CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amlodipine Apotex 5 mg, tablets
Amlodipine Apotex 10 mg, tablets

Apotex BV, the Netherlands

amlodipine (as besylate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow–organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/946/01-02/DC
Registration number in the Netherlands: RVG 34592, 34593

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Pharmacotherapeutic group:	Selective calcium channel blockers with mainly vascular effects, Dihydropyridine derivatives
ATC code:	C08CA01
Route of administration:	oral
Therapeutic indication:	treatment of essential hypertension, and chronic stable and vasospastic angina pectoris.
Prescription status:	prescription only
Date of authorisation in NL:	13 August 2007
Concerned Member State:	IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Amlodipine 5 mg Katwijk, tablets and Amlodipine 10 mg Katwijk, tablets from Katwijk Farma BV. The product is indicated for the treatment of essential hypertension, and chronic stable and vasospastic angina pectoris.

A comprehensive description of the indications and posology is given in the Summary of Product characteristics (SPC).

Amlodipine is a third generation dihydropyridine calcium antagonist. The 5 and 10 mg tablets containing besylate salt, corresponding to 5 mg or 10 mg of amlodipine base, are used for long-term treatment of essential hypertension, and chronic stable and vasospastic angina pectoris.

This application concerns a generic application claiming essential similarity with the innovator products Norvasc® 5 and 10 mg tablets, containing respectively 5 and 10 mg amlodipine base, which have been registered in the Netherlands since 13 June 1990 by Pfizer. In addition, reference is made to Norvasc authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Istin 10 mg tablets by Pfizer Ltd., registered in the United Kindom (Istin® is the trade name for the innovator product in the United Kingdom, which is identical with the innovator product on the Dutch market). A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information
The active substance is amlodipine base, an established active substance described in the European Pharmacopoeia (Ph.Eur.*).

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 9 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months in a transparent LDPE bag enclosed in HDPE drum without special storage conditions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU*

Medicinal Product

Composition
The white to off-white, round, unscored tablets are imprinted with "APO" on one side and "AML" over "5" or "10" on the other side.

Amlodipine Apotex, 5 and 10 mg tablets contain as active ingredient amlodipine besylate (7.0 or 14.0 mg) corresponding to 5.0 mg or 10.0 mg of amlodipine base, respectively. The composition of the two tablet strengths is proportionally identical. The tablets are packed in PVC/PVdC-Aluminium blisters.

The excipients are: Microcrystalline cellulose (E460), lactose monohydrate, magnesium stearate (E470B), maize starch.

The quantities of the excipients used, are all common in immediate release tablets.

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

The purpose was to develop a tablet that would be bio-equivalent with innovator product Norvasc (amlodipine besylate), marketed by Pfizer.

Excipients
The excipients used are common in the manufacture of tablets, and comply with the relevant Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches of each strength in accordance with the relevant European guidelines.

Quality control drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for the tablets includes tests for appearance, mean weight, uniformity of mass, content uniformity, average tablet weight, identity of drug substance, impurities, assay, dissolution and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.

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

Stability tests on the finished product
Stability data on the product have been provided for 4 batches of each strength in accordance with applicable European guidelines demonstrating the stability of the product for 36 months without additional temperature conditions. The drug product is susceptible to degradation in light, therefore it should be stored in the original package. So far, only pilot batches till 12.5% of full scale have been tested. As the manufacturing process is a standard process and the proposed batch size is large, the percentage of the full-scale batch is considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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 medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Norvasc, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of amlodipine besylate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Amlodipine base is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Amlodipine 10 mg Katwijk tablet is compared with the reference product Istin 10 mg tablet. The choice of the British reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product in different EU member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A randomised, single-dose, 2-way cross-over, bioavailability study was carried out under fasting conditions in 20 healthy male subjects with a wash-out period of 21 days. One subject was withdrawn due to non-compliance in the first phase. A total of 19 subjects completed the study and were eligible for pharmacokinetic evaluation. The bioavailability of the proposed Amlodipine 10 mg Apotex (Apotex Europe BV, the Nethetlands) was compared to the reference product Istin 10 mg tablet (Pfizer Ltd, United Kingdom).
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Amlodipine may be taken once daily without reference to food intake. Therefore, the bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean (CV%), t_{max} (median, range) of amlodipine following single-dose administration under fasting conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng.ml	t_{max} h	$t_{1/2el}$ h
Test (%CV)	351 (28)	392 (23)	6.7 (23)	8.0* (5-12)	46 (31)
Reference (%CV)	340 (29)	376 (34)	6.5 (23)	7.0* (5-10)	44 (24)
Ratio (90% CI)	1.04 (0.96-1.11)	1.04 (0.96-1.11)	1.03 (0.98-1.07)	---	---
CV (%)	13.0%	12.6%	8.0%	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity				
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
$t_{1/2}$	half-life				
*	for t_{max} (min-max) is reported				

The 90% confidence intervals calculated for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The difference of 1 hour between the median t_{max} of both products was not statistically significant. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters, it can be concluded that test Amlodipine 10 mg Katwijk tablet and reference Istin 10 mg tablet are bioequivalent with respect to rate and extent of absorption of amlodipine, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The Amlodipine Katwijk 5 and 10 mg tablets are dose proportional. The pharmacokinetics of amlodipine is linear in the range 5-10 mg. The results of the bioequivalence study performed with the 10 mg tablet therefore apply to the other tablet's strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan
Amlodipine was first approved in 1989 in Denmark, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amlodipine can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the approved SPC of the reference product Norvasc 5 and 10 mg tablets marketed by Pfizer, the Netherlands.

Readability Test
The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amlodipine Katwijk, 5 and 10 mg tablets, have a proven chemical-pharmaceutical quality and are generic forms of Norvasc. Norvasc is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the applicant.

The Board followed the advice of the assessors. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Amlodipine Katwijk, 5 and 10 mg tablets with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between concerned member states was reached during a written procedure.

A European harmonised birth date has been allocated (8 March 1989) and subsequently the first data lock point for amlodipine is 31 March 2008. The first PSUR is therefore expected on 30 May 2008. Thereafter the PSUR submission cycle will be 3 years.

In order to facilitate synchronisation of the PSUR submission schedule as well as harmonisation of renewal dates, the date for the first renewal is agreed to be 1 December 2011.

The following post-approval commitments have been made during the procedure:

Quality

- The MAH states that the stability study for the drug product will be continued up to 36 months, and commits to place the next 2 commercial batches on stability under room temperature conditions. The protocol for the planned stability study is identical to the submitted protocol for the running study

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Including batch control/testing.	NL/H/946/ 001-002/ IA/001	IA	29-10-2007	12-11-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/946/ 001-002/ IA/002	IA	29-10-2007	12-11-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/946/ 001-002/ IA/002	IA	29-10-2007	12-11-2007	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change outside the range of the currently approved pack sizes. Additional packsize of 30 tablets.	NL/H/946/ 001-002/ IA/004	IB	29-10-2007	28-11-2007	Approval	N
Widening of particle size limits for the active substance.	NL/H/946/ 001-002/ II/004	II	10-11-2007	14-1-2008	Approval	N
Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material. Other cases.	NL/H/946/ 001-002/ IA/006	IA	19-1-2009	2-2-2009	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/946/ 001-002/ IA/007	IA	24-3-2009	7-4-2009	Approval	N
Change in the name of the medicinal product.	NL/H/946/ 001-002/ IB/008	IB	24-3-2009	23-4-2009	Approval	N
Update of the SPC and PIL in line with EU Core Safety Profile (CSP) for amlodipine.	NL/H/946/ 001-002/ II/009	II	30-7-2009	21-8-2009	Approval	Y, Annex I
• Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. • Change to batch release arrangements and quality control testing of the finished product.	NL/H/946/ 001-002/ IB010/G	IB/G	1-11-2010	1-12-2010	Approval	N
Change in the specification parameters and/or limits of an excipient. Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue.	NL/H/946/ 001-002/ IB/011	IB	2-9-2010	6-10-2010	Approval	N
Implementation of change(s) requested by the EMEA/ National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of	NL/H/946/ 001-002/ IB/012	IB	28-12-2010	27-1-2011	Approval	Y, Annex II

Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC. Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH.						

Annex I - Variation NL/H/946/001-002/II/009

Scope of variation

Update of the SPC and PIL in line with EU Core Safety Profile (CSP) for amlodipine.

Changes to SPC and PIL

Blue = text added
Red = text deleted

SPC (only major changes are shown)

4.6 Pregnancy and lactation

~~There are no adequate data for the use of amlodipine in pregnant women.~~

~~Animal studies have shown reproductive toxicity at high doses (see 5.3). The potential risk for humans is unknown. Amlodipine should not be used during pregnancy unless the therapeutic benefit clearly outweighs the potential risks of treatment.~~

~~It is not known whether amlodipine is excreted in breast milk. It is advised to discontinue breastfeeding during treatment with amlodipine.~~

Pregnancy
The safety of amlodipine in human pregnancy has not been established.

Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater that the maximum recommended dosage for humans.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Lactation
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

4.9 Overdose

~~In humans, there is little experience with deliberate overdosage of amlodipine. The available data suggest that overdosage (>100 mg) could result in excessive peripheral vasodilatation followed by a pronounced and probably prolonged systemic hypotension.~~
In humans experience with intentional overdose is limited.

Symptoms:
Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

~~Clinically significant hypotension as a result of an overdosage of amlodipine requires an active cardiovascular support including frequent check-ups of the heart and the respiratory function, the raising of arms and legs and the monitoring of the volume of the circulating fluids and the urine production.~~

Treatment:

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be useful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of the calcium channel blockage.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

~~A vasoconstrictor could be useful to restore the vascular tonus and the blood pressure on the condition that the use is not contraindicated. The IV administration of calcium gluconate could be useful to reverse the effects of the calcium channel blockage. A gastric lavage might be useful in some cases. In healthy volunteers, it was shown that the administration of active carbon within 2 hours after the administration of amlodipine 10 mg reduced the absorption rate of amlodipine. As amlodipine is strongly plasma protein bound, dialysis will probably have little effect.~~

In addition, chapter 4.8 of the SPC and part 4 of the PI (possible side effects) have been substantially updated because of new data, see current SPC and PI.

Annex II - Variation NL/H/946/001- 002/IB/012

Scope of variation

Implementation of change(s) requested by the EMEA/ National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC. Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH.

Changes to SPC and PIL

Blue = text added
Red = text deleted

SPC

4.2 Posology and method of administration

Adults
For the treatment of hypertension and angina pectoris, the starting dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, the dose can be increased to a maximum of 10 mg daily (given as a single dose) depending on the individual reaction of the patient. Amlodipine can be used as monotherapy or in combination with the anti-anginous medication in patients suffering from angina pectoris.

Children with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in pediatric patients (see section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties). The effect of amlodipine on blood pressure in patients less than 6 years of age is not known
The 2.5 mg dose cannot be obtained with Amlodipine Apotex tablets 5 mg as these tablets are not manufactured to break into two equal halves.

~~**Children and adolescents (< 18 years of age)**~~
~~The use of amlodipine is not recommended for children and adolescents (< 18 years of age).~~

5.1` Pharmacodynamic properties

(…)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.
The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

(…)

Children with hypertension
A population PK study has been conducted in 74 hypertensive children aged from 12 month to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

PIL

2. Before you take Amlodipine

(…)

Precautions in certain groups of patients
- The elderly: care should be taken when increasing the dosage.
- ~~Children and young adults under the age of 18 years: {Amlodipine Tablets} should not be used.~~

Children
Safety and effectiveness have been studied in 6-17 year old boys and in girls. {Amlodipine Tablets} has not been studied in children under the age of 6 years. For more information, talk to your doctor.

(…)

3. How to take Amlodipine

(…)

Children
For children (6 -17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day.
Amlodipine 2.5 mg is not currently available and the 2.5 mg dose cannot be obtained with {Amlodipine Tablets} 5 mg as these tablets are not manufactured to break into two equal halves.