College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Lodisure 1 mg tablets for cats

NL/V/0339/001/DC

Created: November 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0339/001/DC
Name, strength and pharmaceutical form	Lodisure 1 mg tablets for cats
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531AE Bladel Netherlands
Active substance(s)	Amlodipine (as amlodipine besilate)
ATC Vetcode	QN08CA01
Target species	Cats
Indication for use	For the treatment of feline systemic hypertension

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu) and on the Medicines Evaluation Board – Veterinary Medicinal Products Unit website (https://www.diergeneesmiddeleninformatiebank.nl/nl/).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full dossier Article 12.1. of Directive 2001/82/EC
Date of completion of the original decentralised procedure	23 September 2020
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, CZ, DE, DK, EE , EL, ES, FR, FI, HU, HR, IS, IE, IT, LV, LT, LU, NO, PL, PT, RO, SK, SI, SE, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
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 of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The tablet contains 1mg amlodipine (as besilate) and the excipients Brilliant blue (E133), dried yeast extract, chicken flavour, cellulose microcrystalline, sodium starch glycolate type A and magnesium stearate.

The tablet is scored and meant to be broken in halves.

The products are packed in Al/Al blisters, each containing 14 tablets.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. The tests performed during production are described.

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C. Control of Starting Materials

The active substance amlodipine besilate is an established active substance described in the European Pharmacopoeia.

The active substance is manufactured in accordance with the principles of good manufacturing practice.

The CEP procedures have been employed. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are in conformity with the Ph.Eur. requirements with the exception of Brilliant blue, yeast and chicken flavour, for which suitable information is submitted.

The (intermediate) packaging is conformity with the Ph. Eur. and EU Food Directive.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls relevant parameters for the pharmaceutical form. The tests in the specification, and their limits are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the relevant analytical methods have been provided.

Batch analytical data from three batch manufactured at the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

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.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, where it acts as a peripheral arteriolar vasodilator and reduces afterload. It slightly depresses impulse formation and conduction velocity in the cardiac muscle.
Amlodipine has been successfully used in human medicine for the treatment of high blood pressure.

The applicant has also provided bibliographical data which show that after oral administration amlodipine is well absorbed with a mean bioavailability of approximately 80%. Amlodipine is extensively metabolized in the liver to inactive metabolites. Amlodipine has a long plasma half-life of 33 to 86 hours (average 54 h), resulting in significant accumulation.

Toxicological Studies

The applicant has provided bibliographical data which show that

- Single Dose Toxicity

  The LD_{50} values in rats following oral administration of amlopidine were reported as 140 and 150 mg amlodipine maleate/kg bw for respectively female and male. In another study the LD_{50} values were calculated as 393 and 686 mg amlodipine besilate/kg bw for respectively male and female.

  The main clinical signs in the oral studies were somnolence, decreased spontaneous movement, salivation, dyspnea, ptosis, lacrimation, blanching, cyanosis, rough coat, abdominal distension, and eventually coma.

  Two single dose studies in dogs were also reported following oral (gavage) administration of amlodipine. At a dose of 4 mg amlodipine/kg bw adverse effects (vasodilation and increase in plasma aldosterone levels) were observed in one study. Mortality was described when administering a dose of 7 mg amlodipine /kg bw.

- Repeated Dose Toxicity

  Repeated dose studies (1 up to 12 month) in mice, rats and dogs mice following oral administration are reported. From these studies, the lowest NOEL in rat was 1.4 mg amlodipine/kg bw (or 2 mg amlodipine besylate) derived from a 12 month toxicity In dogs, the NOEL was found to be 0.25 mg amlodipine/kg bw in a 12-month study. At 4 mg/kg bw. all dogs died in the 10 days dose escalation study.

- Reproductive Toxicity, including Teratogenicity:

  No effects on reproductivity or embryotoxicity was observed, except for the rat peri- and postnatal study, where a prolongation of the gestation period, an increase in stillborn pups, a decrease in litter size and a reduction in the viability index on pups on day 4 was seen at the high dose level of 7 mg amlodipine/kg bw (i.e. 10 mg amlodipine besilate/kg bw).

- Mutagenicity/carcinogenicity

  Amlodipine has no genotoxic potential. No mutagenic activity was found in literature or in the tests performed for this dossier. No evidence of a carcinogenic effect has been found for amlodipine.

Observations in Humans

Amlodipine is used in human medicine. For adults daily doses of 5 up to 10 mg are recommended. For children (6-17 years) 2.5 up to 5 mg once daily. At these doses adverse reactions may occur such as somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue. Gross overdosage may result in peripheral vasodilatation and possibly reflex tachycardia, though also prolonged hypotension including shock with fatal outcomes have been reported.
From a review it was concluded that the smallest dose to produce a clinically important response (hypotension) in children was 2.5 mg (0.15 mg/kg bw).

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

The user of this product are mainly pet owners. Their children may also get exposed to the product if not properly stored. The users are considered non-professionals.
The main route of exposure is dermal exposure when handling/administering the tablets. Oral exposure may also occur after accidental ingestion (by a child) or due to hand-to-mouth contact if personal hygiene measures are not maintained.
Dermal exposure may occur frequently, i.e. every day the tablets are administered. Oral exposure may occur accidentally. Oral ingestion due to hand-to-mouth contact may also occur frequently if personal hygiene measures are not maintained.

The toxicity of this product is determined by its active substance amlodipine. The excipients are of non/low toxicity. In addition, the excipients are not expected to have irritating or sensitizing properties.

Based on the risk characterisation it can be concluded that there is no risk for the user when administering/handling the tablets. Adverse effects, e.g. hypotension, may occur after accidental ingestion of the tablet by children. Adequate warnings are in place in the product information.

A further warning is included with respect to possible hypersensitivity reactions, however, the applicant did not include information on possible irritating and/or hypersensitivity reactions in their user safety assessment. It is therefore unknown whether this warning is supported by data. The applicant is requested to provide information with respect to possible irritating and/or sensitising properties of amlodipine.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

IV. CLINICAL ASSESSMENT (EFFICACY)

The CVMP has classified this product as MUMS (minor use). Therefore, besides clinical studies, literature can be used to support the efficacy claim.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show the pharmacodynamic properties of the active substance. Amlodipine is a well-known substance within human medicine. It reduces blood pressure by peripheral arterial vasodilatation via inhibiting the voltage gated calcium channels of vascular smooth muscles. This leads to reduction in peripheral vascular resistance (reduction of afterload). It has only slight cardiac effects. See section IIIA for more information.

Pharmacokinetics were described by bibliographical data in which a correlation between plasma amlodipine concentration and decrease in blood pressure was observed in cats. This relationship is also known in humans and rats. Amlodipine is extensively metabolized in the liver and it is therefore contra-indicated in animals suffering from hepatic failure.

The applicant conducted two GLP compliant pharmacokinetic studies in cats using the intended product. In the first study the recommended dose (1 mg/cat) was evaluated in comparison to IV administration of 0.5 and 1 mg/cat. Peak blood concentrations were measured between 2 and 6 hours and plasma half-life ranged between 33 to 86 hours (average 54 h). Bioavailability was approximately 76%. The second study was a combined target animal safety and pharmacokinetic study (see next section)

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose (i.e. 1 mg/cat) in the target species. A placebo was used as a control. All doses were administered orally for 12 weeks. This study indicated a correlation between dose and systemic exposure but with a high degree of variability. Since the smallest individuals had high plasma concentrations of amlodipine a lower starting dose of ½ tablet per animal per day is now recommended in the SPC for animals with a bodyweight range 2 to <4 kg.

Parameters evaluated were haematological and chemical blood examination, daily observations for clinical health, feed intake and body weight. In addition, plasma concentrations of amlodipine were measured.

Minimal adverse effects such as vomiting, lethargy, low food consumption and weight loss were seen following doses up to 5 times the recommended dose. A dose dependent increase in the number of adverse events was demonstrated, particularly vomiting, indicating a treatment related effect. Reduced serum concentrations of potassium were reported at higher doses.

Bibliographical data were also provided which show that digestive tract disorders, hypotension, bradycardia and inappetence might occur. In one article, gingival hyperplasia was observed after long term administration of an overdose.

Two placebo controlled fields studies were conducted using client owned cats. The following adverse events were reported which were considered treatment related: gastrointestinal disorders such as vomiting and diarrhoea, no/less appetite and lethargy. Some patients appeared to develop potassium levels below normal ranges during treatment.

The product literature accurately reflects the type and incidence of adverse effects which might be expected. In addition, warnings are included in section 4.5 (special precautions for use in animals) because special caution is required in patients with hepatic disease as amlodipine is highly metabolised by the liver. Older cats with hypertension and chronic kidney disease may suffer from hypokalaemia as a result of their underlying disease. Amlodipine might result in a decrease in serum potassium and could thus lead to exacerbation of hypokalaemia.

IV.B Clinical Studies

Laboratory Trials

The applicant has provided bibliographical data which show that the recommended dose leads to a significant reduction in systolic blood pressure. (SBP)

Field Trials

The applicant has conducted two multicentred field studies, i.e. several Dutch veterinary practices participated. In the first study, cats exhibiting a SBP higher than 160 mmHg were included. Treatment was considered successful (responder) when SBP < 150 mmHg or a reduction of more than 10% of initial value. Blood pressure was measured 2 weeks and 4 weeks after onset of treatment

The second study was a blinded and a negative controlled study. The following inclusion criteria were used: cats older than 10 years and with a SBP>165 mmHg at two occasions. The treatment was considered successful if SBP<150 mmHg and a decrease from baseline <15% was measured at day 29.

In both studies a significant reduction in blood pressure was observed in treated cats. Moreover, a significant difference in blood pressure was observed between the treatment group and the placebo group. In addition, a significant difference in the proportion of responders was noted between treatment group and placebo group.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

None