example hypotension, heart failure, when cats were given amlodipine and benazepril concomitantly. The bibliographic data provided, did not identify interactions, even though some of the observed animals were also receiving medications which can lower blood pressure, such as ACE inhibitors. Due to the effects of amlodipine on cardiac cells and the potentiation of the effects of other negative chronotropes and inotropes, additional warnings have been included in the SPC.

Tolerance in the Target Species

The applicant has conducted two *in vivo* target animal safety studies. The aim of the first study was to evaluate the tolerance of the test product when given orally in high doses to cats for 14 days. Male and female cats were included in the study. Cats were medicated once daily (target dose 2.5 mg/kg). Cats were offered tablets by hand / from an empty bowl, with canned food or were administered directly into the mouth. After administration cats were given water to ensure swallowing. Mortality and viability were observed at least twice daily. Clinical signs were monitored at least once daily before treatment and twice daily with the first three hours after each treatment. Blood pressure and heart rate were monitored before treatment and two and six hours after each dose on days 1, 3, 7 and 14. Body weight and food consumption were measured daily. Blood samples were taken before treatment and once at end of treatment, haematology and clinical biochemical parameters were also measured. Although the study only examined four cats, it contains valuable information regarding overdose with the product and the levels which are expected to cause morbidity and possible death. The data provided indicate that the risks of giving a cat more than 3.5 times the highest recommended dose may outweigh the benefits.

The aim of the second animal safety study was to evaluate the tolerance for amlodipine when administered to healthy cats for six months. An equal number of male and female cats were included in the study. The test product contained 1.25 mg amlodipine. Cats were medicated once daily in the morning for at least

six months. Cats were offered tablets by and / from an empty bowl, with canned food or were administered tablets directly into the mouth. The cats were divided into four groups; the first group received a placebo, the second group a 1x dose, the third group a 3x dose and the fourth group a 5x dose. Mortality and viability were observed twice daily and clinical signs were monitored prior to administration and twice daily during the test period. Blood pressure (systolic / diastolic) were measured pre-test period and during weeks 4, 13 and 26 of the test period. Systolic and diastolic blood pressure was measured in all animals two and six hours after dosing. Food consumption was noted daily and body weight weekly. Physical and ophthalmic examinations, clinical pathology, ECG, necropsy and histopathology were performed. Statistical methods included Dunnett's test, Steel test and Fisher exact tests. No differences were noted between groups regarding food intake, weight, blood pressure, ECG and ophthalmic findings. Overall the product was well tolerated when given at doses of 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg for six months to healthy cats. After administration of 0.75 mg/kg and 1.25 mg/kg once daily for six months; hyperplastic gingivitis, reactive lymphoid hyperplasia in mandibular lymph nodes and increased Leydig cell vacuolisation and hyperplasia were seen. At the same time dose levels of plasma potassium and chloride levels were decreased and an increase in urinary volume associated with decreased urinary specific gravity was observed. These findings have been included on the SPC.

In addition to the two studies, six target animal safety studies were provided as bibliographic data. In total 217 cats received amlodipine at dose comparable to the SPC. The duration of treatment ranged from 33 days to 13 months. Very few adverse reactions were recorded. In one study an overall reduction of potassium was noted, which concurs with the results of the previous study. In the same study a cat became hypotensive, however the cat was receiving 2.5 mg propranolol three times a day and therefore made the cause difficult to determine.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided literature references relating to the use of amlodipine for the treatment of hypertension in cats. These dose determination / dose confirmation studies are included below.

Dose confirmation studies:

Four of the studies provided did not include a control group. The first study investigated the treatment of systemic hypertension in cats with amlodipine besilate. The aim of the study was to evaluate retrospectively the clinical efficacy and safety of amlodipine besilate when administered as a single agent once daily to cats with systemic hypertension. 12 cats, male and female aged eleven to nineteen years of age were referred for blindness or cardiac illness. All were clinically stable. Some cats were newly diagnosed; others were inadequately controlled with other hypertensive drugs or were controlled but experiencing adverse events. Cats were treated with a dose rate of 0.625 mg Norvasc once

daily. The follow up period ranged from 14 - 233 days with ten cats being treated for more than 80 days. The mean systolic blood pressure (SBP) reduced from 198 mmHg to 155 mmHg (p=0.0022). Cats with SBP ≥ 180 mmHg tended to show greater reduction with treatment than those starting with a SBP ≤ 180 mmHg. No significant changes in serum creatinine, serum potassium or body weight was observed.

The second study investigated feline hypertension – clinical findings and responses to antihypertensive treatment in thirty cats. Cats were aged two and a half to twenty years old. The majority of cats were azotaemic, of which four were being treated for hyperthyroidism; two were untreated hyperthyroid cats and seven were idiopathic. Cats were treated with 0.625 mg/day of Istin tablet which was increased to 1.25 mg/day if no response was observed after seven to fourteen days. Concurrent medications to control hypertension were permissible. Cats were followed up for one to two months or eleven to thirteen months. Amlodipine lowered SBP from 205±16.8 to 153.2±21.3 mmHg within the first fifty days. Systolic blood pressure was kept <165 mmHg in 58% of cases treated for three months or longer. Fifteen of twenty six cats were described as well controlled, eleven were classified as poorly controlled and four were poorly and no classification was provided. Ten of the thirty cats received additional drugs in an attempt to reduce SBP below 165 mmHg. No significant changes in serum creatine, urea or urine specific gravity were noted.

The third study examined the effect of amlodipine on echocardiographic variables in cats with systemic hypertension. 19 male and female cats aged six to eighteen and a half years old had clinical signs consistent with hypertensive retinopathy, five cats had systolic heart murmurs and nine cats had both. Two cats were receiving an ACE[6] inhibitor and one a diuretic before entry. Each cat received 0.625 mg/day of Norvasc which increased in increments of 0.625 mg if SBP has not fallen below 170 mmHg. Re-evaluation was recommended every seven to fourteen days. The study was designed to look at whether controlling hypertension could regress cardiac hypertrophy. Significantly more cats had ventricular hypertrophy before treatment than after treatment (p=0.0062). SBP decreased from a mean of 217 to 142 mmHg. No significant changes were observed in creatinine.

The fourth study examined the effect of control of systolic blood pressure on survival in cats with systemic hypertension. 141 male and female cats were included, where 86.7% of the population were diagnosed with azotaemia, hyperthyroidism or both. Cats were administered 0.625 mg/day Istin tablet, which rose to 1.25 mg/day if SBP remained above 160 mmHg at re-examination seven to twenty one days after the start of treatment. Treatment with amlodipine significantly reduced urine protein to creatine ratio which was strongly associated with survival. Reduction of SBP itself was not an independent variable for survival. Approximately 75% of cats achieved a reduction of SBP to below 160 mmHg. Paired urine creatine ratio data were available for 115 cats. Treatment tended to reduce proteinuria. Cats which were most proteinuric tended to have higher blood pressures that were more difficult to control.

[6] ACE – angiotensin converting enzymes

Two of the remaining studies were placebo controlled. The fifth study was a randomised, placebo-controlled, blinded single centre study. Nine cats with a mean SBP of greater than 170 mmHg who had a normal serum thyroxine concentration and no history of antihypertensive medication in the previous month, received either 0.625mg amlodipine or a placebo daily. SBP was measured on day 7 and if it had not reduced below 170 mmHg or by at least 15%, the cat was switched to the other treatment group and tested again seven days later. All responding cats were also evaluated 16 weeks after treatment. Five cats received amlodipine and four received the placebo at the start of the study. Three cats did not respond adequately to 0.625 mg of amlodipine and their dose was increased to 1.25 mg. Six cats completed the entire 16 week study and their mean SBP decreased from 221 mmHg to 152 mmHg during the period ($p<0.001$). Serum creatinine was unchanged in the amlodipine group at day 7, while a small increase was seen at week sixteen; however this difference was not statistically significant.

In the final study, a number of cats aged between six and twelve months were surgically induced with hypertensive renal insufficiency. Cats were allocated into ten groups (two cats per group) based on mean eight hour SBP readings during the preceding eight hour interval. Within each group, cats were randomly assigned to receive 0.25 mg/kg amlodipine or placebo tablets. Cats were followed up for 36 days. There was a statistically significant reduction in SBP from 145 mmHg to 122 mmHg in the amlodipine group but no statistically significant change in the placebo group. The study found no difference in creatinine levels between groups.

Across all six studies, the amount of amlodipine given was between 0.625 mg and 1.25 mg/per day. However it is difficult to ascertain the exact dose as body weights were not given. Some aspects of the studies are not described in sufficient details to be able to fully evaluate the validity of the results; however the combined evidence suggests that doses over a wide range (0.14 – 0.36 mg/kg) are effective in lowering SBP. The bibliographic data demonstrates that some cats benefit from an increase in dose if they do not respond satisfactorily to one or two weeks of treatments at the initial dose. Pharmacokinetic data also suggested that a doubling of the dose from 0.125 – 0.25 mg/kg significantly increases AUC[7] and C_{max}[8] and that plateauing towards a steady state occurs after 14 days of treatments at the starting dose. The applicants approach in dose finding was considered acceptable by the CVMP and that the consistency of dose and effect on SBP published in the literature means that specific dose-finding studies with the final formulated tablet were not necessary.

[7] AUC – Area under the curve
[8] C_{max} – Observed maximal concentration

Field Trial

Study title	Efficacy and clinical safety of amlodipine in cats with hypertension
Objectives	The primary objective was to confirm the efficacy of palatable amlodipine tablets in reducing systolic blood pressure (SBP) in cats diagnosed with hypertension. The secondary objective was to evaluate clinical safety and relevance of treatment.
Test site(s)	Multi-centre, veterinary practices, EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Amlodipine 1.25 mg
Control product/placebo	Placebo
Animals	77 cats (36 female and 41 male), mainly Domestic and European shorthair, however several other breed represented. Cats ranged from seven to 20 years of age and from 2.5 to 7.5 kg body weight.
Outcomes/endpoints	A reduction in SBP of >15 mmHg or a reduction below 150 mmHg between the baseline reading at the second screening and visit 2 (day 28).
Randomisation	Randomised
Blinding	Double blinded
Method	The study consisted of two phases. In the first phase (efficacy period), which lasted one month, cats were in two groups, one group received amlodipine 0.125 mg/kg orally once daily and the other group received the placebo orally once daily. If systolic blood pressure after two weeks was ≥ 150 mmHg or had decreased <15% from the baseline value, the dose was doubled. The second phase of the study (safety period) involved all cats who had received amlodipine and this phase lasted two to three months. The cats which had received amlodipine continued on their medication for two months, while all placebo cats started to receive 0.125 mg/kg amlodipine for three months. The dose was doubled after two weeks if the systolic blood pressure did not meet the same criteria as in the first phase. From the first visit cats were given the tablets daily with or without food. Each owner was instructed on how to administer the treatment to their cats. Cats had follow-up visits on days 14 (1st), 28 (2nd), 42 (3rd - placebo group only), 90 (4th amlodipine group only) and day 120 (5th placebo group only). Cats were underwent physical examination, blood pressure measurements,

	haematology and clinical biochemistry and urinalysis. Owners were asked to grade quality of life (appetite, drinking, urination, mobility, owner interactions and self-grooming) in addition the owner recorded if tablet intake was spontaneous, facilitated or forced.
Statistical method	Analysis used multivariable logistic regression to examine if amlodipine was superior to placebo. Superiority was demonstrated if the 95% confidence interval for the ratio of odds of response to treatment in the amlodipine group to the odds of response to treatment in the placebo group fell entirely above 1 $p \leq 0.05$. In additional analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were performed. Analysis sets were intended-to-treat (ITT), per protocol (PP) and safety. The ITT and safety datasets contained all randomised cats that had received at least one dose of medication. The PP dataset included all randomised cats with no relevant protocol violations and which had SBP data at baseline and visit 2.
RESULTS	
Participant flow	One hundred and twenty eight cats were initially screened of which 51 failed. 69% failed because they did not achieve all inclusion criteria, with only 18% meeting exclusion criteria. Three cats (two amlodipine treated and one placebo) dropped out of the study during the efficacy period. The withdrawals were acceptable and the small numbers involved were unlikely to affect the validity of the results.
Duration of follow-up	The follow-up period was 168 hours (seven days). No cats were excluded post-inclusion.
Outcomes for endpoints	The percentage of cats that responded successfully to treatment was higher in the amlodipine group (62.5%) than in the placebo group (17.7%). Increasing the dose after 14 days of treatment appeared to have a modest further reduction in success rate and mean SBP compared to visit 1 (day 14). During the blinded efficacy study the mean SBP reduced from 181.6 mmHg to 153.6 mmHg in the amlodipine treated group and from 179.3 mmHg to 169.7 mmHg in the placebo treated group. The statistical analysis demonstrated with reasonable confidence that the amlodipine treated cats saw a reduction in SBP which was at least 8.9 mmHg greater than the reduction seen in placebo treated cats following 28 days of treatment. The mean quality of life score was similar between groups. However as this is only descriptive information and is considered of limited value, it does give reassurance that the product is unlikely to be having a detrimental effect on the wellbeing of patients. It was concluded that, following

	28 days of treatment, there is reasonable confidence that amlodipine treated animals have at least 2 – 3 times the odds of successful outcome than placebo treated cats. In the safety phase there was no appreciable difference between the adverse events seen in the groups during the efficacy period and that adverse events such as anorexia, lethargy, vomiting and diarrhoea might be expected to be seen over such a time period in an elderly population with hypertension and underlying disease. In most cases the adverse events described were unlikely to be linked with amlodipine treatment. There was little or no evidence to suggest that amlodipine effected the liver enzyme levels and certainly not to a high degree.
Adverse events	During the efficacy period, adverse events were reported in 28.6% of cats receiving amlodipine and 28.6% receiving placebo. Three of the adverse events in the amlodipine group and four in the placebo group were considered related to treatment. Adverse events were considered consistent with a sample of older cats with hypertension and primary diseases.
DISCUSSION	The field study examined a range of cats (breed, sex, age, weight, co-morbidities, primary disease) over a broad geographic area. The results demonstrate significant reductions in SBP in amlodipine treated cats which are above the reductions seen in the placebo treated cats.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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