

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

**(Felodipine)
Renedil, Prevex, Plendil**

UK/W/002/pdWS/001

**Marketing Authorisation Holder:
Sanofi-aventis**

Rapporteur:	UK – S. Norton
Start of the procedure (day 0):	1 December 2008
Date of this report:	8 January 2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	9 February 2009
Deadline for CMS's comments (day 85):	24 February 2009
Date re-start procedure (day 90):	15 September 2009
Deadline for CMS's comments (day 115):	10 October 2009
Finalisation procedure (day 120):	15 October 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Munobal, Munobal Retard, Renedil, Hydac Prevex, Plendil, Plendur
INN (or common name) of the active substance(s):	Felodipine
MAH:	Sanofi-aventis, Sandoz, Simesa
Currently approved Indication(s)	Management of hypertension and prophylaxis of chronic stable angina pectoris.
Pharmaco-therapeutic group (ATC Code):	C08CA02
Pharmaceutical form(s) and strength(s):	Modified-release tablet 5 mg, 10 mg Prolonged release tablet 5 mg, 10 mg
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EXECUTIVE SUMMARY

This is an assessment of data for felodipine, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed since the Paediatric Regulation entered into force (26 Jan 2007). The UK is Rapporteur for this procedure.

Felodipine is a highly vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing systemic vascular resistance. It is available as prolonged release tablets of 2.5 mg, 5 mg and 10 mg. Individual dose adjustments is restricted to the fixed tablet strengths since the tablets must not be divided, chewed or crushed.

Felodipine is authorised for the treatment of adults with hypertension and/or in some countries for angina pectoris, with an estimated total patient exposure of over 30 million patient years. It does not have an approved paediatric posology in any country, and the extent of its off-label use is not known.

Felodipine was first approved for marketing in 1987 in Denmark, via national procedure and is currently being marketed in all EU countries.

The current submission includes: two clinical paediatric studies, a brief clinical overview and a cumulative safety review.

These studies however had been previously submitted to MHRA in July 2004 in relation to the available paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity Granted list. The MHRA evaluation of the data was reviewed by Paediatric Working Group of the Committee on Safety of Medicines (PWG – CSM) on May 2005.

RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy, the Rapporteur considers that: the results of these studies do not support paediatric posology. None the less these findings should be briefly included in section 5.1 of the SmPC. However, the incorporation of detailed summaries of the efficacy data in section 5.1 of the SmPC will not be helpful to prescriber and might be over interpreted.

Based on the provided clinical data, the SPC should be amended as follows:

Section 5.1

There is limited clinical trial experience of the use of felodipine in hypertensive paediatric patients. *In a randomised, double-blind, 3-week, parallel group study in children aged 6-16 years with primary hypertension, the antihypertensive effects of once daily felodipine 2.5 mg (n=33), 5 mg (n=33) and 10 mg (n=31) were compared with placebo (n=35). The study failed to demonstrate the efficacy of felodipine in lowering blood pressure in children aged 6-16 years.*

The long-term effects of felodipine on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy as therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Section 5.2

*“In a single dose (felodipine **prolonged** release 5 mg) pharmacokinetic study **with a limited number of** children aged between 6 and 16 years **(n=12)** there was no apparent relationship between the age and AUC, Cmax or half-life of felodipine.”*

I. INTRODUCTION

On 6 November 2008, 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. This is in response to the CMD (h) and the EMEA requirement that paediatric studies of authorised medicinal products not previously submitted should be submitted for assessment to European Health Agencies.

The submitted document consisted of two studies of felodipine extended release (ER) tablets/solution in hypertensive paediatric patients: a single dose safety, tolerability and pharmacokinetic study and a multicentre, double-blind, placebo-controlled, dose ranging, efficacy and safety study with an optional 14-week open-label extension.

These studies however had been previously submitted to MHRA in July 2004 in relation to the available paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity Granted list. The MHRA evaluation of the data was reviewed by Paediatric Working Group of the Committee on Safety of Medicine (PWG – CSM) on May 2005. It was recommended that; although the efficacy is not demonstrated, sections 5.1 and 5.2 of the SmPC should be updated to reflect the results of the studies (Annex II). A type II variation application was submitted by the MAH to that effect and subsequently approved by MHRA on March 2006.

The FDA also found the documentation presented was inadequate to support a labelling change and the MAH agrees that the submitted paediatric studies do not influence the benefit risk for felodipine.

A cumulative review of safety, including all clinical trials and spontaneous reports arising from off label use was included in the 2004 submission to MHRA. Although this is not a compulsory requirement of Art 45, it will be briefly mentioned in last part of section II of this assessment report.

A short critical expert overview has also been provided.

The MAH stated that *“the submitted paediatric studies do not influence the benefit risk for felodipine and that there is no consequential regulatory action”*.

II. Scientific discussion

II.1 Background

Felodipine is a highly vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing systemic vascular resistance. It was originally developed by AstraZeneca and is available for once daily administration as a prolonged release tablet formulation of 2.5 mg, 5 mg and 10 mg.

Felodipine was first approved for marketing in 1987 in Denmark. It is authorised via national procedures and is currently approved for marketing in over 90 countries worldwide, including all EU countries. Felodipine is authorised for the treatment of adults with hypertension and/or in some countries for angina pectoris. It does not have an approved paediatric posology in any country.

Post marketing experience with felodipine is extensive and the estimated total patient exposure to date is over 30 million patient years.

Condition to be treated - Hypertension

Hypertension in children is defined as average systolic BP or diastolic BP that is $\geq 95^{\text{th}}$ percentile for gender, age, and height on at least three separate occasions. Primary (essential) hypertension in children is usually mild or Stage 1 hypertension. It is often associated with a positive family history of hypertension or CVD risk factors or comorbidities. Renal parenchymal and renovascular diseases are the most common (60% to 70%) causes of secondary hypertension in children.

The most common causes of hypertension by age group are:

- Newborn infants: renal artery thrombosis, renal artery stenosis, congenital renal abnormality, coarctation of the aorta
- Infancy to 6 years: renal parenchymal and structural renal disease, coarctation of the aorta, renal artery stenosis
- 6 to 10 years: renal parenchymal disease, renal artery stenosis, primary hypertension
- Adolescence: primary hypertension, renal parenchymal disease

Left-ventricular hypertrophy is the most prominent clinical evidence of target-organ damage in Paediatric hypertension, and can be seen in as many as 41% of Paediatric patients. Paediatric patients with severe cases of hypertension are also at increased risk of developing hypertensive encephalopathy, seizures, cerebrovascular events, and congestive heart failure.

Due in part to the increasing prevalence of childhood obesity as well as growing awareness of the disease, the prevalence and rate of diagnosis of hypertension in children and adolescents appears to be increasing from the estimated > 1% in the 1980s to 2.2%-3.6% at present. This increase also reflects an epidemiologic shift from secondary hypertension, most often caused by renal and renovascular diseases, to primary hypertension as the main cause of paediatric hypertension.

II.2 Information on the pharmaceutical formulation used in the clinical studies

Study 235 (SH-FEH-0025)

Felodipine Extended release (ER) 5.0 mg study supplies were provided as blistered, unit-dose tablets. One blistered tablet was provided in a 75 cc bottle incorporating a child-resistant cap. Felodipine was also provided as a solution. This solution contained felodipine at a concentration of 1 mg/ml, containing 0.1 ml of ethanol per 1 ml of solution, 10 ml of solution per bottle. A single, oral dose of felodipine ER 5.0 mg administered to school-age children and adolescents or a single, oral dose of felodipine solution (2.69 mg/m²) given to infants and toddlers, and pre-school children. The dose of felodipine solution administered to each subject age 1 month to 6 years old was calculated based on body surface area in order to provide an exposure comparable to 5.0 mg felodipine ER administered to older subjects.

Study 216 (SH-FEH-0024) double blind (part A) and open label extension (part B)

Patient received felodipine 2.5mg, 5.0mg and 10 mg extended release tablets. The diameter is 8.5 mm for the 2.5 mg tablet, respectively 9 mm for both the 5mg and 10 mg tablets. Due to the prolonged release formulation properties, the tablets must not be divided, chewed or crushed. Consequently, individual dose adjustment was restricted to the fixed felodipine tablet strengths.

II.3 Non-clinical aspects

N/A.

II.4 Clinical aspects

The MAH submitted reports for:

- US No. 235 (SH-FEH-0025); A multicenter, open-label, single-dose study of the safety, tolerability and pharmacokinetics of felodipine in paediatric subjects.
- US No. 216 (SH-FEH-0024); Dose ranging, safety and tolerability trial of felodipine ER in paediatric patients; a multicenter, double-blind, placebo-controlled, randomized, parallel group trial with an open-label extension.

- In the original submission of this data to MHRA in 2004, a cumulative review of safety, including all clinical trials and spontaneous reports arising from off label use.

US No. 235 (SH-FEH-0025); A multicenter, open-label, single-dose study of the safety, tolerability and pharmacokinetics of felodipine in paediatric subjects.

➤ **Description**

Trail 235 was a multicenter, open-label, single dose study of the safety, tolerability and pharmacokinetics of felodipine in children aged 1 month to 16 years. 23 children were divided in to 4 groups according to age. The design included a one-week screening period and a 24-hour post-dose observation period in a hospital or Clinical Research Unit. The C_{max} (the observed maximum plasma concentration), T_{max} (the time of the first occurrence of C_{max}), the AUC (the area-under-the-plasma-concentration vs. time curve) and T_{1/2} (terminal elimination half-life) for felodipine were determined.

The safety variables included the assessment of adverse events, discontinuations due to adverse events, serious adverse events, and changes from baseline in physical examinations, vital signs, ECG and laboratory parameters.

➤ **Methods**

- **Objectives**

The study objective was to examine the safety, tolerability and pharmacokinetics of a single, oral dose of felodipine in paediatric subjects.

- **Study design**

School age children and adolescents (6-16 years old) received one 5.0 mg tablet of felodipine ER while infants, toddlers and pre-school children (1 month up to 6 years of age), received a single, oral dose of felodipine solution (2.69 mg/m²). The design included a one-week screening period and a 24-hour post-dose observation period.

Blood samples (1 ml for each time point) for analysis of total felodipine concentration were drawn at scheduled times over a twenty-four hour period. Subjects were seen for a follow-up visit 4 to 42 days after dosing.

- **Study population /Sample size**

The study population included: Group A: 5 infants and toddlers (1 month up to 24 months of age), Group B: 6 pre-school children (age 2 years up to 6 years old), Group C: 6 school-age children (age 6 years up to and including Tanner Stage 3) and Group D: 6 adolescents (Tanner Stage 4 up to and including 16 years old) of both sexes. A total of 23 subjects were dosed in the study.

- **Treatments**

School age children and adolescents (6-16 years old) received one 5.0 mg tablet of felodipine ER while infants, toddlers and pre-school children (1 month up to 6 years of age), received a single, oral dose of felodipine solution (2.69 mg/m2).

- **Outcomes/endpoints:**

Pharmacokinetics:

The Cmax (the observed maximum plasma concentration), Tmax (the time of the first occurrence of Cmax), the AUC (the area-under-the-plasma-concentration vs. time curve) and T1/2 (terminal elimination half-life) for felodipine were determined.

Safety:

The safety variables included the assessment of adverse events (AE), discontinuations due to adverse events, serious adverse events, and changes from baseline in physical examinations, vital signs, ECG and laboratory parameters. Tolerability was defined as the proportion of subjects who prematurely terminated the study due to adverse events.

- **Statistical Methods**

Pharmacokinetic parameters and safety data were summarized descriptively, as well as for Groups A, B, C, and D separately.

Summary statistics (mean, median and standard deviation) were calculated for plasma felodipine concentrations at each scheduled time point.

➤ **Results**

- **Recruitment/ Number analysed**

A total of 24 subjects were screened, 1 was excluded from dosing due to elevated liver enzymes and 23 subjects were dosed at a total of 3 investigative sites. All dosed subjects completed the study.

- **Baseline data**

The study population of 23 included the following:

	Description	Age	Number	Dose
Group A	Renal disease patients	1 month - 2 years	5	2.96mg/M2 sol
Group B	Healthy volunteers	2 – 6 years	6	2.96mg/M2 sol
Group C	Healthy volunteers	6 – 12 years	6	5mg xr tab
Group D	Healthy volunteers	12 – 16 years	6	5mg xr tab

All group A subjects were patients with renal disease, with or without hypertension. Groups B, C and D were healthy children. Groups A and B received felodipine solution (2.96mg/M2) while groups C and D received 5 mg felodipine tablets. Group A consisted of males only, and the other groups had an even distribution of subjects by gender.

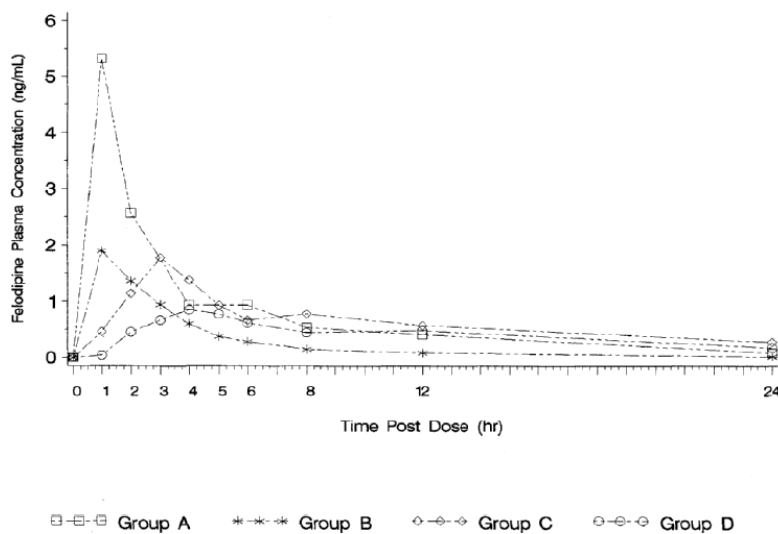
Group A was mainly Caucasian while groups B, C and D almost exclusively Hispanic. All subject in group A had a history of renal disease.

- **Pharmacokinetic results**

Parameters measured – Cmax, Tmax, AUC and T_{1/2}.

	A	B	C	D
Age (mean)	1.2	4.5	11.5	14.3
SD	0.6	0.8	1.8	1.0
Tmax	1.3	1.1	3.7	4.7
Cmax	4.16	1.82	2.03	0.95
Range	(1.64 - 12.8)	(0.94 - 2.32)	(1.68 – 2.29)	(0.36 – 1.79)
AUC	12.16	6.08	14.30	7.81
Range	(3.45 – 35.47)	(3.57 – 7.31)	(10.54 – 21.16)	(3.97 – 19.87)

FIGURE 1
Mean Felodipine Plasma Concentration Versus Time
(All Subjects)



Correlation of age with pharmacokinetics:

Groups A and B both had apparently quicker mean Tmax scores, reflecting the use of the extended release preparation in the other two groups. Cmax was also highest in group A, but patient in this group had renal pathology which might have affected this result. No age related changes were seen in either of these two groups.

The use of extended release felodipine in groups C and D was reflected in higher Cmax values compared to the other groups. Individual scatter plots of AUC, Tmax and Cmax overlapped suggesting that there were no age related differences in these parameters in

the two groups. Of the 23 subjects enrolled, 16 had sufficient data to calculate the half life.

	Half life (hrs)
Group A	4.3 hrs (SD 2.1) (range 4.4 – 8.2)
Group B	2.5 hrs (SD 0.6) (range 1.7 - 3.3)
Group C	7.6 hrs (SD 2.0) (range 4.9 – 9.6)
Group D	6.5 hrs (SD 5.0) (range 2.2 – 11.9)

The scatter plot of half life versus age for all 16 subjects showed no age related changes.

Safety results

There were no deaths or serious adverse events. There were 5 adverse events all occurring in the group A, all considered unrelated to felodipine. They included vomiting, coughing, rhinitis, otitis media and mild diarrhoea.

Summary of the study 235:

- There were differences in the baseline groups
- Subjects in the group A (1 – 24 months) all had renal disease and also were ethnically distinct from the other group.
- Subjects in groups A and B took 2.96 mg/M2 felodipine solution
- Subjects in groups C and D took extended release tablets
- There were no correlation of age with the half life across all age groups
- Comparison of the subjects in groups C and D showed the individual scatter plots overlapped suggesting that there were no trend between age and any particular pharmacokinetic parameter including C_{max}, T_{max}, AUC and T_{1/2}.
- There was a low incidence of adverse event with a single dose of felodipine. They were only seen in group A and were considered unrelated to felodipine.

US No. 216 (SH-FEH-0024); Dose ranging, safety and tolerability trial of felodipine ER in paediatric patients; a multicenter, double-blind, placebo-controlled, randomized, parallel group trial with an open-label extension.

➤ Description

Trail 216 was a 3-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group study (216A) to determine the antihypertensive dose range and efficacy in children and adolescents, followed by an optional, 14-week, open-label extension (216B) to investigate safety and tolerability of felodipine ER in hypertensive paediatric patients. The design included a 1- to 3-week screening phase, a 3-week double-blind treatment period and a 14-week optional open-label extension.

➤ Methods

- Objectives:

The purpose of this study was to investigate the antihypertensive dose range, efficacy, safety and tolerability of felodipine prolonged release in hypertensive paediatric patients.

- **Study design:**

This was a 3-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group study with an optional, 14-week, open-label extension to determine the antihypertensive dose range, efficacy, safety and tolerability of felodipine ER in hypertensive paediatric patients. Hypertensive school age children (age 6 – 12 years) and adolescents (12 – 16 years) of both sexes, that met the inclusion criteria, were randomized to once-daily felodipine ER 2.5, 5.0, and 10.0 mg or placebo. Patients randomized to 5.0 mg and 10.0 mg were titrated up from 2.5 mg dose to the target dose over a 1-week to 2-week period respectively. At the end of the 3-week double-blind period, all patients had the option to enter a 14-week open-label treatment period. On entering the open-label phase, all patients were given felodipine ER 2.5 mg once daily, that subsequently could have been titrated up to felodipine ER 10.0 mg once daily depending on the patient's blood pressure response. Patients were closely monitored and evaluated at least every week during the double-blind period, every 2 weeks during the up titration phase of the open-label extension period and every 4 weeks thereafter until the end of the study. Patients were seen for a follow-up visit two weeks after last receiving study medication.

- **Study population /Sample size**

The study population included 50.4% of school age children (age 6 – 12 years or \leq Tanner stage 3) and adolescents (>12 years or $>$ Tanner stage 3 – 16 years) of both sexes, as well as both black and non-black patients with reproducible sitting systolic or diastolic blood pressure (SBP or DBP), that fell at or above the 95th percentile for age and sex (height adjusted), on two consecutive visits during the screening period. A total of 133 patients with reproducible sitting systolic or diastolic blood pressure (SBP or DBP), that fell at or above the 95th percentile for age and sex (height adjusted), on two consecutive visits during the screening period.

Out of the 133 patients randomised to the first part of the study, 101 patients chose to enter the open-label part of the study (Study 216B).

- **Treatments**

133 patients recruited for the first part of the study, were randomized to one of the four, double-blind treatment groups: felodipine ER 2.5, 5.0, 10.0 mg or placebo, once daily. Patients randomized to 5.0 mg and 10.0 mg were titrated up from 2.5 mg dose to the target dose over a 1-week to 2-week period respectively. At the end of the 3-week double-blind period, all patients had the option to enter a 14-week open-label treatment period. On entering the open-label phase, all patients (n=101) were given felodipine ER 2.5 mg once daily that subsequently could have been titrated up depending on the patient's blood pressure response. Patients were closely monitored and evaluated at least every week during the double-blind period, every 2 weeks during the up titration phase of the open-label extension period and every 4 weeks thereafter until the end of the study. Patients were seen for a follow-up visit two weeks after last receiving study medication.

- **Outcomes/endpoints**

Efficacy

The primary measurement of antihypertensive efficacy was the change from baseline (last observation before randomization) in trough (24 ± 2 hours after dosing) sitting diastolic blood pressure at Week 3 (with the last observation carried forward) of the double-blind treatment period. Secondary analyses included assessments of trough sitting systolic blood pressure and trough standing and supine diastolic and systolic blood pressure, calculation of the proportion of responders and an analysis of the relationship between felodipine ER doses in change from baseline in trough sitting diastolic blood pressure.

Trough blood pressure (24 ± 2 hours after dosing) was measured (sitting, standing, and supine diastolic and systolic assessments) at every office visit in the open-label treatment period.

Safety:

The safety variables included the incidence of AEs, discontinuations due to AEs, serious AEs, and changes from baseline (Week 0) and open-label entry (Week 3) in physical examinations, vital signs, ECG and laboratory parameters. Tolerability was defined as the proportion of patients who discontinued the double-blind portion of the study due to AEs.

- **Statistical Methods**

The changes from baseline in each primary and secondary blood pressure efficacy variable were analyzed using analysis of covariance including the corresponding baseline value (the covariant), treatment and centre in the model.

Pair-wise comparisons of least squares means for each active treatment group were made with the placebo group with no adjustment for multiple comparisons. Ninety-five percent confidence intervals for the difference between the least squares mean change from baseline in each felodipine ER treatment group and the placebo group were also constructed.

To assess the dose response, a simple linear regression model was fit for the change from baseline in trough sitting diastolic blood pressure at Week 3 and for the change from baseline in trough sitting systolic blood pressure at Week 3 using the General Linear Models (GLM) procedure. The simple linear regression model included only linear and quadratic functions of the natural logarithm of the felodipine ER dose as independent variable (two separate models), with the placebo corrected change from baseline as the dependent variable.

➤ **Results**

- **Recruitment/ Number analysed**

Intension to treat (ITT) or last observation carried forward (LOFC) analysis was performed on a total of 133 patients who were randomized and included in the safety analysis. 132 had at least one treatment, while 125 completed the study protocol. The number of patients on felodipine was 98.

- **Baseline data**

A Summary of overall patient demographic and baseline characteristics by treatment groups, (all randomized patients) is provided below (Table 1):

Table 1

Characteristics	Placebo	F-ER 2.5 mg	F-ER 5.0 mg	F-ER 10.0 mg	Total
<u>Age (years)</u>					
n	35	33	34	31	133
Mean	12.2	12.4	12	11.8	12.1
SD	2.7	2.7	2.8	2.7	2.7
<u>Tanner Stage</u>					
n	35	33	34	31	133
Age 6 yrs – ≤ Tanner Stage 3	16 (45.7%)	16 (48.5%)	18 (52.9%)	17 (54.8%)	67 (50.4%)
≥Tanner Stage 4 – 16 yrs	19 (54.3%)	17 (51.5%)	16 (47.1%)	14 (45.2%)	66 (49.6%)
<u>Gender</u>					
n	35 (100%)	33 (100%)	34 (100%)	31 (100%)	133 (100%)
Male	20 (57.1%)	22 (66.7%)	19 (55.9%)	19 (61.3%)	80 (60.2%)
Female	15 (42.9%)	11 (33.3%)	15 (44.1%)	12 (38.7%)	53 (39.8%)
<u>Race</u>					
n	35	33	34	31	133
Black	14 (40%)	14 (42.4%)	14 (41.2%)	10 (32.3%)	52 (39.1%)
Non-Black	21 (60%)	19 (57.6%)	20 (58.8%)	21 (67.7%)	81 (60.9%)
Caucasian	20 (57.1%)	15 (45.5%)	17 (50%)	15 (48.4%)	67 (50.4%)
Asian	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (0.8%)
Other	1 (2.9%)	3 (9.1%)	3 (8.8%)	6 (19.4%)	13 (9.8%)
<u>Weight (lb.)</u>					
n	35	33	34	31	133
Mean	177.8	166.7	156.8	181.8	170.6
SD	75.6	64.0	56.3	63.0	65.2
<u>Criteria Sitting DBP</u>					
≥ 95% (Met)	28 (80.0%)	21 (63.6%)	23 (67.6%)	24 (77.4%)	96 (72.2%)
< 95% (Not Met)	7 (20.0%)	12 (36.4%)	11 (32.4%)	7 (22.6%)	37 (27.8%)
<u>Criteria Sitting SBP</u>					
≥ 95% (Met)	34 (97.1%)	28 (84.8%)	32 (94.1%)	27 (87.1%)	121 (91.0%)
< 95% (Not Met)	1 (2.9%)	5 (15.2%)	2 (5.9%)	4 (12.9%)	12 (9.0%)
<u>Criteria Both Sitting SBP and DBP</u>					
≥ 95% (Met)	27 (77.1%)	16 (48.5%)	21 (61.8%)	20 (64.5%)	84 (63.2%)
< 95% (Not Met)	8 (22.9%)	17 (51.5%)	13 (38.2%)	11 (35.5%)	49 (36.8%)

The sample population for this study was 60.2% male, 39.1% black, with an overall mean age of 12.1 years. Differences were identified in the baseline groups in terms of body weight and proportion of patients meeting the inclusion DBP or SBP criteria. Compared with the placebo group, the 2.5 mg felodipine dose group had less subjects how were $\geq 95^{\text{th}}$ percentile for BP distribution for both SBP and DBP. The 10mg dose group had the highest average body weight (181.8 ± 63 lbs.) and the 5 mg group had the lowest body weight, though this difference did not reach statistical significance. Otherwise the treatment groups were broadly similar.

- **Efficacy results**

**Part A, blind phase of the study-
The primary end point results**

The primary measurement of antihypertensive efficacy was the change from baseline in trough sitting diastolic blood pressure.

Efficacy measures

Table 2 below shows the least square means (LSM) and 95% confidence intervals for the change in trough sitting diastolic blood pressure for each treatment groups at week 3:

Table 2

Treatment group	N	LSM mmHg	95%CI
Placebo	35	-2.5	-5.9, -0.9
F 2.5mg	33	-4.5	-8.3, -0.8
F 5.0mg	33	-7.1	-10.8, -3.4
F 10mg	31	-1.2	-4.7, 2.4

Pair wise comparison

Table 3 below shows the pair wise comparisons based on placebo adjusted mean change in diastolic blood pressure at week 3:

Table 3

Treatment comparison	LSM	95%CI	p-value
F-ER 2.5mg dose vs. Placebo	-2.07	-6.82,2.69	0.3907
F-ER 5.0mg dose vs. placebo	-4.64	-9.18,-0.09	0.0456
F-ER 10mg dose vs. placebo	1.31	-3.5, 6.11	0.5909

No group achieved significant changes from baseline in sitting, supine or standing systolic pressure categories compared to placebo.

From the results presented in the dossier it appears that there is a significant difference compared to placebo with the 5 mg felodipine arm. However the *p* value is very close to 0.05.

Responder rate

Responders were defined as patients whose trough sitting diastolic and systolic blood pressure fell below the 90th percentile adjusted for age, height and sex. The proportion of responders in the three treatment groups ranged from 15.2% to 19.4%, as compared to 11.4% in the placebo group.

Subgroups and Dose-Response relationship

Only 2 subgroups, male and subjects aged 6-12 years showed significantly greater drops in blood pressure compared to placebo on pair-wise comparison (table 4).

Table 4

Sub population	F-ER 2.5mg vs. placebo LSM (p-value)	F-ER 5.0mg vs. placebo LSM (p-value)	F-ER 10.0mg vs. placebo LSM (p-value)
Age 6 years <=Tanner stage 3	-2.67 (0.5024)	-11.8(0.0047)	-1.39(0.7162)
>=Tanner stage4 – 16 years	-4.08 (0.2206)	1.11(0.7488)	2.61(0.4931)
Male	-2.64(0.4213)	-10.05(0.0047)	3.56(0.3049)
Female	-1.6(0.7807)	-2.05(0.6775)	0.68(0.9025)
Black	0.91(0.8351)	-3.36(0.476)	3.25(0.4865)
Non-black	-5.66(0.1303)	-5.88(0.1081)	0.85(0.8264)

However the regression analysis of these variables showed no significant correlation between dose and response.

- **Safety results**

Headache, respiratory infection and nausea were reported by $\geq 10\%$ of patients in the felodipine ER Total group. Headache, rhinitis and pharyngitis were reported by $\geq 10\%$ of patients in the placebo group. Oedema and leg oedema were uncommon (2%) and occurred in two patients, a single patient in each of the felodipine ER 2.5 and 5.0 mg groups, and was absent in the felodipine ER 10.0 mg group.

In the placebo group, 65.7% patients reported an adverse event while 65.3% of patients who received felodipine had an adverse event. There were no deaths or serious adverse events during the double-blind treatment period of this study. Only 1 of 98 patients

treated with felodipine withdrew from the double-blind phase of the study due to an adverse event.

Felodipine did not produce any clinically significant changes in haematology, blood chemistry and urinalysis vital signs and ECG findings of the paediatric hypertensive patients. There were no reports of orthostatic hypotension during the double blind phase of the study.

In summary, in hypertensive children 6 to 16 years of age, the tolerability profile of felodipine ER 2.5, 5.0 and 10.0 mg once daily was similar to that seen in adults, although peripheral oedema was uncommon.

Summary

- The efficacy of this felodipine preparation in lowering BP in children aged 6-16 years was not demonstrated. Confidence intervals were wide and overlapping, and though the value of placebo controlled mean differences in BP was highest for 5 mg dose, the p value for the significance was very close to 0.05. On recalculation of the p values for the published paper the p value was just over 0.05. Efficacy was neither proven nor disproven.
- In terms of percentage of patients whose trough DBP and SPB fell below the 90 percentile adjusted for sex, age and height, the percentages in the 3 treatment groups ranged from 15.2% to 19%, compared to 11.4% in the placebo group.
- The tolerability of felodipine was similar to that seen in adults.
- In general the BP responses of the subpopulation were variable across age, gender, race and doses of felodipine.
- This study was limited in that it excluded those with secondary hypertension- the larger group of children with hypertension.
- The study was also limited to those could not swallow the tablet. The extended release formulation precluded chewing or dividing of the dose.

Open label phase of the study

Base line results

The sample of the population for this study was 60.4% male and 36.6% black, with a mean age of 12.1 years; 47.5% were school age children (age 6, Tanner Stage 1 to Tanner Stage 3) and 52.5% were adolescents (Tanner Stage 4 and Tanner Stage 5 to 16 years old). From a total of 101 patients, 17 were in the Maximum Dose Received (MDR), (= 2.5 mg) group, 34 in the MDR (5<10 mg) group, and 50 the MDR (\geq 10 mg) group.

Results of the groups were analyzed depending on the final maximum dose received:

Table 5- Patient disposition:

	Overall	Maximum Dose Received ^a		
		F-ER 2.5 mg	F-ER 5 to <10.0 mg	F-ER ≥10.0 mg
Entered Open-Label ^b	101 (100.0%)	17 (100.0%)	34 (100.0%)	50 (100.0%)
Completed Open-Label ^{b,c}	82 (81.2%)	13 (76.5%)	25 (73.5%)	44 (88.0%)
Discontinued Open-Label ^b	19 (18.8%)	4 (23.5%)	9 (26.5%)	6 (12.0%)
Lack of Response	2 (2.0%)	-	-	2 (4.0%)
Adverse Event	3 (3.0%)	-	2 (5.9%)	1 (2.0%)
Consent Withdrawn	6 (5.9%)	2 (11.8%)	3 (8.8%)	1 (2.0%)
Lost to Follow-up	3 (3.0%)	1 (5.9%)	2 (5.9%)	-
Sponsor/Investigator Decision	5 (5.0%)	1 (5.9%)	2 (5.9%)	2 (4.0%)

Efficacy results covering 17 week study period

Trough blood pressures (24 ± 2 hours post dose) were measured (sitting, standing and supine DBP and SBP) at each visit in the open label treatment period.

Changes in the trough sitting DBP

From week 0 to week 3 there was a mean fall in DBP of 5.2 mmHg (SD 8.98) from week 3 to 17 there was a mean fall in DBP of 2 mmHg (SD 10.5), shown in table 6 below:

Table 6

		OL Entry (Week 3)	Week 5	Week 7	Week 9	Week 13	Week 17	Week 17 (LOCF)
Change from Baseline ^a (Week 0)	n	101	99	96	90	84	84	100
	Mean	-3.5	-3.6	-4.9	-6.2	-5.2	-5.0	-5.2
	SD	9.99	9.53	9.06	10.44	8.86	8.55	8.98
Change from OL Entry ^a (Week 3)	n	-	99	96	90	84	84	100
	Mean	-	-0.5	-1.9	-3.2	-2.1	-2.0	-2.0
	SD	-	10.13	11.48	11.38	9.66	10.71	10.50

The 14-week, open-label extension of the study showed that felodipine produced a small, sustained reduction in trough sitting diastolic blood pressure compared to baseline (Week 0) and a slight further reduction in trough sitting diastolic blood pressure compared to open-label entry (Week 3).

Changes in the trough sitting SBP

From week 0 to week 3 there was a mean fall in DBP of 4.5 mmHg (SD 8.02) from week 3 to 17 there was a mean fall in DBP of 0.6 mmHg (SD 8.39) shown in table 7 below:

Table 7

		OL Entry (Week 3)	Week 5	Week 7	Week 9	Week 13	Week 17	Week 17 (LOCF)
Change from Baseline ^a (Week 0)	n	101	99	96	90	84	84	100
	Mean	-4.3	-4.1	-4.8	-6.3	-6.1	-4.5	-4.2
	SD	8.29	8.13	7.94	8.39	8.18	8.02	8.57
Change from OL Entry ^a (Week 3)	n	-	99	96	90	84	84	100
	Mean	-	0.3	-0.5	-2.0	-2.3	-0.6	0.1
	SD	-	8.57	7.52	7.98	8.11	8.39	8.81

The open-label extension showed that felodipine ER produced a small, sustained reduction in trough sitting SBP compared to baseline (Week 0), but there was no further reduction in trough sitting systolic blood pressure reduction compared to open-label entry (Week 3).

Overall response rate

Responders were defined as patients whose trough DBP and SBP both fell below the 90th percentile adjusted for age, sex and height. Response rate was defined as the proportion of responders at week 17. The mean response rate was <9.5%.

Table 8- (%) of responders at week 17 by Maximum dose received group (ITT population)

	Maximum Dose Received (n = 84)		
	F-ER 2.5 mg	F-ER 5 to <10.0 mg	F-ER ≥10.0 mg
Responders ^a at Week 17			
Number per Group	14	25	45
Number of Responders	3	4	1
Percentage of Responders ^b	21.4%	16.0%	2.2%

The lowest response was seen with the ≥ 10 mg arm (2.2%) and the highest response was seen with the 2.5 mg arm (21.4%). These results show that patient how received the maximum doses of felodipine had the poorest response.

Subgroups

Changes in the trough sitting DBP and SBP appeared to be slightly lower in the younger children (tanner stage < 3) and males. Changes in the SBP and DBP were otherwise comparable across all groups.

Safety results of open label study

There were no deaths during the open-label phase of the study. One of 101 patients had a serious adverse event due to an exacerbation of nonspecific corneal ulcer that was considered unlikely to be related to study medication by the investigator's assessment.

A total of 3 of 101 (3.0%) patients withdrew from the open-label phase of this study due to headache/malaise, rash and syncope. The incidence of adverse events were 82.5%, 88.2% and 72.0% in the MDR (2.5 mg), (5 < 10 mg) and (\geq 10mg) groups respectively. There was however only one serious adverse event and 3 discontinuation due to adverse events.

Laboratory adverse events

Changes from base line and open label entry (week 3) to the final measure in haematology, biochemistry and urinalysis findings were small, and there were no clinically significant changes in mean lab values.

Table 9 - treatment emergent summary during open label study. Number (%) of patients.

Number (%) of Patients	Overall (n=101)	Maximum Dose Received ^a		
		F-ER 2.5 mg (n=17)	F-ER 5 to <10.0 mg (n=34)	F-ER \geq 10.0 mg (n=50)
With \geq 1 AE	80 (79.2%)	14 (82.4%)	30 (88.2%)	36 (72.0%)
With an SAE	1 (1.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Discontinued due to AE	3 (3.0%)	0 (0.0%)	2 (5.9%)	1 (2.0%)

Summary

- This part of the trial was uncontrolled and designed to be descriptive only in terms of efficacy. The safety results appeared to show no new or unexpected adverse events.
- 17-week treatment with felodipine produced a small reduction in the trough sitting diastolic blood pressure (approximately 5mmHg and this was mainly over the first 3 weeks) compared to baseline.
- The actual response rate to felodipine (defined above) was low – 21.4% in the lowest MDR (2.5 mg) group and 2% in the highest MDR (10 mg) group. (Approximately 9.5% of patients overall responded to therapy at week 17 and had both DBP and SBP controlled on felodipine).
- There were a large number of treatment emergent adverse events in all groups, but these may have been due to common childhood infections.

- There were no deaths and only one (unrelated) serious adverse event. There were 3 discontinuations due to adverse events in total, 2 in the 5 to <10mg MDR group, and 1 in the highest MDR (10 mg) group. These were headache, malaise, rash and syncope.

Spontaneous reports

The following cumulative review of safety, (including all clinical trials and spontaneous reports arising from off label use); has not been submitted by the applicant at this stage. In accordance with the ART 45 requirements, submission of PSURs and safety reviews are recommended but not compulsory. The MAH is in line with the regulation. However as it was included in the original package for US FDA Exclusivity and the consequent MHRA evaluation that formed PWG-CSM decision, it is briefly mentioned below:

This summary takes account of all spontaneously reported adverse events in children up till May 24, 2004. The total number of exposed children is unknown.

In MAH database there are 20 reports which include 47 events (between 1989 to 2002). In some of these reports there was no adverse event reported, e.g. 'overdose' could be the reported event term but the patient had no symptoms. 19 reports were medically confirmed and one was a consumer report.

Overdosage

There were 11 reports of overdosage, in 5 of which there were no symptoms. In those that did experience symptoms at all, the children experienced mainly symptoms like hot flushes, hypotension and increased heart rate. All patients recovered.

Other spontaneous reports

These were all listed SmPC side effects, except for paradoxical hypertension seen in a 17-year-old male patient with a glomerulonephritis and five concomitant drugs. He recovered 2 days later.

There were 4 case reports relating to maternal exposure during pregnancy. Of the 2 that lead to suspected teratogenesis, one of these was subsequently reclassified as not a skeletal malformation. The other case report involved a 42-year-old woman being treated with metoprolol, felodipine, losartan and hydrochlorothiazide during early pregnancy. Losartan was continued throughout the pregnancy. At week 36, a female baby was born with limb deformities w, pulmonary hypertension, 'hyperechogenic' kidneys, neonatal anuria, and respiratory distress. She died of respiratory failure on day 4. All 4 drugs were suspected according to the reporter.

Many of the spontaneously reported adverse events were non-serious. A majority of the patients, where outcome is documented, resolved or improved. Although the numbers are low, the types of events seem to be similar in adults and children.

II.4.2. Discussion of clinical aspects

On 10th of February, 2009 the Rapporteur circulated the day 70 assessment reports for the EU Worksharing Procedure for the assessment of paediatric data for felodipine. There were no specific questions raised by any of the MS to ask the company, hence no list of questions were drawn. However some of the concerned MSs responded to the Rapporteur's PPdAR and made comments and suggestions to the SmPC text. Three rounds of discussion ensued that led to an agreement on the proposed SmPC text.

On 15th of September 2009, the two main applicants have agreed with the proposed changes in general and requested a minor alteration.

Following concerned MSs endorsement of proposed SmPC changes, the EU worksharing procedure of paediatric data for felodipine was finalised on the 15 October 2009.

III. Rapporteur's overall conclusion and recommendation

➤ Overall conclusion

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy, it was concluded that the results of these studies do not support paediatric posology. None the less these findings should be briefly included in section 5.1 of the SmPC. However, the incorporation of detailed summaries of the efficacy data in section 5.1 of the SmPC will not be helpful to prescriber and might be over interpreted.

➤ Recommendation

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

Section 5.1

There is limited clinical trial experience of the use of felodipine in hypertensive paediatric patients. *In a randomised, double-blind, 3-week, parallel group study in children aged 6-16 years with primary hypertension, the antihypertensive effects of once daily felodipine 2.5 mg (n=33), 5 mg (n=33) and 10 mg (n=31) were compared with placebo (n=35). The study failed to demonstrate the efficacy of felodipine in lowering blood pressure in children aged 6-16 years.*

The long-term effects of felodipine on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy as therapy in

childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Section 5.2

*“In a single dose (felodipine **prolonged** release 5 mg) pharmacokinetic study **with a limited number of** children aged between 6 and 16 years **(n=12)** there was no apparent relationship between the age and AUC, C_{max} or half-life of felodipine.”*

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