

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Amlodipine**

**NL/W/0002/pdWS/001**

**Marketing Authorisation Holder:  
Pfizer**

<b>Rapporteur:</b>	Netherlands
<b>Start of the procedure (day 0):</b>	10 February 2009
<b>Date of this report:</b>	9 November 2009
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):</b>	21 April 2009
<b>Deadline for CMS's comments (day 85):</b>	6 May 2009
<b>Date re-start procedure (day 90):</b>	2 September 2009
<b>Deadline for CMS's comments (day 115):</b>	27 September 2009
<b>Finalisation procedure (day 120):</b>	21 October 2009

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Norvasc
INN (or common name) of the active substance(s):	Amlodipine
MAH:	Pfizer
Pharmaco-therapeutic group (ATC Code):	C08CA02
Pharmaceutical form(s) and strength(s):	Tablets 5 mg, 10 mg

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## I. INTRODUCTION

Amlodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing systemic vascular resistance. It was originally developed by Pfizer and is available for once daily administration as a tablet formulation of 5 mg and 10 mg.

Amlodipine is authorised for the treatment of adults with hypertension and/or for angina pectoris in certain countries.

Post marketing experience with amlodipine is extensive.

The aim of this EU Work sharing project is the assessment of paediatric data for an extension for the use of amlodipine in hypertensive children and adolescents from 6 years of age and older.

The MAH submitted two completed paediatric studies in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. These submitted studies of amlodipine tablets in hypertensive paediatric patients were: a dose ranging open label, population pharmacokinetic trial, and a randomized, double-blind, placebo-controlled trial.

The following documentation has been included as per the procedural guidance:

- A line listing of paediatric cases in post-marketing experience
- An annex including SPC wording of different sections related to the paediatric use of the medicinal product:
  1. Section 4.1 does not contain an explicitly worded indication for the paediatric use of amlodipine. The posology section implicitly relates to an indication for children and adolescents of 6 to 17 years of age.
  2. Section 4.2 (Posology and method of administration) contains a description for the use of amlodipine in children and adolescents (6-17 years of age). Inclusion of this information was the clear consensus from the various EU Competent Authorities. The MAH believes that the clinical data available supports the use of amlodipine in children and adolescents, and therefore it is appropriate to describe the posology.
  3. Section 5.1 describes a clinical study in children and adolescents. Inclusion of this information was the clear consensus from the various EU Competent Authorities.
  4. The term "paediatric patients" has been changed to "children and adolescents."
- A recommendation to submit a proposal for registration of a 2.5 mg dose, currently marketed in the USA.

## **II. SCIENTIFIC DISCUSSION**

### **II.1. Background**

Amlodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing systemic vascular resistance. It was originally developed by Pfizer and is available for once daily administration as a capsule and tablet formulation of 5 mg and 10 mg.

Amlodipine is authorised for the treatment of adults with hypertension and/or for angina pectoris in certain countries.

Post marketing experience with amlodipine is extensive.

### **II.2. Information on the pharmaceutical formulation used in the clinical study(ies)**

N/A

### **II.3. Non-clinical aspects**

N/A

### **II.4. Clinical aspects**

#### **II.4.1. Clinical studies**

The MAH submitted 2 studies:

- Protocol A0531023: A multicenter, open-label, trial evaluating the population pharmacokinetics and safety of amlodipine in children aged 6 months to 17 years.
- Protocol A0531018: An 8-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group dose-ranging study to evaluate the efficacy and safety of amlodipine in hypertensive paediatric patients.

### **PROTOCOL A0531023 THE PEDIATRIC USE OF AMLODIPINE IN THE TREATMENT OF HYPERTENSION: A POPULATION PHARMACOKINETIC TRIAL (PATH-2)**

#### **➤ Description**

This study was a multicenter, open-label, population pharmacokinetic and safety study of amlodipine in children aged 6 months to 17 years. Seventy-four children on a stable amlodipine dose (for 2-4 weeks during the screening phase) were included in the study. Pharmacokinetic sampling took place during four visits over a period of four weeks following screening.

#### **➤ Methods**

##### **• Objectives**

The primary objective of the study was to obtain estimates for steady state pharmacokinetic parameters of amlodipine in hypertensive children 6 months to 17 years of age. Secondary objectives included an assessment of (1) the safety of amlodipine when used to treat hypertensive children, and (2) blood pressure control as measured by 24-hour ambulatory blood pressure monitoring (ABPM) in hypertensive children currently being treated with amlodipine.

- **Study design**

An initial 40 children between 6 months and 17 years old received a stable dose of amlodipine according to their dose in the 4-week screening phase, however this was extended to 74 patients to account for data variability and to obtain more data from patients in the lower age range. In the 4-week pharmacokinetic sampling phase, samples up to 24 hours were obtained during Visit 2 (out of 4 visits).

- **Study population**

The study population included males and females aged 6 months to 17 years of age, with a history of hypertension. Included patients had to have been receiving a stable dose of amlodipine for four weeks prior to study entry and were expected to remain on that dose throughout the duration of the study. Subjects were to be excluded from the study if treatment dose was altered or dosing was discontinued.

- **Treatments**

The dose and schedule of amlodipine administration was determined by the investigator according to the clinical needs of each subject. There were no amlodipine dose adjustments during the study.

- **Outcomes/endpoints**

Clearance rate and volume of distribution were determined.

- **Statistical Methods**

The pharmacokinetic analysis plan pre-specified in the protocol called for the application of a non-linear mixed effects modeling approach. Covariates explored for relationship to amlodipine drug exposure included: dose, frequency of administration, gender, age, Tanner stage, weight, height, body surface area, race, time of most recent meal, serum creatinine, creatinine clearance (estimated from serum creatinine), AST, ALT, alkaline phosphatase, serum albumin, total proteins, etiology, and concomitant medications.

➤ **Results**

- **Recruitment/ Number analysed**

A total of 80 subjects were screened and 74 were enrolled. Pharmacokinetic analyses were performed on 73 patients.

- **Baseline data**

Table 1: Baseline data

	Amlodipine		
	MALE	FEMALE	TOTAL
Number of Subjects	49	25	74
Age (years):			
<2	1	2	3
2-5	6	3	9
6-12	21	13	34
13-16	19	4	23
>=17	2	3	5
Mean	10.7	9.6	10.4
SD	4.2	4.9	4.4
Range	1-17	1-17	1-17
Race:			
WHITE	25	17	42
BLACK	19	7	26
HISPANIC	4	0	4
OTHER	1	1	2
Weight (kg):			
Mean	53.7	48.0	
SD	33.3	28.3	
Range	13-142	6-101	
N	49	25	
Height (cm):			
Mean	144.8	133.3	
SD	27.1	29.0	
Range	88-191	64-166	
N	49	25	

Table 2: Tanner stage

Number of subjects	Amlodipine
Number of Subjects	74
Male subjects	46
Pubic hair	
Stage 1	21 ( 45.7%)
Stage 2	3 ( 6.5%)
Stage 3	4 ( 8.7%)
Stage 4	8 ( 17.4%)
Stage 5	10 ( 21.7%)
Female subjects	25
Breast	
Stage 1	15 ( 60.0%)
Stage 2	0
Stage 3	1 ( 4.0%)
Stage 4	3 ( 12.0%)
Stage 5	6 ( 24.0%)
Female subjects	25
Pubic hair	
Stage 1	15 ( 60.0%)
Stage 2	0
Stage 3	1 ( 4.0%)
Stage 4	3 ( 12.0%)
Stage 5	6 ( 24.0%)

All 74 subjects were diagnosed with hypertension for a mean of 3.4 years. The range of diagnosis duration was 0.1 – 16.8 years. The youngest child treated was 12.2 months old.

- **Pharmacokinetic results**

Therapy was administered for a median duration of 17.0 days. Duration of therapy during the study ranged from 7 days to 90 days. Two patients discontinued on day 14 and 27. The first was related to an adverse event.

Amlodipine plasma concentrations were quite variable, ranging from less than 1 ng/ml to 57.2 ng/ml for subjects receiving medication once daily and from less than 3 ng/ml to 43.4 ng/ml for all but one of the subjects receiving medication twice daily. One subject consistently had concentrations above 150 ng/ml.

Table 3: Parameters estimated for the final population kinetics model with weight (first order conditional estimation with interaction)

<b>Structural Model and Interindividual Variance Parameters</b>		
<b>Parameter</b>	<b>Typical Value (%RSE*)</b>	<b>Interindividual %CV (%RSE*)</b>
<b>CL/F (L/hr)</b>	$CL = \theta_1 + \theta_4*(WT-45) - \theta_5*SEX$	43.24% (22%)
<b><math>\theta_1</math></b>	23.7 (6%)	-
<b><math>\theta_4</math></b>	0.176 (29%)	-
<b><math>\theta_5</math></b>	6.09 (36%)	-
<b>V/F (L)</b>	$V = \theta_2 + \theta_6*(WT-45)$	48.68% (52%)
<b><math>\theta_2</math></b>	1130 (11%)	-
<b><math>\theta_6</math></b>	16 (35%)	-
<b><math>k_a</math> (hr<sup>-1</sup>)</b>	$k_a = \theta_3$	50.60% (52%)
<b><math>\theta_3</math></b>	0.807 (62%)	-
<b>Residual Error</b>		
<b>Parameter</b>	<b>Estimate (%RSE*)</b>	<b>Interindividual %CV (%RSE*)</b>
<b><math>\sigma^2_{prop}</math></b>	%CV=22.07% (14%)	-

This model used study population weight (median values) and gender (M/F) as co-variates in the calculation of typical clearance values. Since gender was found to be a significant covariate in the model, the typical clearance values were calculated separately for males and females. Using the median weight value of 38.3 kg and female as gender, the typical clearance value for females aged 6-12 years was calculated as 16.4 L/hr; the typical clearance value for males aged 6-12 years using this median weight in our model was calculated as 22.5 L/hr. Using the median weight value of 65.8 kg and female as gender, the typical clearance value for females aged 13-17 years was calculated as 21.3 L/hr; the typical clearance value for males aged 13-17 years using this median weight in our model was calculated as 27.4 L/hr.

- **Correlation of age with pharmacokinetics**

Table 4: Pharmacokinetic variables according to age category

	1 month to 2 years (N = 2)	2 to < 6 years (N = 9)	≥ 6 to < 13 years (N = 34)	≥ 13 to < 17 years (N = 23)	≥17 years (N = 5)
CL/F (L/hr)					
Mean	12.85	19.03	24.89	28.50	24.92
Range	5.77 – 19.93	10.64 – 25.52	5.40 – 66.03	7.92 – 55.62	11.99 – 38.81
CL/F (L/hr/kg)					
Mean	1.200	0.964	0.634	0.407	0.380
Range	0.891 – 1.510	0.595 – 1.654	0.069 – 2.024	0.159 – 0.699	0.189 – 0.614
V/F (L)					
Mean	492	816	1180	1500	1505
Range	376 - 607	599 – 1074	230 - 3139	567 – 3264	1043 – 1838
V/F (L/kg)					
Mean	52.02	42.83	27.01	21.11	23.94
Range	45.99 – 58.04	23.91 – 66.42	10.83 – 58.01	7.88 – 32.21	12.89 – 31.90

- **Safety results**

Among the 74 subjects evaluable for adverse events, 6 adverse events that were considered to be treatment-related, occurred in 4 (5.4%) of the subjects.

No subject reported an SAE that was considered to be treatment-related. Six of the SAEs were considered to be related to other illnesses and one was due to concomitant treatment.

- **Summary**

- The range and absolute values of amlodipine plasma concentration variability is similar following medication administration on either a once a day or twice a day schedule.
- Both regimens resulted in concentrations that were usually between 1 and 50 ng/ml.
- Based on a population kinetic model, the typical clearance values were calculated according to age group, gender and median weight within each group.

**PROTOCOL A0531018 PATH-I (PEDIATRIC USE OF AMLODIPINE IN THE TREATMENT OF HYPERTENSION). A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AMLODIPINE IN THE TREATMENT OF HYPERTENSION IN CHILDREN.**

➤ **Description**

This was an 8-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group study to determine the antihypertensive dose range efficacy and safety of amlodipine in hypertensive paediatric patients. The design included a 2-week screening phase, a 4-week double-blind treatment period and a 4-week withdrawal period.

## ➤ Methods

### • Objective(s)

The primary objective of the study was to compare the effect of amlodipine versus placebo on systolic blood pressure in hypertensive children aged 6 to less than 17 years. Secondary objectives of the study were to compare the effect of amlodipine versus placebo on diastolic blood pressure in these hypertensive children; to evaluate the effect of amlodipine on systolic and diastolic blood pressure as a function of dose and body size; and to evaluate the safety of amlodipine in hypertensive children.

### • Study design

This randomized, double-blind, dose-ranging, placebo controlled, parallel group, multicenter study consisted of a 2-week screening period followed by two 4-week treatment phases. In treatment Phase 1 of the study, all subjects were randomized to receive oral amlodipine qd (2.5mg for 4 weeks; or 2.5mg for 2 weeks followed by 5mg for 2 weeks). In treatment Phase 2 of the study subjects were randomized to continue on oral amlodipine at a dose of 2.5mg or 5mg for 4 weeks; or were randomized to withdraw to oral placebo qd for 4 weeks. Randomization was stratified by age range into two stratum (Stratum 1: ages greater than or equal to 6 years and less than but not equal to 13 years; Stratum 2: ages greater than or equal to 13 years and less than but not equal to 17 years). Subjects were evaluated at screening, baseline, and weeks 1, 2, 3, 4, 5, 6, 7 and 8.

### • Study population /Sample size

Males and females aged 6 to less than 17 years, with seated systolic blood pressure greater than or equal to the 95th percentile for age, gender, and height, measured on at least 3 separate occasions (at least one day apart) prior to entry into the study.

### • Treatments

In Phase 1, subjects were randomized in equal proportions to receive 2.5 mg qd or 5 mg qd (2.5 mg in first 2 weeks). In Phase 2, one third of each treatment group was randomly withdrawn to placebo, while the other subjects continued on their Phase 1 medication. This was accomplished by assigning subjects to 4 groups in the ratio 2:1:2:1 (see following table). Randomization was stratified by age range. Stratum 1 consisted of younger subjects aged greater than or equal to 6 years and less than but not equal to 13 years.

Group (allocation ratio)	Phase 1	Phase 2
A (2)	Amlodipine 2.5 mg qd	Amlodipine 2.5 mg qd
B (1)	Amlodipine 2.5 mg qd	Placebo
C (2)	Amlodipine 5 mg qd	Amlodipine 5 mg qd
D (1)	Amlodipine 5 mg qd	Placebo

### • Outcomes/endpoints

#### Efficacy

The primary efficacy endpoint of the study was change in seated systolic blood pressure at the end of study treatment in Phase 2 compared to baseline. Only subjects who entered Phase 2 were included in the primary efficacy analysis. Secondary efficacy endpoints included the change in seated diastolic blood pressure at the end of study treatment in Phase 2 compared to baseline. In addition, the effect of amlodipine on systolic and diastolic blood pressure was examined as a function of dose and body size.

### Safety

Safety evaluations included laboratory tests (screening and end of study), pregnancy test (menstruating females) screening and week 4, adverse events (weeks 1 through 8), and blood pressure and heart rate (screening, baseline and weeks 1 through 8).

- **Statistical Methods**

The primary analysis employed a linear model with terms for treatment, gender, race, etiology, and baseline age, weight, and height. The primary hypothesis was tested using least squares means from this model with a 0.05 level of significance (one-sided with amlodipine providing the greater reduction). Secondary analyses included: regression vs mg/kg exposure, relationship to Tanner Stage, changes from baseline to the end of Phase 1, and changes from end of Phase 1 to end of Phase 2. Diastolic blood pressure was analyzed using the same models as employed for systolic blood pressure.

➤ **Results**

- **Recruitment/ Number analysed**

A total of 344 subjects were screened for the study and 268 were assigned to treatment. In Phase 2 of the study, 84 subjects were randomized to continue in the amlodipine 2.5mg treatment group, 94 subjects were randomized to continue in the amlodipine 5.0mg treatment group, and 90 subjects were randomized to withdraw to placebo. 81, 84, and 85 subjects, respectively, completed Phase 2 treatment, and 2, 4, and 2 subjects, respectively, were discontinued

Table 5: Patient disposition

	Phase 1 Treatment Group		Phase 2 Treatment Group		
	Amlodipine 2.5 mg	Amlodipine 5.0 mg	Amlodipine 2.5 mg	Amlodipine 5.0 mg	Placebo
Number (%) of Subjects					
Screened	344				
Assigned to Treatment	268				
Treated	127	141	83	88	87
Completed	125 (98.4)	133 (94.3)	81 (97.6)	84 (95.5)	85 (97.7)
Discontinued	2 (1.6)	8 (5.7)	2 (2.4)	4 (4.5)	2 (2.3)
Analyzed for Safety:					
Adverse events	127 (100.0)	141 (100.0)	83 (100.0)	88 (100.0)	87 (100.0)
Laboratory data	3 (2.4)	5 (3.5)	83 (100.0)	86 (97.7)	85 (97.7)

- **Baseline data**

A summary of overall patient demographic and baseline characteristics by treatment groups, (all randomized patients) is provided below.

Table 6: Baseline characteristics

<b>Demographic Characteristics</b>				
	Amlodipine 2.5mg / 2.5mg	Amlodipine 2.5mg / Placebo	Amlodipine 5.0mg / 5.0mg	Amlodipine 5.0mg / Placebo
Number of Subjects (male/female)	84 (52/32)	43 (23/20)	94 (69/25)	47 (33/14)
Mean Age, years (male/female)	12.6 (12.9/12.0)	11.4 (11.5/11.3)	12.0 (12.2/11.2)	12.3 (12.9/10.9)
Race: (male/female)				
White	55 (34/21)	23 (13/10)	61 (48/13)	24 (17/7)
Black	19 (11/8)	14 (6/8)	22 (16/6)	15 (8/7)
Asian	0	0	2 (0/2)	0
Hispanic	5 (4/1)	5 (4/1)	8 (4/4)	7 (7/0)
Other	5 (3/2)	1 (0/1)	1 (1/0)	1 (1/0)
Mean Weight (kg) male/female	73.5 / 64.5	63.9 / 58.1	66.8 / 58.1	70.2 / 62.5
Mean Height (cm) male/female	160.8 / 150.4	151.5 / 146.7	156.2 / 144.6	156.4 / 145.4
<b>Tanner Stages of Sexual Development</b>				
Number of Subjects	84	43	94	47
<b>Male Subjects: Pubic Hair</b>	51	22	68	32
Number n (%)	n (%)	n (%)	n (%)	n (%)
Stage 1	17 (33.3%)	9 (40.9%)	21 (30.9%)	5 (15.6%)
Stage 2	3 (5.9%)	4 (18.2%)	12 (17.6%)	6 (18.8%)
Stage 3	4 (7.8%)	3 (13.6%)	3 (4.4%)	6 (18.8%)
Stage 4	6 (11.8%)	3 (13.6%)	13 (19.1%)	6 (18.8%)
Stage 5	21 (41.2%)	3 (13.6%)	19 (27.9%)	9 (28.1%)
<b>Female Subjects: Breast/Pubic Hair</b>	31	20	24	14
Number n (%)	n (%) / n(%)	n (%) / n(%)	n (%) / n(%)	n (%) / n(%)
Stage 1	8 (25.8%) / 7 (22.6%)	7 (35.0%) / 9 (45.0%)	10 (41.7%) / 12 (50.0%)	5 (35.7%) / 6 (42.9%)
Stage 2	2 (6.5%) / 4 (12.9%)	2 (10.0%) / 0	1 (4.2%) / 1 (4.2%)	3 (21.4%) / 2 (14.3%)
Stage 3	6 (19.4%) / 4 (12.9%)	4 (20.0%) / 4 (20.0%)	2 (8.3%) / 0	0/0
Stage 4	5 (16.1%) / 5 (16.1%)	1 (5.0%) / 1 (5.0%)	4 (16.7%) / 3 (12.5%)	4 (28.6%) / 4 (28.6%)
Stage 5	10 (32.3%) / 11 (35.5%)	6 (30.0%) / 6 (30.0%)	7 (29.2%) / 8 (33.3%)	2 (14.3%) / 2 (14.3%)

- **Efficacy results**

Table 7: Decline in systolic blood pressure for the different treatment arms from baseline to end of phase 2 and from end of phase 1 to end of phase 2.

Primary Efficacy Analysis: Estimated Differences Between Treatments in Change in Systolic Blood Pressure (mmHg) from Baseline to the End of Phase 2		
Phase 2	Contrast (Standard Error):	P-value*
Amlodipine 5.0mg vs Placebo#	-5.05 (1.93)	0.0046
Amlodipine 2.5mg vs Placebo	-3.29 (1.93)	0.0449
Amlodipine 5.0mg vs Amlodipine 2.5mg	-1.77 (1.93)	0.1803
#Primary Efficacy Comparison		
*One-sided test for null hypothesis: contrast=0		

Estimated Differences Between Treatments in Change in Systolic Blood Pressure (mmHg) from End of Phase 1 to End of Phase 2		
Phase 2	Contrast (Standard Error)	P-value*
Amlodipine 5.0mg vs Placebo#	-3.92 (1.77)	0.0139
Amlodipine 2.5mg vs Placebo	-2.25 (1.78)	0.1028
Amlodipine 5.0mg vs Amlodipine 2.5mg	-1.66 (1.78)	0.1755
#Primary Efficacy Comparison		
*One-sided test for null hypothesis: contrast=0		

Diastolic blood pressure demonstrated to be significantly lower for both the 2.5 and 5 mg compared to placebo from end of phase I to end of phase II (-1.71 mmHg, p=0.0442; -2.984 mmHg, p=0.0083, respectively).

Baseline systolic BP value was 138.0 (SD 12.7). Placebo value at week 8 was 132.4 (SD 15.4).

- **Subgroups and Dose-Response relationship**

Table 8: Change in Systolic Blood Pressure (mmHg) from Baseline to End of Phase 2 by Baseline Characteristics

	Amlodipine 2.5 mg	Amlodipine 5.0 mg	Placebo
Patients Randomized	84	94	90
<b>Baseline Systolic BP</b>			
< 132.0			
N	22	25	39
Mean (SD)	-4.1 (11.4)	-2.4 (10.8)	-0.3 (13.2)
132.0 - 141.3			
N	31	25	27
Mean (SD)	-7.7 (15.7)	-7.6 (10.7)	-4.4 (13.9)
> 141.3			
N	30	36	21
Mean (SD)	-10.4 (13.5)	-13.5 (14.2)	-6.3 (11.1)
<b>Age</b>			
< 13 years			
N	33	43	48
Mean (SD)	-8.7 (13.8)	-6.5 (14.1)	-3.9 (12.8)
>= 13 years			
N	50	43	39
Mean (SD)	-7.0 (14.1)	-10.6 (11.7)	-1.9 (13.4)
<b>Gender</b>			
Male			
N	51	63	54
Mean (SD)	-6.9 (14.5)	-6.6 (12.3)	-2.5 (12.8)
Female			
N	32	23	33
Mean (SD)	-8.9 (13.1)	-14.0 (13.7)	-3.8 (13.6)
<b>Tanner stages</b>			
Missing			
N	2	2	2
Mean (SD)	-6.0 (4.2)	-22.5 (40.8)	-1.2 (16.7)
Stage 1			
N	24	30	28
Mean (SD)	-10.4 (14.0)	-5.0 (11.7)	-3.1 (12.7)
Stage 2			
N	7	11	11
Mean (SD)	-10.0 (23.9)	-8.1 (15.5)	-4.4 (15.0)
Stage 3			
N	8	2	13
Mean (SD)	-5.5 (13.3)	-12.5 (19.6)	-5.2 (14.2)
Stage 4			
N	11	16	13
Mean (SD)	-4.5 (13.6)	-5.5 (6.9)	-2.7 (12.8)
Stage 5			
N	31	25	20
Mean (SD)	-7.0 (12.3)	-13.6 (12.5)	-0.9 (12.8)

Race			
White			
N	54	58	46
Mean (SD)	-5.3 (12.2)	-7.7 (12.1)	-2.8 (13.8)
Black			
N	19	19	27
Mean (SD)	-10.5 (16.3)	-9.1 (14.7)	-3.7 (13.2)
Asian			
N		2	
Mean (SD)		-32.3 (26.9)	
Hispanic			
N	5	1	2
Mean (SD)	-17.8 (18.2)	-17.7 ( )	-11.3 (2.4)
Other			
N	5	6	12
Mean (SD)	-12.9 (14.8)	-5.7 (5.4)	-0.7 (10.7)
Weight			
< 48.9			
N	24	31	30
Mean (SD)	-14.2 (14.9)	-6.4 (15.0)	-5.7 (13.4)
48.9 - 77.3			
N	26	31	27
Mean (SD)	-3.0 (10.7)	-7.4 (10.2)	0.6 (10.4)
> 77.3			
N	33	24	30
Mean (SD)	-6.7 (14.1)	-12.8 (13.3)	-3.5 (14.4)
Height			
< 148.0			
N	23	32	33
Mean (SD)	-13.9 (14.8)	-4.7 (15.1)	-5.9 (13.0)
148.0 - 164.0			
N	29	22	30
Mean (SD)	-5.2 (12.0)	-13.1 (13.4)	-1.0 (13.0)
> 164.0			
N	31	32	24
Mean (SD)	-5.4 (14.0)	-9.3 (9.3)	-1.4 (13.0)

The effect of 5 mg dose was found to be lower than the 2.5 mg dose in patients with a systolic BP less than 132, patients <13 years, male gender, Tanner stage 1 and 2, weight less than 49 kg, Black and Hispanic patients and height less than 148 cm.

Table 9: Change in systolic blood pressure and diastolic blood pressure from baseline to end of study according to exposure of amlodipine.

	Adjusted Mean	Standard Error
Exposure		
< 0 mg/kg	-3.660	1.337
> 0 - .05869 mg/kg	-6.309	1.444
> .05869 mg/kg	-9.247	1.423
Exposure		
< 0 mg/kg	-0.746	1.027
> 0 - .05869 mg/kg	-3.096	1.111
> .05869 mg/kg	-4.922	1.097

In table 9 systolic and diastolic blood pressure demonstrated to decrease with increased dose.

Analyses of the effect of treatment on systolic blood pressure (SBP) and diastolic blood pressure (DBP) were conducted with drug exposure (in mg/kg) and other variables as covariates. There were significant treatment effects observed in the analyses. Drug exposure (as a continuous variable in mg/kg), corresponding baseline blood pressure, and gender were the significant contributing covariates in the model (table 10).

Table 10: Model for change in Systolic and diastolic blood pressure with study drug exposure

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Model for Change in Systolic Blood Pressure (mmHg) with Study Drug Exposure (mg/kg) as a Covariate

	DF	Coefficient	F or T	P-value*
Number of Patients included in model	256			
Overall F-Statistic and p-value for treatment effect	4.71, 0.0310			
Root Mean Square Error	12.3			
Exposure (mg/kg)	1	-35.00	-2.17	0.0310
Baseline systolic blood pressure (mmHg)	1	-0.437	-6.08	0.0001
Age (years)	1	0.471	1.21	0.2271
Gender (males vs. females)	1	4.191	2.48	0.0140
Race	2		1.28	0.2808
Height (cm)	1	-0.006	-0.10	0.9215
Etiology of Hypertension	5		2.19	0.0558

\*Two-sided test for null hypothesis: coefficient=0

Table 5.7.3

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Model for Change in Diastolic Blood Pressure (mmHg) with Study Drug Exposure (mg/kg) as a Covariate

	DF	Coefficient	F or T	P-value*
Number of Patients included in model	256			
Overall F-Statistic and p-value for treatment effect	5.21, 0.0233			
Root Mean Square Error	9.5			
Exposure (mg/kg)	1	-28.41	-2.28	0.0233
Baseline diastolic blood pressure (mmHg)	1	-0.433	-7.74	0.0001
Age (years)	1	-0.008	-0.03	0.9774
Gender (males vs. females)	1	0.338	0.26	0.7962
Race	2		1.41	0.2451
Height (cm)	1	-0.039	-0.81	0.4181
Etiology of Hypertension	5		0.37	0.8697

\*Two-sided test for null hypothesis: coefficient=0

## Safety results

Table 11: Adverse events by body system

Number of Subjects with Adverse Events	Phase 1 Amlodipine 2.5mg N=127	Phase 1 Amlodipine 5.0mg N=141	Phase 2 Amlodipine 2.5mg N=83	Phase 2 Amlodipine 5.0mg N=88	Phase 2 Placebo N=87
	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a Whole	79 (62.2%)	87 (61.7%)	33 (39.8%)	36 (40.9%)	37 (42.5%)
Respiratory	43 (33.9%)	42 (29.8%)	23 (27.7%)	28 (31.8%)	25 (28.7%)
Digestive	23 (18.1%)	36 (25.5%)	8 (9.6%)	13 (14.8%)	17 (19.5%)
Nervous	23 (18.1%)	24 (17.0%)	9 (10.8%)	7 (8.0%)	9 (10.3%)
Cardiovascular	14 (11.0%)	21 (14.9%)	0	5 (5.7%)	3 (3.4%)
Musculoskeletal	8 (6.3%)	8 (5.7%)	5 (6.0%)	10 (11.4%)	6 (6.9%)

Table 12: Treatment related adverse events by body system

Number of Subjects with Adverse Events	Phase 1 Amlodipine 2.5mg N=127	Phase 1 Amlodipine 5.0mg N=141	Phase 2 Amlodipine 2.5mg N=83	Phase 2 Amlodipine 5.0mg N=88	Phase 2 Placebo N=87
	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a Whole	42 (33.1%)	42 (29.8%)	18 (21.7%)	16 (18.2%)	15 (17.2%)
Nervous	13 (10.2%)	15 (10.6%)	4 (4.8%)	4 (4.5%)	4 (4.6%)
Cardiovascular	11 (8.7%)	15 (10.6%)	0	4 (4.5%)	1 (1.1%)
Digestive	7 (5.5%)	13 (9.2%)	2 (2.4%)	2 (2.3%)	6 (6.9%)
Respiratory	3 (2.4%)	6 (4.3%)	6 (7.2%)	1 (1.1%)	0

There were no deaths in this study. Five study subjects experienced serious adverse events, including one subject receiving amlodipine 2.5 mg and four subjects who were receiving or had received amlodipine 5.0 mg. None of the cases were considered by the investigators to be related to study drug.

### • Summary

- The efficacy of this amlodipine preparation in lowering systolic BP in children aged 6-16 years was demonstrated for both 2.5 and 5 mg based on the period from baseline to end of phase 2, and for only the 5 mg dose for end of phase 1 to end of phase 2.
- The 5 mg dose did not reduce systolic BP significant more than the 2.5 mg dose in both periods.
- Several subgroups (e.g. younger age, lower Tanner stage and less weight) showed less effect for the 5 mg group compared with the 2.5 mg group. However, in the model treatment exposure demonstrated a significant effect.
- In general, the 5 mg dose seemed to be accompanied with more adverse events than the lower 2.5 mg dose.

### ➤ Spontaneous reports

The databases were reviewed cumulatively through 31 October 2008 for paediatric cases (defined as  $\leq 18$  years of age) meeting PSUR criteria and medically confirmed. There were 141 paediatric cases identified. The Periodic Safety Update Report (PSUR) covering 01 January 2005 through 31 March 2008 indicated the review of the cases and events involving children less than 6 years of age revealed no relevant safety concerns. There were seven deaths identified in the cumulative review for patients eighteen years of age and younger. Two deaths were related to intentional overdose and the use of several drugs. In both cases neither subject was receiving amlodipine chronically as treatment, and hence not associated with the suicidal ideation. Evaluation of cases in the overall paediatric population revealed no new safety information.

### II.4.2. Discussion of clinical aspects

On 6 April, 2009 the Rapporteur circulated the day 70 assessment report for the EU Worksharing Procedure for paediatric data for amlodipine. Comments were received from Member States and a List of Questions was subsequently sent to the MAH.

The List of Questions was as follows:

1. The applicant should provide and discuss more on the findings for several subgroups
  - i. The applicant should provide and discuss systolic and diastolic blood pressure effect in relation to exposure for the several subgroups.
  - ii. The applicant should discuss the inconsistent findings of the response to the 2.5 and 5 mg doses within the several subgroups.
  - iii. The applicant should provide a dose recommendation based on the discussion from point a and b.
2. The applicant should discuss the inconsistent finding of a non-significant blood pressure of the 2.5 mg dose in phase 2 compared to a significant blood pressure reduction on the 2.5 mg dose from baseline to the end of phase 2. This should be done in addition to our speculations of a lack of a stable baseline (regression to the mean) where no treatment would have been indicated at all, or a second speculation that the 4 week withdrawal period is too short to wash out all effect of amlodipine treatment.

On 13 July 2009 the MAH submitted the Applicant's Responses to the Request for Supplementary Information.

On 2 September, 2009 the Rapporteur circulated the second assessment report. Following the comments from the Member States, it was decided to send additional questions to the MAH.

Following assessment of the MAH responses received at 19 and 21 October, all points were resolved.

## III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

### ➤ Overall conclusion

#### Efficacy

Amlodipine reduces blood pressure further in children (6-17 years) when dose levels are increased. However, several subgroups are present where the dose response is less straightforward. This picture does not change when dose levels are corrected for bodyweight in post hoc analyses. Dose titration based on

bodyweight is therefore not considered necessary. Blood pressure lowering efficacy is maintained during the total 8 week study duration. Upon withdrawal of active therapy BP increases again to nearly baseline levels, although the effect is less pronounced for SBP in the 2.5mg/placebo arm. Therefore, a prudent approach starting would be to start with amlodipine 2.5 mg once daily and then titrate the dose up to 5 mg OD when after 4 weeks blood targets are not met.

### Safety

In general, no new safety concerns are identified. Limited information from the clinical trials is available on safety. In general, the 5 mg dose seemed to be accompanied with more adverse events than the lower 2.5 mg dose.

### ➤ **Recommendation**

Based on the provided clinical data, it is recommended to amend the SPC and Package Leaflet:

## **SPC**

### **Section 4.2 Posology and method of administration**

#### 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

*For capsules or tablets without a break-line:* The 2.5 mg dose cannot be obtained with “Product name” tablets 5 mg as these tablets are not manufactured to break into two equal halves

### **Section 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.

### **Section 5.2 Pharmacokinetic properties**

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.

## **Package Leaflet**

### **Section 2. BEFORE YOU TAKE <Product name>**

#### Children

Safety and effectiveness have been studied in 6-17 year old boys and in girls. <Productname> has not been studied in children under the age of 6 years. For more information, talk to your doctor.

### **Section 3. HOW TO TAKE <Product name>**

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

*For capsules or tablets without a break-line:* Amlodipine 2.5 mg is not currently available and the 2.5 mg dose cannot be obtained with “Product name” tablets 5 mg as these tablets are not manufactured to break into two equal halves

#### **Registration of the 2.5 mg dose**

In addition, it is acknowledged that dose recommendations are not possible with the currently registered products of Pfizer. The MAH is encouraged to submit a proposal for a registration for the 2.5 mg dose.

## **IV. REQUEST FOR SUPPLEMENTARY INFORMATION**

No additional data have been requested.