

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205003Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY SECONDARY REVIEW

<b>NDA</b>	205003
<b>Submission date</b>	March 21, 2014
<b>Submission type</b>	Original, 505(b)(2) – Standard Review
<b>Brand Name</b>	Prestalia®
<b>Applicant</b>	Symplmed Pharmaceuticals, LLC
<b>Formulation</b>	Oral immediate release tablet
<b>Dosage strengths</b>	PERa/AMLb 3.5/2.5, 7/5, 14/10 mg
<b>Proposed doses &amp; regimen</b>	PERa/AMLb 3.5/2.5, 7/5, 14/10 mg Once-daily
<b>Proposed indication</b>	Treatment of (b) (4) hypertension
<b>Review Division</b>	Division of Clinical Pharmacology – 1 (OCP) Division of Cardiovascular and Renal Products (OND)
<b>Primary Reviewer</b>	Peter H. Hinderling, MD
<b>Secondary Reviewer</b>	Sudharshan Hariharan, Ph.D.
<b>Director DCP-1</b>	Mehul Mehta, Ph.D.

Symplmed is seeking approval of Prestalia®, a fixed-dose combination (FDC) of perindopril arginine and amlodipine besylate (PERa/AMLb) for the treatment of hypertension. The primary clinical pharmacology review was performed by Dr. Peter Hinderling. The aim of this secondary review is to provide an alternate view point on the clinical utility of the intermediate strength [PERa/AMLb 7/5 mg].

### Background

The applicant submitted two clinical trials in support of this FDC neither of which evaluated the efficacy or safety of the intermediate strength, PERa/AMLb 7/5 mg. Therefore, the primary reviewer made an attempt to provide an assessment of benefit-risk for the intermediate strength, based on the results of the two trials which evaluated the lowest and highest strength, respectively. Assuming a linear dose-response relationship for efficacy and safety, the primary reviewer interpolated the effect size for blood pressure reduction and incidence of peripheral edema for the intermediate strength. Based on Dr. Hinderling's review, the projected decrease in diastolic blood pressure (DBP) is about 2.5 mmHg and the increase in incidence of peripheral edema is about 2.3% going from the lowest to the intermediate strength. As the incidence of peripheral edema is relatively higher in women, Dr. Hinderling concludes "It is difficult to justify the use of the intermediate strength tablet given that the projected decrease in DBP of 2.5 mm Hg is accompanied by a projected increase in incidence of peripheral edema of 3.1% in females." For additional details, please refer to the primary clinical pharmacology review by Dr. Hinderling [NDA 205003, DARRTS date: 12/08/2014]

## Secondary reviewer summary

### Blood pressure lowering effect

The dose of perindopril and amlodipine in the intermediate strength [i.e., PERa 7 mg and AMLb 5 mg] lie in the linear range of dose-blood pressure lowering effect relationship for the individual components. Therefore, deriving the blood pressure lowering effect of the intermediate strength using a linear interpolation seems reasonable. However, the precision around the derived effect size is low, as this exercise was performed based on assuming a range of placebo values and is unadjusted for differences between trials.

### Dose-incidence of peripheral edema relationship for amlodipine monotherapy

The incidence of peripheral edema with use of amlodipine is known to be dose-dependent. However, based on the clinical trial experience accumulated thus far, the relationship does not seem to be simply linear. Table 1 shows the placebo corrected incidence of peripheral edema across various trials which evaluated amlodipine as monotherapy. The increase in incidence of peripheral edema with increase in amlodipine dose from 5 mg to 10 mg is significantly larger than the marginal increase observed from 2.5 mg to 5 mg amlodipine [Table 2, Norvasc®]. Moreover, the incidence of peripheral edema with amlodipine 5 mg as seen from various development programs seem to be low [ $\leq 3\%$ ]. Hence, in the current program, a linear interpolation for projecting the incidence of peripheral edema of the intermediate strength will provide an over estimate of the risk. This will result in a less favorable perception of the benefit-risk profile for the intermediate strength, PERa/AMLb 7/5 mg.

**Table 1:** Incidence of peripheral edema with amlodipine (monotherapy arms only) across various development programs

Trials	Placebo corrected incidence of peripheral edema (%)		
	AMLb 2.5 mg	AMLb 5 mg	AMLb 10 mg
Norvasc® [amlodipine]	1.2	2.4	10.2
Azor® [olmesartan+amlodipine]	--	1.3	15.9
Tekamlo® [aliskiren+amlodipine]	--	3.3	12.8
Twynsta® [telmisartan+amlodipine]	--	0.7	17.8
Exforge® [valsartan+amlodipine]	5.2	-0.4	11.4

'--' not evaluated

### Impact of RAS inhibitor on the incidence of peripheral edema when used in combination with amlodipine

There is trend for lower incidence of peripheral edema with FDCs utilizing amlodipine and a renin-angiotensin system (RAS) inhibitor when compared to amlodipine monotherapy. Table 2

compares the peripheral edema rates between amlodipine as monotherapy and when used in combination with a RAS inhibitor across various development programs. Clearly, there is a numerical decrease with peripheral edema rates for the combination across many development programs including that of Prestalia®. The protective effect of a RAS inhibitor towards peripheral edema when used in combination with a calcium channel blocker (CCB) has also been reported in the literature<sup>1</sup>. Makani and colleagues performed a metanalysis of 25 randomized controlled trials [N=17,206 patients] evaluating CCB either as monotherapy or in combination with a RAS inhibitor and showed that the combination reduces the risk of peripheral edema [risk ratio: 0.62; 95% CI: 0.53, 0.74] when compared to CCB monotherapy. Standard limitations of any metanalysis may exist with this finding, however, the trend for a decrease in peripheral edema with the combination of CCB and RAS inhibitor is in line with what is observed across various FDC development programs of amlodipine.

**Table 2:** Comparison of peripheral edema rates between amlodipine as monotherapy and when used in combination with a RAS inhibitor across various development programs

Trials	Placebo corrected incidence of peripheral edema (%)	
	Highest strength FDC	AMLb 10 mg
Azor® [olmesartan+amlodipine]	10.5	15.9
Tekamlo® [aliskiren+amlodipine]	12.6	12.8
Twynsta® [telmisartan+amlodipine]	11.3	17.8
Exforge® [valsartan+amlodipine]	5.9	11.4
Lotrel® [benazepril+amlodipine]	-0.1*	2.9*
Prestalia® [perindopril+amlodipine]	7.2†	12.5†

\*Data pooled across doses of amlodipine and FDC; Includes all edema

†Not corrected for placebo

### Conclusion

In summary, when used as initial therapy the intermediate strength represents a clinically relevant titration step, as it lies in the linear range of the dose-response curve for the individual components with no meaningful increase in incidence of peripheral edema. The intermediate strength seems to be a viable option for patients who need modest reductions in blood pressure to reach their goal, but are sensitive to peripheral edema. As the standard dose of amlodipine in females and elderly is 5 mg, it would be clinically meaningful to have a comparable FDC strength containing amlodipine 5 mg. Finally, due to beneficial effects of combining RAS inhibitor with a CCB, the intermediate strength may potentially alleviate peripheral edema concerns for patients who are not tolerable to amlodipine 5 mg.

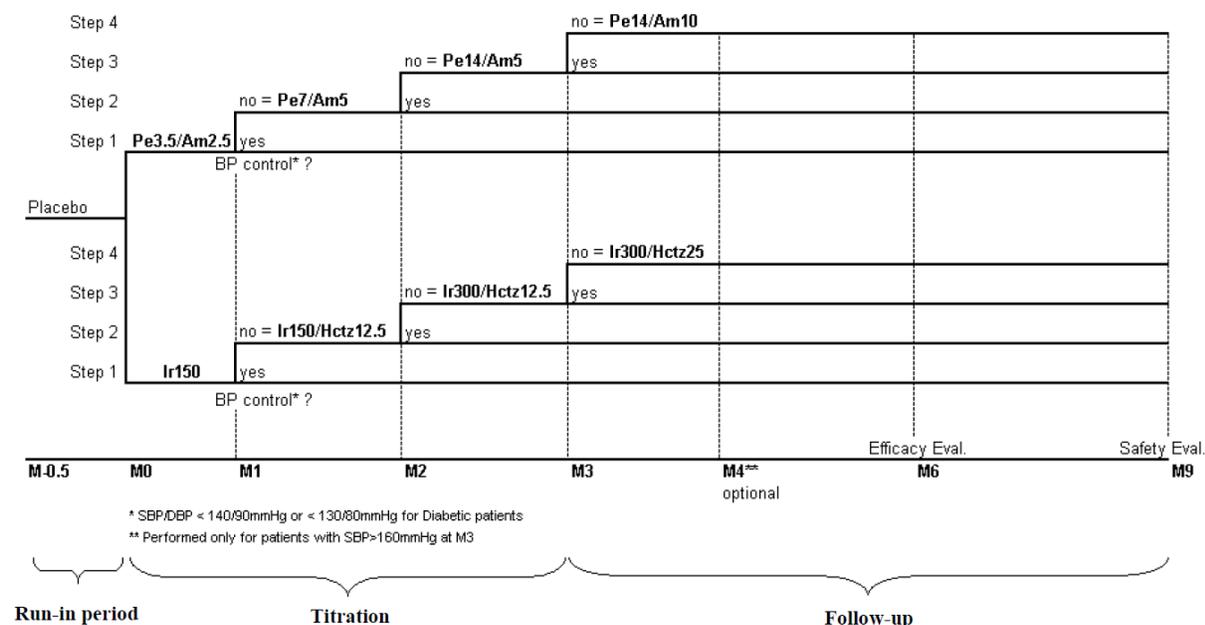
<sup>1</sup> Makani et al. *Am J Med*. 2011 Feb; 124(2):128-35

## Appendix

### CL3-05985-006: Preliminary results

The clinical utility of intermediate strength can further be substantiated based on results of trial CL3-05985-006, which the applicant submitted late in the review cycle [11/20/2014]. The primary objective of this trial was to assess the efficacy and safety of increasing doses of PERa/AMLb FDC in comparison to another commonly administered antihypertensive drug combination [irbesartan/hydrochlorothiazide] at different doses. For the purpose of this document, the focus will only be on the results obtained following treatment with PERa/AMLb FDC.

Briefly, the study enrolled approx. 3000 hypertensive patients who were treatment naïve [ $150 \text{ mmHg} \leq \text{SBP} < 180 \text{ mmHg}$  and/or  $95 \text{ mmHg} \leq \text{DBP} < 115 \text{ mmHg}$ ] or treated with no more than two antihypertensives and needed a change of medication due to lack of efficacy or poor tolerability [ $\text{SBP} < 165 \text{ mmHg}$  and  $\text{DBP} < 105 \text{ mmHg}$ ]. All patients entered a two week placebo run-in period, following which they were randomized to either of the two FDC groups. Following randomization, the patients entered a 9-month double-blind active treatment period with titration steps every month as outlined in Fig. 1. Primary efficacy variable was the proportion of patients with controlled blood pressure [supine  $\text{SBP} < 140 \text{ mmHg}$  and  $\text{DBP} < 90 \text{ mmHg}$ , or in diabetic patients as  $\text{SBP} < 130 \text{ mmHg}$  and  $\text{DBP} < 80 \text{ mmHg}$ ] measured at trough.



**Figure 1:** CL3-05985-006 study design

This review will focus on two key results – (i) change in blood pressure upon each dose increment of PERa/AMLb, and (ii) new incidences of peripheral edema upon each dose increment of PERa/AMLb. Table 3 shows the change in supine SBP following each dose increment compared to the previous step. It is clearly observed that the incremental change in

SBP [-4.4 mmHg] with an increase in dose from 3.5/2.5 mg to 7/5 mg is in line with the increment observed [-2.06 + -1.88 = -3.92 mmHg] when the dose is increased from 7/5 mg to 14/10 mg. The results are suggestive of the fact that the proposed intermediate strength lies in the linear portion of the dose-blood pressure lowering effect relationship substantiating the conclusion made earlier. The time confound with a titration design is negligible as maximum blood pressure reduction for this FDC is achieved by 4 weeks.

**Table 3:** Change in supine SBP with each dose increment

Period	PERa/AMLb dose increment	Change in supine SBP, mmHg [95%CI]
Baseline → M1	→ 3.5/2.5 mg	-14.13 [-14.75, -13.50]
M1 → M2	3.5/2.5 mg → 7/5 mg	-4.36 [-4.98, -3.74]
M2 → M3	7/5 mg → 14/5 mg	-2.06 [-2.63, -1.49]
M3 → M6	14/5 mg → 14/10 mg	-1.88 [-2.54, -1.23]

Adapted from CL3-05985-006 study report, table (11.1.2.2)1; full analysis set

Table 4 shows the new incidence of peripheral edema with each dose increment of this FDC. Clearly, the newer incidence of peripheral edema with dose increment from 14/5 mg to 14/10 mg is much greater in comparison to the newer incidence of peripheral edema at lower dose increments. These results are in line with the shape of the dose-incidence of peripheral edema relationship for amlodipine.

**Table 4:** New onset of peripheral edema with each dose increment

Period	PERa/AMLb dose increment	New onset of peripheral edema under each dose and not recovered under treatment period n (%)
Baseline → M1	→ 3.5/2.5 mg	36 (2.2)
M1 → M2	3.5/2.5 mg → 7/5 mg	27 (1.9)
M2 → M3	7/5 mg → 14/5 mg	26 (2.3)
M3 → M6	14/5 mg → 14/10 mg	125 (15.1)

Adapted from CL3-05985-006 study report, table (12.1.2.3)2; safety set

Therefore, the results from trial CL3-05985-006 show that the intermediate strength would provide a reasonably meaningful titration step in terms of blood pressure reduction without any significant increase in peripheral edema. The existing data support approval of this intermediate strength [PERa/AMLb 7/5 mg].

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/s/  
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SUDHARSHAN HARIHARAN  
12/08/2014

MEHUL U MEHTA  
12/08/2014  
I concur.

## CLINICAL PHARMACOLOGY REVIEW

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**NDA Number:** 205003  
**Submission Type:** 505 (b) (2)  
**Applicant Name:** Symplmed Pharmaceuticals  
**Submission Date:** March 21, 2014  
**Brand Name:** Prestalia®  
**Generic Name:** Fixed dose combination tablet of perindopril arginine (PERa) and amlodipine besylate (AMLb)  
**Dosage Form:** Immediate release tablets  
**Dosage Strengths:** PERa/AMLb 3.5/2.5, 7/5, 14/10 mg  
**Proposed Indication:** Treatment of <sup>(b) (4)</sup> hypertension  
**OCP Division:** DCP1  
**OND Division:** DCRP, HFD 110  
**Primary Reviewer:** Peter H. Hinderling, MD  
**Secondary Reviewer:** Sudharshan, Hariharan, PhD  
**Tertiary Reviewer:** Mehul U. Mehta, PhD

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### 1. EXECUTIVE SUMMARY

Symplmed submitted NDA 205003 for Prestalia®, a fixed dose combination (FDC) immediate release (IR) tablet of perindopril arginine (PERa) and amlodipine besylate (AMLb), for the indication treatment of hypertension. Amlodipine, a calcium channel blocker, and perindopril through its main metabolite, perindoprilat, an angiotensin converting enzyme inhibitor, reduce blood pressure.

The rationale for co-administering perindopril and amlodipine is the expectation that the effect of a combination of antihypertensive agents with different mechanisms of action will exceed the effect of either individual mono-component. The proposed FDC tablets of Prestalia are to be administered QD in doses of either PERa/AMLb 3.5/2.5, 7/5 or 14/10 mg. There are 3 strengths available that correspond to the proposed doses of Prestalia. The individual mono-components, the erbumine salt of perindopril (PERe) as ACEON and amlodipine besylate (AMLb) as NORVASC, are on the market in the US for the treatment of hypertension. FDC formulations containing perindopril arginine and amlodipine besylate are marketed outside of the US by Servier.

The development program for Prestalia consisted of 5 studies including 2 clinical trials investigating safety and antihypertensive efficacy using factorial designs and 3 pharmacokinetic studies, a food interaction study, a bioequivalence study and a drug interaction study. Only the Phase 3 study and the food effect study used to be marketed Prestalia FDC tablet, namely the highest strength which for clarity reasons is called XOMA FDC tablet (PERa/AMLb 14/10 mg) in the following. The Phase 2 study used the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) corresponding to the lowest strength.

The Phase 2 efficacy and safety study, using a parallel group, randomized, placebo controlled double-blind design administered placebo, the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) and Servier mono-component tablets (PERa 3.5, PERa 5, AMLb 2.5 and AMLb 5 mg) for 8 weeks to patients with mild to moderate hypertension without complications. The main Phase 2 study investigated the treatment effects on

office blood pressure (BP) at trough, whereas a sub-study determined the effect on ambulatory BP over a 24 h dosing interval. The Phase 3 efficacy and safety study using a randomized, double-blind, parallel group design, administered the highest strength XOMA FDC tablet (PERa/AMLb 14/10 mg), AUROBINDO tablets (PERe 2 x 8 mg), a generic version of ACEON, and NORVASC tablets (AMLb 10 mg) for 6 weeks to patients with mild to moderate hypertension possibly with target organ damage and diabetes. The primary endpoint in both studies was DBP.

The 3 pharmacokinetic studies used randomized cross-over designs and measured the exposure measures for perindopril, perindoprilat and amlodipine. The drug interaction study assessed the potential of a pharmacokinetic interaction among the mono-components when co-administered. The Servier FDC tablet (PERa/AMLb 14/10 mg) and the Servier mono component tablets (PERa 14 mg or AMLb 10 mg) were administered. The bioequivalence study used the Servier FDC tablet (PERa/AMLb 10/10 mg) and the Servier mono-components tablets (PERe 8 mg or AMLb 10 mg).

The Sponsor requested 3 Biowaivers: Biowaiver #1 for a comparative bioavailability study for a 505 (b) (2) NDA, Biowaiver #2 for a BE study to bridge data from studies using the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) and Biowaiver #3 for a dosage form equivalence study for the 3 strengths of to be marketed Prestalia. The sponsor provided results of cross-study comparisons on the biocomparability of perindopril, perindoprilat and amlodipine with the XOMA FDC tablet (PERa/AMLb 14/10 mg) relative to ACEON and NORVASC. The comparisons used the data from the food effect study and studies reported in the SBA of NDAs 20184 for ACEON and 22401 and 21540 for NORVASC.

The Clinical Pharmacology Review examined the 5 clinical studies submitted in the NDA and the findings from the cross-study comparisons. Of note, the Clinical Pharmacology Review was originally submitted to DARTTS on November 19, 2014, ahead of the deadline of November 21. The revised review submitted on December 6 includes the evaluation of the dose-effect relationship of study CL3-05985-006 submitted by the Sponsor on November 20, 2014.

## **1.1 Summary of Important Clinical Pharmacology Findings**

### **Issue**

The more than 2 fold increase in the exposure of perindopril, with the XOMA FDC tablet (PERa/AMLb 14/10 mg) relative to the referenced ACEON tablet (PERe 2 x 8 mg) is difficult to interpret. The cross-study approach used by the sponsor is known to be unreliable, because differences in assay, populations and conditions between the compared studies may affect the estimated bioavailability. Although the cause of the discrepancy is not certain, the observed discrepancy in exposure to perindopril and perindoprilat with the FDC tablet and the ACEON tablet is most likely explained by a difference in the bioavailability of perindopril and perindoprilat or a difference in the

accuracy between the assays resulting in systematically different concentrations of the analytes of interest or a combination of these causes.

## **PD Results**

- The baseline corrected antihypertensive effect of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) and the XOMA FDC tablet (PERa/AMLb 14/10 mg) were significantly greater than the effect of either mono-component. The lack of a placebo arm in the Phase 3 study impaired significantly the analysis of the dose-response relationship for the FDC tablets and the assessment of the not tested intermediate strength FDC tablet. The mean baseline and placebo corrected reduction of DBP with the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) is 4 mm Hg. Only rough estimates of the reduction in DBP with the highest strength XOMA FDC tablet (PERa/AMLb 14/10 mg) (9 mm Hg) and the intermediate strength FDC tablet (PERa/AMLb 7/5 mg) (6.5 mm Hg) can be provided.
- The placebo corrected incidence of peripheral edema (IPE) tends to increase with dose 0.1% [Servier FDC tablet (PERa/AMLb 3.5/2.5 mg)] vs. 4.6% [XOMA FDC tablet (PERa/AMLb 14/10 mg)]. The IPE with the highest strength XOMA FDC tablet (PERa/AMLb 14/10 mg) tends to be smaller (4.6%) than with NORVASC (AMLb 10 mg) (8.8%) calculated from the label. A rough estimate for IPE with the intermediate strength FDC tablet (PERa/AMLb 7/5 mg) is 2.3% for a population with equal representation of females and males. It is difficult to justify the use of the intermediate strength tablet given that the projected decrease in DBP of 2.5 mm Hg may be accompanied by a projected increase in IPE of 3.1% in females.
- About 80% of the full antihypertensive effect is seen after 2 weeks and the full effect is attained after 3 weeks with the FDC tablets administered QD.

## **PK Results**

- The cross-study comparison of amlodipine data from the food interaction study and a submitted published study indicated that the ratio of the mean exposures is within the BE limits. The sponsor had no right of reference to the data from studies reported in NDAs 22401 and 21540 for amlodipine.
  - No pharmacokinetic interaction takes place among perindopril, perindoprilat and amlodipine when co-administered
  - Food has no impact on the exposure measures for perindopril, perindoprilat and amlodipine
- The Servier FDC tablet (PERa/AMLb 10/10 mg) and the Servier mono-component tablets containing PERe 8 mg or AMLb 10 mg are bioequivalent for perindopril, perindoprilat and amlodipine. The results indicate that the arginine and erbumine salts of

perindopril are bioequivalent. The relevance of the findings is diminished because the bioavailability of perindopril erbumine with the Servier and ACEON tablets is unknown.

## 1.2 Recommendations

The Office of Clinical Pharmacology has reviewed NDA 205003. The more than 2 fold increase in absolute bioavailability of perindopril, respectively, with the XOMA FDC tablet (PERa/AMLb 14/10 mg) relative to the referenced ACEON tablet (PERe 2 x 8 mg) precludes bridging pharmacokinetic information on perindopril and perindoprilat from ACEON to Prestalia. Thus, the submission is only acceptable if the administration of Prestalia is restricted to those populations whose safety and efficacy was demonstrated in the Phase 2 and 3 studies. However, the special populations, elderly, patients with renal impairment (creatinine clearance < 60 mL/min), and patients with hepatic impairment or congestive heart failure, who were not enrolled in the Phase 2 and 3 studies, are to be excluded from the prescribing information. Only PK information on perindopril and perindoprilat obtained after administration of the XOMA FDC Tablet (PERa/AMLb 14/10 mg) should go in the label of Prestalia. A rationale is provided in the Appendix. PK information on amlodipine from the label of NORVASC can be used in the label of Prestalia.

## 1.3 Postmarketing Requirements

The sponsor is asked to conduct a standard bioequivalence study and determine the biocomparability of perindopril and perindoprilat with the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the ACEON tablet (PERe 2 x 8 mg) using validated specific and sensitive assays allowing a determination of AUC<sub>0-∞</sub> and C<sub>max</sub>. Confirmation of the bioequivalence of amlodipine with the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the NORVASC tablet (AMLb 10 mg) is highly desirable.

Peter H. Hinderling, MD  
Primary Reviewer

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Date \_\_\_\_\_

Sudharshan Hariharan, PhD  
Secondary Reviewer

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Date \_\_\_\_\_

Mehul Mehta, PhD  
Division Director, DCP1, OCP

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Date \_\_\_\_\_

The Clinical Pharmacology Briefing was held on November 14, 2014  
Attendees included: Drs. M. Mehta, R. Uppoor, A. Thompson, K. Hicks, V. Sinha, C. Jewell, T.-C. Wu, M. Wang, D. Menon-Andersen, R. Madabushi, S. Sabarinath, S. Hariharan, X. Wang

## 2 Question Based Review

### 2.1 General Attributes of the Drug

#### 2.1.1 History of Regulatory Development

IND 108233 for Prestalia was initially held by XOMA LLC. Symplmed obtained sponsorship of IND 108233 from XOMA LLC in 2013. Sponsorship of NDA 20184 was transferred from XOMA LLC to Symplmed on July 22, 2014.

Perindopril erbumine (ACEON) in doses of 2, 4, 8 <sup>(b) (4)</sup> mg is marketed by XOMA. Amlodipine besylate (NORVASC) in doses of 2.5, 5 and 10 mg is marketed by Pfizer.

#### 2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Prestalia is a combination of perindopril arginine and amlodipine besylate. Perindopril is an acid of pKa 3.8 and exhibits a log P of about 2.6. Amlodipine is a base of pKa 8.6 and a log P of about 3.0. The solubility of perindopril arginine in water is > 100 mg/mL. The highest dose of perindopril arginine is 14 mg and soluble in 250 mL water. The solubility of amlodipine besylate in water is 100 mg/mL at 25 °C.

The composition of the XOMA 985 FDC tablets and the Servier FDC tablets (S05985) is shown in the below table:

**Table 1. Formulation Comparison: EU S05985 FDC and US XOMA 985 FDC**

Ingredient	Tablet Strength Perindopril Arginine/Amlodipine (mg)					
	3.5/2.5 mg		7/5 mg		14/10 mg	
	S05985	XOMA 985	S05985	XOMA 985	S05985	XOMA 985
Perindopril arginine [perindopril free acid]	3.5 [2.38]	3.5 [2.38]	7 [4.76]	7 [4.76]	14 [9.51]	14 [9.51]
Amlodipine besylate [amlodipine free base]	3.47 [2.5]	3.47 [2.5]	6.94 [5]	6.94 [5]	13.87 [10]	13.87 [10]
Microcrystalline cellulose	(b) (4)					
Lactose						
Magnesium stearate						
Colloidal silicone dioxide						
Final tablet mass	52	52	104	104	208	208
Ratio (drug substance/total mass)						
Perindopril arginine	6.7%		6.7%		6.7%	
Amlodipine	4.8%		4.8%		4.8%	
EU = European Union; FDC = fixed-dose combination; US = United States. Sources: Module 3.2.P.2.2.1						

The composition of the 3 strengths of the XOMA FDC tablets and the Servier FDC tablets is proportionally similar. Each of the strengths of the XOMA- or Servier FDC tablets is compositionally proportional.

### **2.1.3 What are the proposed mechanism of action and therapeutic indications?**

The active metabolite of perindopril, perindoprilat, is an angiotensin converting enzyme (ACE) inhibitor. ACE is a dipeptidase catalyzing the conversion of the inactive angiotensin I to the vasoconstrictor angiotensin II. Amlodipine is a dihydropyridine calcium channel blocker acting as a peripheral arterial vasodilator by impacting vascular smooth muscle cells resulting in a reduction of peripheral vascular resistance.

The proposed indication for the combination product is treatment of (b) (4) hypertension.

### **2.1.4 What are the proposed dosages and routes of administration?**

The proposed oral dosages of Prestalia are PERa/AMLb 3.5/2.5 mg, 7/5 mg and 14/10 mg. Of note the doses of perindopril refer to perindopril arginine, whereas the doses of amlodipine refer to amlodipine base.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?**

The Phase 2 efficacy and safety study was a randomized, parallel group, double-blind, placebo-controlled study with a factorial design. The Phase 2 study contained a sub-study. The Phase 3 efficacy and safety study was a randomized, parallel group, double blind study with a factorial design. The food interaction and bioequivalence studies used open-label, randomized 2-treatment, 2-period-, 2-sequence, cross over designs. The drug-drug interaction study applied an open-label, randomized, 3- period, 3-treatment, 3-sequence cross-over design.

**2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

DBP and SBP when measured at rest in a defined body position are generally accepted surrogate endpoints for assessing the efficacy of antihypertensive drugs. The BP is measured by a cuff at the end of the dose interval or over an entire dose interval using an ambulatory BP device.

**2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

In the PK studies the main active components, perindoprilat and amlodipine, were measured in plasma. However, exposure in plasma for these compounds was not assessed in the 2 efficacy- and safety studies. Therefore, only dose-response information is available for the FDC- and mono-components tested.

**2.2.4 Exposure-Response**

**2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?**

**Phase 2 Study**

The primary endpoint of the Phase 2 study (CL2-05985-005) and the Phase 3 study (X985-400) is the reduction in baseline controlled DBP. However, in order to establish a dose-effect relationship, the baseline and placebo controlled reduction in DBP should be used. The baseline and placebo controlled effect on DBP was obtained by subtracting the mean placebo value from the mean baseline corrected effect. The Phase 2 main and ancillary studies measured antihypertensive efficacy and safety of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) and the Servier mono-component tablets (PERa 3.5, PERa 5, AMLb 2.5 and AMLb 5 mg). The main Phase 2 study measured office DBP and SBP at trough. The ancillary Phase 2 study measured ambulatory DBP and SBP over a dose interval. The Phase 3 efficacy- and safety study measured office DBP and SBP at trough after administration of the XOMA FDC tablet (PERa/AMLb 14/10 mg); the AUROBINDO tablet (PERe 2 x8 mg) and NORVASC tablet (AMLb 10 mg). Of note PERe 16 mg corresponds to PERa 20 mg.

The antihypertensive treatments effects on the primary endpoint, DBP, seen in the Phase 2 and 3 studies are listed in the below tables. The first table shows the results obtained for the Phase 2 main study:

Table 2. Phase 2 Main Study: Comparison of the Antihypertensive Treatment Effects on Supine Diastolic Blood Pressure at Trough at Week 8

Treatment, mg	$\Delta$ DBP, mm Hg <sup>a</sup>	$\Delta\Delta$ DBP, mm Hg <sup>b</sup>	% $\Delta\Delta$ DBP <sup>c</sup>
PERa/AMLb 3.5/2.5	13.6 (9.2)	4.3	100
Placebo	9.3 (9.2)	0	0
PERa 3.5	9.7 (9.9)	0.4	9
AMLb 2.5	10.3 (9.7)	1.0	23
PERa 5	10.5 (9.7)	1.2	28

AMLb 5	12.6 (8.9)	3.3	77
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<sup>a</sup> mean (SD) baseline corrected effect on DBP <sup>b</sup> baseline and placebo corrected effect on DBP <sup>c</sup> baseline and placebo corrected effect of the mono-components in % of the effect of the Servier FDC tablet (PERa/AMLb 2.5 mg)

Of note in establishing the dose-effect relationship bioequivalence for perindopril, perindoprilat and amlodipine among all formulations in the Phase 2 and 3 studies is assumed. The results of the Phase 2 main study indicate an inter-subject variability of 70 to 100 % (% coefficient of variation about the mean) in the baseline corrected DBP values. The baseline corrected antihypertensive effect of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) is statistically significantly greater than that of placebo and the Servier mono-component tablets containing PERa 3.5 and 5 mg and AMLb 2.5 mg. The effect of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) is not statistically significantly smaller than that of AMLb 5 mg or PERa 5 mg.

The mean effect size of the active treatments in reducing baseline and placebo controlled DBP ( $\Delta\Delta$ DBP) is small. Of the mono-components only AMLb 5 mg reduces DBP slightly more than 3 mm Hg. The respective baseline and placebo controlled mean effects of the mono-component tablets containing PERa 3.5 mg or AMLb 2.5 mg appear to be much smaller than the effect of the FDC tablet (PERa/AMLb 3.5/2.5 mg). However, the small size of the antihypertensive effect should be considered when interpreting these results. About 80% of the full antihypertensive effect is attained after 2 weeks of treatment and the full effect is seen after 4 weeks. Normalization of BP occurs in significantly more patients with the FDC tablet (PERa/AMLb 3.5/2.5 mg) (44%) than placebo (27%), PERa 5 mg (33%) and AMLb 5 mg (38%).

The below table shows the results of the Phase 2 ancillary study:

Table 3. Phase 2 Ancillary Study: Comparison of the Antihypertensive Treatment Effects on Ambulatory Diastolic Blood Pressure at Week 6

Treatment, mg	$\Delta$ DBP, mm Hg <sup>a</sup>	$\Delta\Delta$ DBP, mm Hg <sup>b</sup>	% $\Delta\Delta$ DBP <sup>c</sup>
PERa/AMLb 3.5/2.5	5.8 (8.3)	3.9	100
Placebo	1.9 (8.7)	0	0
PERa 3.5	3.7 (9.2)	1.8	46
AMLb 2.5	3.0 (7.1)	1.1	28
PERa 5	3.6 (7.8)	1.7	44
AMLb 5	5.9 (7.8)	4.0	103

<sup>a</sup> baseline corrected effect on DBP <sup>b</sup> baseline and placebo corrected effect on DBP <sup>c</sup> baseline and placebo corrected effect of the mono-components in % of the effect of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg)

The ancillary study confirms that the baseline corrected effects on DBP are subject to a large inter-subject variability ranging from 140 to 300%. The baseline corrected antihypertensive effects of the treatments are consistently smaller than in the main study indicating a smaller placebo effect when ABPM instead of office BP is measured. The

baseline corrected effect of the FDC tablet (PERa/AMLb 3.5/2.5 mg) on DBP is statistically significantly greater than that of placebo, PERa 3.5 and PERa 5 mg and AMLb 2.5 mg.

The respective baseline and placebo corrected effects of the Servier mono-component tablets (PERa 3.5 mg or 2.5 mg AMLb) are clearly smaller than the effect of the FDC tablet (PERa/AMLb 3.5/2.5 mg) confirming the results of the main Phase 2 study that the antihypertensive effect of the FDC tablets exceed that of each of the mono-component tablets.

The sum of the individual effects with the mono-components expressed in % of the effect with the FDC tablet appears smaller than 100 % in the main and ancillary Phase 2 studies suggesting a possible supra-additivity of the effects of perindopril/perindoprilat and amlodipine when co-administered as shown below:

Table 4. Phase 2 Study: Comparison of the Antihypertensive Treatment Effects on Supine Diastolic Blood Pressure by the Fixed Dose Combination Tablet and the Mono-Component Tablets at Week 8

Study	Treatment, mg	$\Delta\Delta$ DBP mm Hg <sup>a</sup>	% $\Delta\Delta$ DBP mm Hg <sup>b</sup>
Phase 2 Main	PERa/AMLb 3.5/2.5	4.3	100
	PERa 3.5 + AMLb 2.5	1.4	33
Phase 2 Ancillary	PERa/AMLb 3.5/2.5	3.9	100
	PERa 3.5 + AMLb 2.5	2.9	74

<sup>a</sup> baseline and placebo corrected effect on DBP <sup>b</sup> baseline and placebo corrected effect of Mono-components in % of effect of FDC tablet

However, the findings with the lowest strength of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) (lowest strength) should be interpreted with caution, because they are based on mean values without an estimate of variability. Also, the doses of the Servier mono-component tablets elicited only small borderline effects.

### Phase 3 Study

The below table shows the results of the Phase 3 study:

Table 5. Phase 3 Study: Comparison of Antihypertensive Treatment Effects on Sitting Diastolic Blood Pressure by the Fixed Dose Combination Tablet and the Monocomponent Tablets at Week 6

Treatment, mg	$\Delta$ DBP, mm Hg <sup>a</sup>	Diff. DBP, mm Hg <sup>b</sup>
PERa/AMLb 14/10	15.7 (8.4)	
PERe 16 <sup>c</sup>	9.5 (8.8)	6.2
AMLb 10	13.2 (8.3)	2.5

<sup>a</sup> baseline corrected DBP <sup>b</sup> difference between placebo controlled effect with XOMA FDC tablet and AUROBINDO tablet or NORVASC tablet <sup>c</sup> corresponds to 20 mg PERa

The results of the Phase 3 study show that the baseline corrected effect of the XOMA FDC tablet (PERa/AMLb 14/10) on DBP is statistically significantly greater than the effects of ACEON (PERe 2 x 8 mg) or NORVASC (AMLb 10 mg). The effect of NORVASC (AMLb 10 mg) is significantly greater than that of AUROBINDO (PERe 2 x 8 mg) making amlodipine the main contributor to the antihypertensive effect of the XOMA FDC tablet (PERa/AMLb 14/10 mg).

The antihypertensive effect of the XOMA FDC tablet (PERa/AMLb 14/10 mg) after 3 and 6 weeks is similar suggesting attainment of the full reduction in BP occurs after 3 weeks. The number of responders (BP < 140/90 mm Hg or < 130/80 for diabetics) with the XOMA FDC tablet (PERa/AMLb 14/10mg) (52%) is greater than with ACEON (PERe 2 x 8 mg) (27%) and NORVASC (AMLb 10 mg) (38%).

### *Estimating the Placebo Effect*

The size of the placebo effect on DBP in the Phase 3 study is not known because the study was not placebo controlled. Consequently, a comparison of the results of the Phase 3- and Phase 2 studies based on baseline and placebo controlled values is significantly impaired. As a consequence delineating the dose-response relationship and estimating the incremental antihypertensive effects of the 3 proposed strengths of Prestalia have become a challenge. Attempts were made to estimate the unknown placebo effect of the XOMA FDC tablet (PERa/AMLb 14/10 mg) in the Phase 3 trial. To this end a range of plausible placebo effect values was identified from reviews of other antihypertensive drugs that had measured sitting or supine DBP at trough in double-blind, placebo controlled studies. Using the identified values for the placebo effect, ranges of baseline and placebo controlled treatment effects were then calculated for the XOMA FDC (PERa/AMLb 14/10 mg) -, ACEON- and NORVASC tablets. In a second plausibility check the so obtained baseline and placebo controlled effect values for the ACEON- and NORVASC tablets were then compared with those reported in their Package Inserts [ACEON (5-6 mm Hg reduction with 8 and 16 mg PERe) and NORVASC (7 mm Hg reduction with 5 and 10 mg AMLb)]. Estimated treatment effects for ACEON and NORVASC that agreed with those reported in the respective Package Inserts were considered plausible. The results of the attempts to estimate baseline and placebo controlled treatment effect for the XOMA FDC tablet (PERa/AMLb 14/10 mg) are summarized in the below table:

Table 6: Phase 3 Study: Estimating Difference between Treatment Effects

	<b>Assumed Placebo Effect, mm Hg</b>				
	9.3	8.2	6.2	4.2	2.6
<b>Treatment</b>	<b><math>\Delta\Delta</math> DBP, mmHg<sup>a</sup></b>				
PERa/AMLb 3.5/2.5	4.3	4.3	4.3	4.3	4.3
PERa/AMLb 14/10 <sup>b</sup>	6.4	7.5	9.5	11.5	13.1
PERe 16 <sup>c</sup>	0.2	1.3	3.3	5.3	6.9
AMLb 10	3.9	5.0	7.0	9.0	10.6
$\Sigma$ PERe 16 + AMLb 10	4.1	6.3	10.3	14.3	17.5

$\Delta$ PERa/AMLb 14/10 – 3.5/2.5	2.1	3.2	5.2	7.2	8.8
Supra-/infra-additive effect	2.3	1.2	-0.8	-2.8	-4.4

Red: Unlikely low or high baseline and placebo corrected DBP values <sup>a</sup> baseline and placebo controlled DBP <sup>b</sup> placebo corrected DBP of 5-6 mm Hg for ACEON (8 and 16 mg PERe) and 7 mm Hg for NORVASC (5 and 10 mg AMLb) reported in the respective Package Inserts <sup>c</sup> corresponds to 20 mg PERa

The most plausible range for the size of the placebo effect in the Phase 3 study appears to be between > 4.2 mm Hg and < 8.2 mm Hg. With a placebo effect in this range the estimated incremental antihypertensive effect of the XOMA FDC tablet (PERa/AMLb 14/10 mg) (highest strength) relative to the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) (lowest strength) is  $\geq 3.2$  mm Hg and  $\leq 7.2$  mm Hg, so that the reduction of DBP by the highest strength XOMA FDC tablet (PERa/AMLb 14/10 mg) is estimated to be about 9 mm Hg. Using linear interpolation the estimated reduction of DBP by the middle strength FDC tablet (PERa/AMLb 7/5 mg) is about 6.5 mm Hg. Thus, by increasing the dose from PERa/AMLb 3.5/2.5 mg to PERa/AMLb 7/5 mg or reducing the dose from PERa/AMLb 14/10 mg to PERa/AMLb 7/5 mg, DBP changes by  $\pm 2.5$  mm Hg. The estimates from this analysis should be considered as approximations. The projected increments agreed reasonable well with the measured increments of the antihypertensive effect in Study CL3-05985-006 when the dose of PERa/AMLb was increased correspondingly (see Appendix 2).

The uncertainty about the true value of the placebo effect limited the exploration of the type of interaction involved between perindopril and amlodipine with the highest strength XOMA FDC tablet (PERa/AMLb 14/10 mg)

#### 2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The below tables lists the incidence of peripheral edema (IPE) observed with the different treatments of the Phase 2 and 3 studies and reported in the label of NORVASC:

Table 7. Phase 3 Study. Mean Placebo Controlled Incidence\*<sup>^</sup> of Peripheral Edema in the Different Treatments

% Incidence of Peripheral Edema, n~ 273 per treatment		
PERe 16 mg	AMLb 10 mg	PERa/AMLb 14/10 mg
-1.1	9.5	4.6

\*Placebo controlled incidence of peripheral edema: 1.5% (mean of perindopril- and placebo treatments of Phase 2 and 3 studies) <sup>^</sup> equal numbers of males and females

Table 8. Phase 2. Study Mean Placebo Controlled Incidence\* of Peripheral Edema in the Different Treatments

% Incidence of Peripheral Edema, n~ 260 per treatment				
PERe 3.5 mg	PERe 5 mg	AMLb 2.5 mg	AMLb 5 mg	PERa/AMLb 3.5/2.5 mg
1.4	0	-0.8	3.4	0.1

\*Placebo corrected incidence of peripheral edema:1.5% (mean of perindopril- and placebo treatments in Studies 2 and 3) ^ equal numbers of males and females

Table 9. NORVASC: Mean Placebo Controlled Incidence of Peripheral Edema\*<sup>^</sup>  
Calculated from Label

Incidence of Peripheral Edema, n ~ 280 per active treatment		
AMLb 2.5 mg	AMLb 5 mg	AMLb 10 mg
0.2	1.0	8.8

\*Placebo corrected incidence of peripheral edema: 2.0% (mean of 2 placebo treatment ^ distribution of males and females not known)

The NORVASC label indicates that IPE is not zero in patients treated with placebo. Also, IPE is significantly greater in females than in males, whether they are receiving amlodipine or placebo. These findings suggest that IPE should be controlled for the placebo effect when comparing data from different studies with different treatments and populations with different sex distributions. From the data listed in the NORVASC label it can be calculated that the IPE for NORVASC is 3 times greater in females than in males. The NORVASC label also reports that IPE increases dose dependently in a population receiving treatments with 2.5, 5 and 10 mg amlodipine. The Phase 2 and 3 studies with the FDC tablets enrolled equal numbers of females and males. The IPE of patients receiving amlodipine treatments in the Phase 2 and 3 studies shows a dose dependency in agreement with the findings reported in the NORVASC label. The respective placebo corrected IPEs in patients receiving NORVASC (AMLb 10 mg or 5 mg) reported in the NORVASC label and the patients enrolled in the Phase 2 and 3 studies are comparable. The IPE with the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) (lowest strength) appears not to be different from placebo. The IPE of 4.5% with the XOMA FDC tablet (PERa/AMLb 14/10 mg) (highest strength) is lower than the IPE with NORVASC (AMLb 10 mg) in the Phase 3 study (9.5%) and the IPE calculated from the NORVASC label (8.8%]. This is a desirable trend. The difference in the IPE between the highest and lowest strengths of the FDC tablets is 4.5 % confirming the dose dependency of this undesirable effect caused by amlodipine containing products.

As discussed above, the middle strength of the FDC tablet (PERa/AMLb 7/5 mg) was not tested. In order to provide a rough estimate of the placebo corrected IPE for the intermediate strength FDC tablet, a linear interpolation was performed using the IPE

estimates for the lowest and highest strengths FDC tablets. The so calculated IPE is 2.3% for the intermediate strength FDC tablet.

The above estimated reduction of DBP by the intermediate strength FDC tablet (PERa/AMLb 7/5 mg) is about 6.5 mm Hg, compared to a reduction of 4 mm Hg by the lowest strength FDC tablet and 9 mm Hg by the highest strength tablet. Thus, by increasing the dose from PERa/AMLb 3.5/2.5 to PERa/AMLb 7/5 mg or reducing the dose from PERa/AMLb 14/10 mg to PERa/AMLb 7/5 mg, DBP changes by  $\pm 2.5$  mm Hg and IPE by  $\pm 2.3\%$ . Of note the above IPE estimates are for populations with equal numbers of females and males. For females the IPE for the intermediate FDC tablet is expected to be about 3.2 %. It is difficult to justify use of the intermediate strength tablet given that the projected decrease in DBP of 2.5 mm Hg is accompanied by a projected increase in IPE of 3.2 % in females.

#### ***2.2.4.3 Does this drug prolong QT/QTc Interval?***

No studies have been performed testing the impact of perindopril/perindoprilat or amlodipine on the QTc interval in in vitro- and in vivo dog models or in humans.

#### ***2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?***

The Sponsor, tacitly requesting primary use status for Prestalia, recommends initiation of treatment with the XOMA FDC tablet (PERa/AMLb 3.5/2.5 mg (lowest strength)). The Sponsor then recommends an upwards adjustment of the dose according to blood pressure goals. The sponsor has not provided a rationale for the clinical utility of the proposed intermediate strength tablet. The proposed dose interval of 24 h for Prestalia is appropriate.

#### ***2.2.5 What are the PK characteristics of the drug?***

*Perindopril/Perindoprilat:* The label for ACEON indicates that the PK of perindopril is dose proportional. Following absorption approximately 30 to 50% of systemically available perindopril is hydrolyzed to its active diacid metabolite perindoprilat and glucuronidated. The plasma protein binding of perindopril and perindoprilat is 60% and 15%, respectively. The apparent t<sub>1/2</sub> of perindopril is about 1 h. Perindoprilat peak plasma concentrations are attained 3 to 7 h after administration of perindoprilat. Perindoprilat is eliminated predominantly by the renal route. The terminal phase t<sub>1/2</sub> of 30 to 120 h reflects slow dissociation from plasma/tissue ACE binding sites.

*Amlodipine:* The label of NORVASC states that the PK of amlodipine is dose proportional and non-stereospecific. The plasma protein binding of amlodipine is about 93%. Amlodipine is extensively metabolized mainly by CYP3A with only 10% excreted unchanged in urine. Elimination of amlodipine is biphasic with a terminal t<sub>1/2</sub> of 30 to 50 h.

#### ***2.2.5.1 What are the single and multiple dose PK parameters?***

*Perindopril/Perindoprilat*: The label for ACEON states that following a QD dose regimen perindoprilat accumulates by a factor of 1.5 to 2 and attains steady-state in 3-6 days. The dosing interval is 12 or 24 h.

*Amlodipine*: Steady-state levels are reached after 7-8 days of a QD regimen. The dosing interval for amlodipine is 24 h.

#### ***2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?***

*Perindopril/Perindoprilat*: The label of ACEON states that the PK of perindopril/perindoprilat is not expected to be importantly different between mildly to moderately hypertensive patients with normal gastrointestinal, cardiac, renal and hepatic functions and healthy subjects of the same age group.

*Amlodipine*: The PK of amlodipine is not expected to be importantly different between mildly to moderately hypertensive patients with normal gastrointestinal, cardiac, renal and hepatic function and healthy subjects of the same age group.

#### ***2.2.5.9 How do the PK parameters change with time following chronic dosing?***

The label of ACEON does not indicate that the main parameters (CL/F, V<sub>ss</sub>/F and t<sub>1/2</sub>) of perindopril or perindoprilat are different after single and multiple dosing.

*Amlodipine*: There is no overt evidence that the main parameters (CL/F, V<sub>ss</sub>/F and t<sub>1/2</sub>) of amlodipine are different after single and multiple dosing.

#### ***2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?***

*Perindopril*: The inter-subject variability for AUC and C<sub>max</sub> expressed as coefficient of variation about the mean, CV, is 24% for perindopril and 30% for perindoprilat, respectively, in healthy subjects.

*Amlodipine*: The inter-subject variability for AUC and C<sub>max</sub> ranges between 20% and 35% and 20% and 30%, respectively, in healthy subjects.

Estimates for the intra-subject variability for perindopril, perindoprilat or amlodipine have not been reported.

### **2.3 Intrinsic Factors**

#### ***2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?***

*Perindopril/Perindoprilat*: The label of ACEON states that age (>65 y), renal impairment, hepatic impairment and heart failure increase exposure. However, the ACEON label does not provide information on the consequences of increased exposure on the response in these populations. The effectiveness of perindopril/perindoprilat in black patients is reduced when compared to non-black patients. However, no quantitative information is available.

*Amlodipine*: Age (> 65 y) and hepatic impairment increase exposure. However, there is no information on the consequences of increased exposure on the response in this population. The incidence of peripheral edema is increased in females relative to males.

The impact of a difference in exposure for safety is addressed in the individual sections below.

### **2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?**

*Perindopril:* The label of ACEON states that the usually effective dose range is 4-16 mg QD. However, the dose-response relationship is flat in the 8-16 mg dose range.

*Amlodipine:* The usually effective dose range is 5-10 mg QD.

*Prestalia:* A statistically significant antihypertensive effect is seen with doses between PERa/AMLb 3.5/2.5 mg and PERa/AMLb 14/10 mg. The inter-subject variability measured as % coefficient of variation about the mean reduction of the baseline corrected DBP ranges between 70 and 300%.

#### **2.3.2.1 Elderly**

*Perindopril/perindoprilat:* According to the ACEON label the exposure to perindopril and perindoprilat in the elderly is approximately twice that in younger patients. Initiation of therapy should use a small dose and titration should be slow. Experience with perindopril in elderly patients at daily doses exceeding 8 mg perindopril erbumine is limited.

*Amlodipine:* The exposure to amlodipine in the elderly is increased by 50% relative to young subjects. A lower initial dose of 2.5 mg may be required.

*Prestalia:* The cause for the discrepancy of the exposure of perindopril and perindoprilat between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and ACEON (PERe 2 x 8 mg) is uncertain. Thus, importing exposure measures reported in the label of ACEON into the label of Prestalia is inappropriate. Elderly patients who were not enrolled in the Phase 2 and 3 studies should be excluded from the prescribing information.

#### **2.3.2.2 Pediatric Patients**

*Perindopril/perindoprilat:* Effectiveness and safety of perindopril in pediatric patients have not been established.

*Amlodipine:* Amlodipine is effective in lowering blood pressure in patients 6 to 17 years of age. Body weight adjusted clearance and volume of distribution in children of age 6 to 17 years are similar to values in adults. Prestalia is not approved for use in the pediatric population. The sponsor requested a waiver for the conduct of studies with Prestalia in the pediatric population because the article “*does not present a meaningful therapeutic benefit over existing therapies for pediatric patients and the article is not likely to be used in a substantial number of pediatric patients*”.

#### **2.3.2.3 Race**

*Perindopril/perindoprilat:* The ACEON label states that the effectiveness of perindopril in black patients is smaller than in non-black patients.

*Amlodipine:* The NORVASC label does not indicate the impact of race on effectiveness.

*Prestalia:* The effectiveness of Prestalia is reduced in black patients.

#### **2.3.2.4 Renal Impairment**

*Perindopril/Perindoprilat:* The label of ACEON reports that the AUC of perindopril in patients with a creatinine clearance of 30 to 80 mL/min is about double that at 100 mL/min. When the creatinine clearance falls below 30 mL/min the increase in AUC is more marked. Perindoprilat elimination is decreased in renally impaired patients and an adjustment of the dose may be necessary in patients with renal impairment. Treatment with perindopril is not recommended in patients with creatinine clearance < 30 mL/min. The dialysis clearance of perindoprilat ranges between 40 and 90 mL/min.

*Amlodipine:* The NORVASC label states that renal impairment does not impact the exposure to amlodipine.

*Prestalia:* The cause for the discrepancy of the exposure of perindopril and perindoprilat between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and ACEON (PERe 2 x 8 mg) is uncertain. Thus, importing exposure measures reported in the label of ACEON into the label of Prestalia is inappropriate. Patients with renal impairment (CLcr < 60 mL/min) who were not enrolled in the Phase 2 and 3 studies should be excluded from the prescribing information.

### **2.3.2.5 Hepatic Impairment**

*Perindopril/perindoprilat:* The label of ACEON states that the bioavailability of perindoprilat is increased by 50% in patients with impaired hepatic function relative to healthy subjects or hypertensive patients with normal liver function. Perindopril should be titrated slowly in patients with severe hepatic impairment.

*Amlodipine:* According to the NORVASC label amlodipine is extensively metabolized by the liver and the plasma elimination t<sub>1/2</sub> is 56 h in patients with impaired hepatic function. A lower initial dose of 2.5 mg may be required.

*Prestalia:* The cause for the discrepancy of the exposure of perindopril and perindoprilat between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and ACEON (PERe 2 x 8 mg) is uncertain. Thus, importing exposure measures reported in the label of ACEON into the label of Prestalia is inappropriate. Patients with hepatic impairment who were not enrolled in the Phase 2 and 3 studies should be excluded from the prescribing information.

### **2.3.2.6 Sex**

*Perindopril/perindoprilat:* The ACEON label states that sex does not impact the effectiveness of perindopril/perindoprilat.

*Amlodipine:* The NORVASC label does not discuss the impact of sex on the effectiveness of amlodipine. The dose dependent incidence of angioedema in females is well documented.

*Prestalia:* The impact of sex on the pharmacokinetics of perindopril, perindoprilat and amlodipine is not known. No overt dependence of the antihypertensive effect of Prestalia on sex is seen. However, in females the incidence of peripheral edema is greater than in males.

### **2.3.2.7 Heart Failure**

*Perindopril/perindoprilat:* The ACEON label reports that the exposure to perindopril is increased by 40% in heart failure patients.

*Amlodipine:* The NORVASC does not discuss the impact of heart failure on the exposure to amlodipine.

*Prestalia:* The cause for the discrepancy of the exposure of perindopril and perindoprilat between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and ACEON (PERe 2 x 8 mg) is uncertain. Thus, importing exposure measures reported in the label of ACEON into the label of Prestalia is inappropriate. Patients with congestive heart failure who were not enrolled in the Phase 2 and 3 studies should be excluded from the prescribing information.

### ***2.3.3 What pregnancy and lactation use information is there in the label?***

*Perindopril/perindoprilat:* The label of ACEON states that the use of drugs affecting the renin-angiotensin system during the second and third trimester of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity. When pregnancy is detected, perindopril/perindoprilat should be discontinued as soon as possible. It is not known whether perindopril is secreted in human milk.

*Amlodipine:* The NORVASC label states that there are no adequate and well-controlled studies in pregnant women. Amlodipine should be used in pregnancy only if the potential benefit justifies the risk to the fetus. It is not known whether amlodipine is excreted in human milk. Nursing should be discontinued while amlodipine is administered.

*Prestalia:* Prestalia should not be used in pregnant women. Nursing should be stopped while Prestalia is administered.

## ***2.4 Extrinsic Factors***

### ***2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any difference in exposure on efficacy or safety responses?***

*Perindopril/perindoprilat:* The label of ACEON indicates that co-administered other drugs can impact the exposure to perindopril/perindoprilat. Also, co-administered other antihypertensive drugs can affect the response to perindopril/perindoprilat.

*Amlodipine:* The label of NORVASC indicates that co-administered other drugs can impact the exposure to amlodipine. Also, co-administered other antihypertensive drugs impacting BP can affect the response to amlodipine

*Prestalia:* Co-administered other drugs can impact the antihypertensive effect of Prestalia by changing the exposure of its constituents, perindopril, perindoprilat or amlodipine. Co-administered other antihypertensive drugs impacting BP can also affect the response to Prestalia.

### ***2.4.2 What are the drug-drug interactions?***

*Perindopril/perindoprilat:* The label of ACEON indicates that PK- and PD- based interactions of perindopril/perindoprilat with co-administered other drugs can occur.  
PK based interactions: Co-administered diuretics can reduce exposure to perindoprilat  
PD based interactions: Co-administered diuretics can increase the hypotensive effect of perindoprilat, potassium sparing diuretics (e.g. triamterene, amiloride, spironolactone, potassium supplements) and co-administered other drugs capable of increasing serum potassium (e.g. indomethacin, heparin, cyclosporine) can increase the risk of hyperkalemia, ACE inhibitors co-administered with lithium can increase serum lithium, Nitritoid reactions (facial flushing, nausea, vomiting, hypotension) have been reported

rarely in patients on therapy with injectable gold (aurothiomalate) and concomitant ACE inhibitor therapy including perindopril

*Amlodipine:*

PK based interactions: The label of NORVASC indicates that amlodipine increases the exposure to co-administered simvastatin 1.8 fold. Amlodipine also increases the exposure to co-administered cyclosporine 1.4 fold; Co-administration of the moderate CYP3A inhibitor diltiazem increases the exposure to amlodipine 1.6 fold and co-administered strong CYP 3A inhibitors (e.g. ketoconazole, itraconazole, ritonavir) are expected to increase the exposure to amlodipine more than 1.6 fold.

PD based interactions: None reported

*Prestalia:* The response to Prestalia is expected to be affected by all extrinsic factors that impact exposure or response to perindopril, perindoprilat or amlodipine listed above for the individual components.

***2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?***

PK based interactions:

*Perindopril/perindoprilat* and amlodipine: The labels of ACEON and NORVASC do not provide in vitro evidence to suspect possible in vivo interactions

***2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?***

*Perindopril/perindoprilat:* The ACEON label states that perindopril is primarily eliminated by Phase II enzymes. Perindoprilat is renally eliminated unchanged. There is no evidence supporting relevance of genetics for the disposition of perindopril/perindoprilat.

*Amlodipine:* The NORVASC label states that amlodipine is a substrate of CYP3A. There is no evidence supporting relevance of genetics for the disposition of amlodipine.

*Prestalia:* See Section 2.4.2.1. Prestalia is not expected to be impacted by Pharmacogenetics

***2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?***

*Perindopril/perindoprilat:* The label of ACEON does not indicate that perindopril or perindoprilat are inducers or inhibitors of CYP enzymes.

*Amlodipine:* The NORVASC label indicates that amlodipine is a weak CYP3A inhibitor.

*Prestalia:* Because of the component amlodipine, co-administration of simvastatin and Prestalia increases the exposure to simvastatin. Limit the dose of simvastatin in patients on Prestalia to 20 mg.

***2.4.2.4 Is the drug an inhibitor and/or an inducer of P-gp transport processes?***

*Perindopril/perindoprilat* and amlodipine: The ACEON and NORVASC labels do not indicate whether perindopril or perindoprilat are inhibitors or inducers of P-gp.

*Prestalia:* It is not known whether co-administered Prestalia can impact the exposure of P-gp substrates.

***2.4.2.5 Are there other metabolic/transporter pathways that may be important?***

Perindopril/perindoprilat: Unknown  
Amlodipine: Unknown  
Prestalia: Unknown

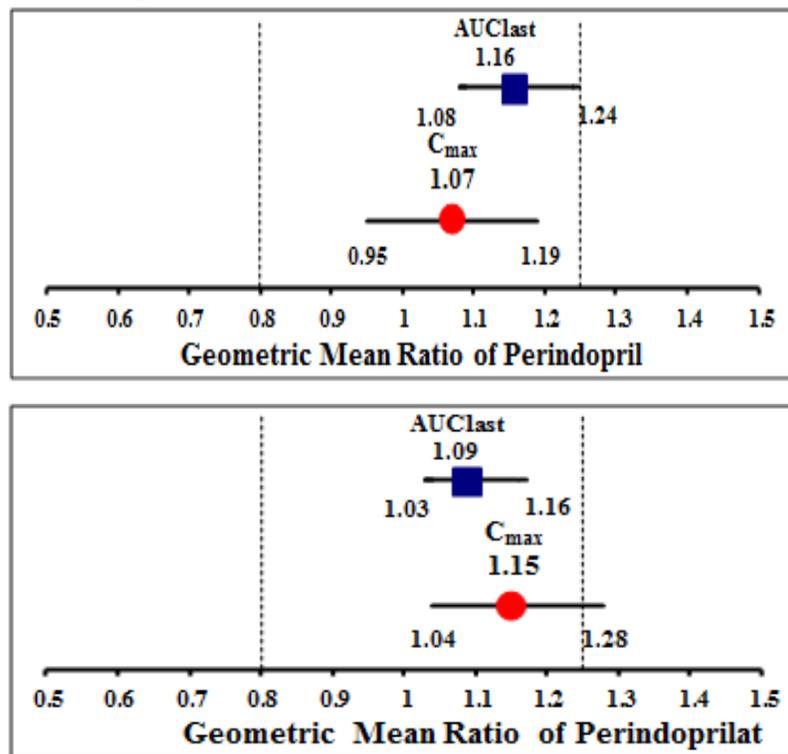
**2.4.2.7 What other co-medications are likely to be administered to the target population?**

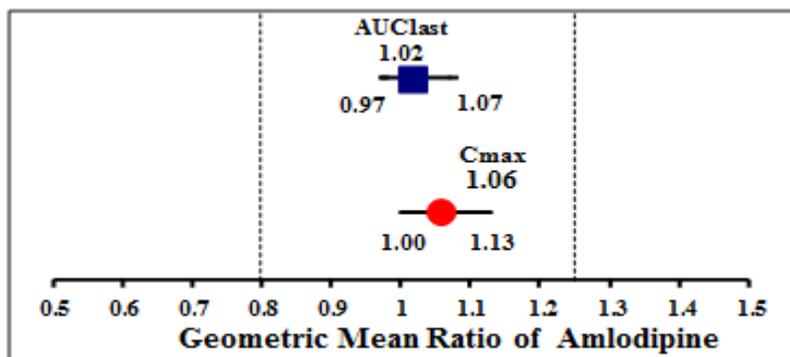
Diuretics, beta-blockers, anticoagulants, inotropes, statins, antidiabetics

**2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

A study in healthy subjects using a randomized, 3- period crossover design investigated the possible pharmacokinetic interaction between perindopril, perindoprilat and amlodipine after separate administrations of the Servier FDC tablet (PERa/AMLb 14/10) mg, and Servier mono-components tablets (PERa 14 mg or AMLb 10 mg). The results shown in the below figures indicate no significant PK based interaction between perindopril/perindoprilat and amlodipine:

Figure 1. Results of the Study Investigating a Possible Interaction between the Mono-components of the Servier FDC tablet (PERa/AMLb 14/10 mg)





Thus, the additive hypertensive effect of the FDC tablets used in the Phase 2 and 3 studies is entirely due to a pharmacodynamic interaction.

**2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

*Perindoprilat and amlodipine:* Co-administered antihypertensives with different mechanism of action are expected to exhibit additive effects.

*Perindopril/perindoprilat:* The ACEON label states that perindopril Can increase serum potassium levels and when co-administered with other drugs with hyperkalemic effects the impact on serum potassium can be additive. The mechanism responsible for the hyperkalemic effect of perindopril and other ACE inhibitors is a reduction in aldosterone levels.

*Amlodipine:* The NORVASC label does not provide evidence for a mechanism that could lead to a pharmacodynamically based interaction.

**2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?**

No

**2.4.2.11 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

The Phase 3 study was not placebo controlled making the task to estimate the antihypertensive effect and the incidence of peripheral edema for the untested intermediate strength tablet (PERa/AMLb 14/10 mg) challenging. Thus, only rough estimates for the efficacy and safety parameters can be provided. As discussed in Section 2.2.4.2 the use of the intermediate strength tablet is difficult to justify in females since the reduction in DBP of 2.5 mm Hg is accompanied by an increase in IPE of 3.2%

**2.5 General Biopharmaceutics**

**2.5.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

*Perindopril/perindoprilat:* The solubility of perindopril arginine in water is > 100 mg/mL. The highest dose of perindopril arginine is 14 mg and soluble in 250 mL water.

According to the label of ACEON the absolute bioavailability of perindopril erbumine is < 90 %. Perindopril erbumine is likely a BCS III compound.

*Amlodipine:* The solubility of amlodipine besylate in water is 100 mg/mL at 25°C. The highest dose of amlodipine besylate is 10 mg and soluble in 250 mL water. The absolute bioavailability of amlodipine besylate is < 90%. Amlodipine besylate is likely a BCS III compound.

***2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation relative to the service formulation used in the adequate and well controlled studies?***

The development program of Prestalia did not include an in vivo bioequivalence study of to be marketed XOMA FDC tablet (PERa/AMLb 14/10 mg). The sponsor requested a Biowaiver (Biowaiver # 1) for a relative bioavailability study comparing the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the mono components ACEON and NORVASC.

To determine the biocomparability of the Servier FDC tablet (PERa/AMLb 3.5/2.5 mg) and to be marketed XOMA FDC tablet (PERa/AMLb 14/10 mg) the sponsor provided dissolution data obtained at 3 pH values and requested a Biowaiver (Biowaiver #2). The acceptability of Biowaiver #2 is discussed in the ONDAQ review by Dr. S. Suarez.

An additional requirement was demonstration of bioequivalence of perindopril/perindoprilat and amlodipine among the 3 strengths of to be marketed XOMA FDC tablet. The sponsor provided in vitro dissolution data for perindopril, perindoprilat and amlodipine obtained at 3 different pH values and requested a Biowaiver (Biowaiver #3). The acceptability of the Biowaiver #3 is discussed in the ONDAQ review by Dr. S. Suarez.

**Cross-Study Comparison to Demonstrate Bioequivalence for Perindopril, Perindoprilat and Amlodipine between the XOMA FDC Tablet (PERa/AMLb 14/10 mg) and ACEON (PERe 16 mg) and NORVASC (AMLb 10 mg)**

NDA 205003, as a 505 (b)(2) submission, was to demonstrate bioequivalence of perindopril/perindoprilat and amlodipine between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the referenced ACEON tablet (PERe 2 x8 mg) and NORVASC tablet (AMLb 10 mg). The sponsor, requesting Biowaiver #1, provided estimates for the exposure measures obtained for perindopril/perindoprilat and amlodipine by cross-study comparisons of Study X985401, the food effect study (fasted state), conducted in 2013 with historic studies including Study MS 193 in NDA 20184 for perindopril/perindoprilat and studies reported in NDA 22401 and 21540 for amlodipine. Whereas the sponsor had the right of reference for study MS 193 for perindopril, they did not for the studies with amlodipine in NDA 22401 and 21540. The sponsor's submission contained a published study (Vincent et al., 2000) reporting on the exposure to amlodipine in the presence and absence of grapefruit juice after administration of NORVASC (AMLb 10 mg). However, the data from the Vincent study and the food interaction study did only allow calculation

of the geometric mean ratio and 90% confidence intervals for the AUC and C<sub>max</sub> values for amlodipine.

The results of the cross-study comparisons are shown below:

#### Perindopril/Perindoprilat

The dose normalized mean and peak exposures to perindopril with the XOMA FDC tablet (PERa/AMLb 14/10 mg) were 2.1 and 1.5 fold greater, respectively, than with the ACEON tablet (PERe 16 mg). The mean and peak exposures to perindopril were 1.2 and 0.83 fold greater, respectively, with the XOMA FDC tablet (PERa/AMLb 14/10 mg) than with the ACEON tablet (PERe 16 mg). Also, the bounds of the 90% confidence intervals about the geometric mean ratios of the exposure measures for perindopril and perindoprilat were outside of the bioequivalence limits as shown in the below schemes:

Figure 2. Biocomparability of Perindopril with the XOMA FDC Tablet (PERa/AMLb 14/10 mg) and the ACEON Tablet (PERe 2x8 mg)

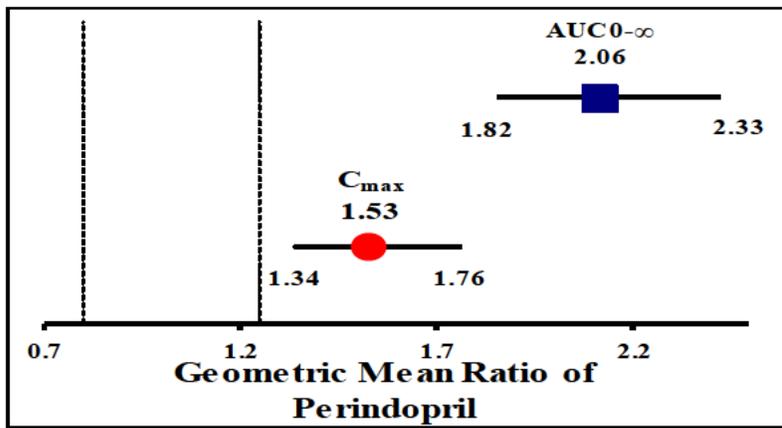
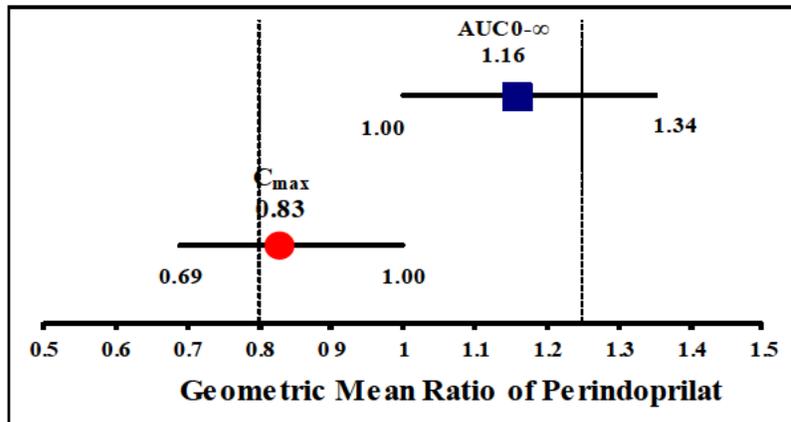


Figure 3. Biocomparability of Perindoprilat with the XOMA FDC Tablet (PERa/AMLb 14/10 mg) and the ACEON Tablet (PERe 2x8 mg)



Because the LC-MS/MS assay used in Study X985401 with the XOMA FDC tablet (PERa/AMLb 14/10 mg) was more sensitive than the capillary GC assay used in the ACEON (PERe 2 x 8 mg) study MS 193, the sponsor truncated the AUC values for perindopril and perindoprilat of Study X985401 prior to determining bioequivalence. Truncated AUC0-8 h for perindopril, and AUC0-48 h for perindoprilat were used in the cross-study comparison of the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the ACEON tablet (PERe 2 x 8 mg). Of note the plasma concentrations of perindopril were in the log linear terminal phase  $\geq 3$  h after administration so that it can be assumed that the absorption phase is completed. Therefore, the use of partial instead of total AUCs may not have introduced a major bias for perindopril. Truncation of the AUC for perindoprilat resulted in a loss of 30-40% of total AUC and may have contributed to the observed discrepancy in the exposure of perindopril between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the ACEON (PERe 2 x 8 mg) tablet.

In conclusion, the bioavailability estimates for perindopril and perindoprilat of the XOMA FDC tablet (PERa/AMLb 14/10 mg) relative to the ACEON tablet (2x 8 mg) obtained with the cross-study comparison are difficult to interpret. The use of cross-study comparisons to examine the bioavailability of different products violates the principle underlying the very assessment of bioavailability, namely the requirement to keep all variables, except the target variable, i.e. bioavailability, constant during the treatments. Therefore, cross-study comparisons are liable to bias. At this point the cause for the difference in exposure for perindopril and perindoprilat between the XOMA FDC tablet (PERa/AMLb 14/10 mg) is uncertain. Whereas the study conditions and populations appear not to be importantly different, the discrepancy in the exposure is more likely explained by a difference in the bioavailability of perindopril and perindoprilat or a difference in the accuracy between the two assays used resulting in systematically different concentrations of the analytes of interest. Also, a combination of these causes cannot be excluded. Only the results of a standard bioequivalence study that uses validated and sensitive assays can resolve this issue.

## Amlodipine

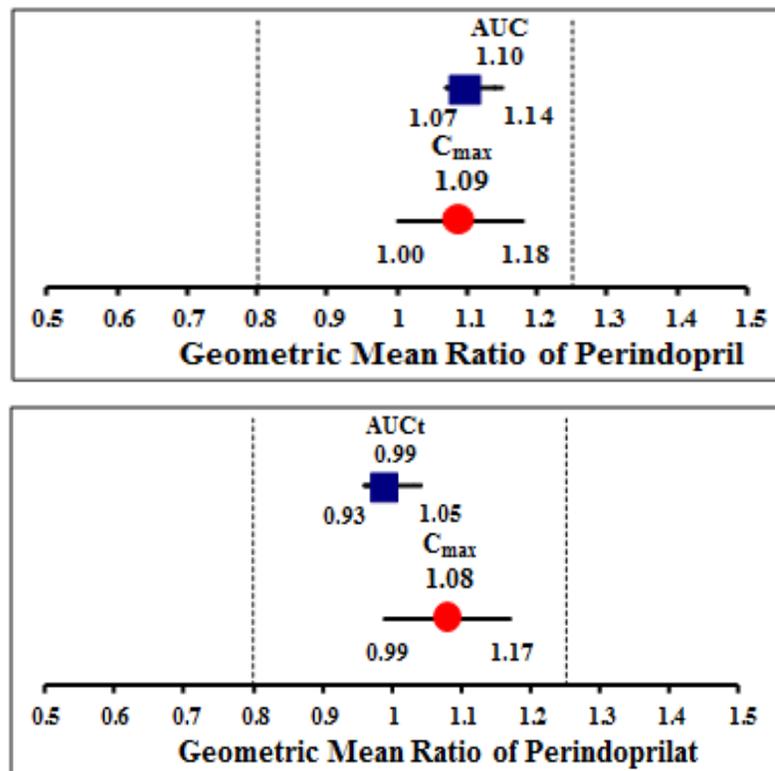
Using the exposure data from the published study by Vincent et al. 2000 and the food interaction study the respective ratios for AUC and C<sub>max</sub> was 1.01 and 0.95, respectively suggesting apparent bioequivalence for amlodipine between the XOMA FDC tablet (PERa/AMLb 14/10 mg) and the XOMA (AMLb 10 mg) tablet.

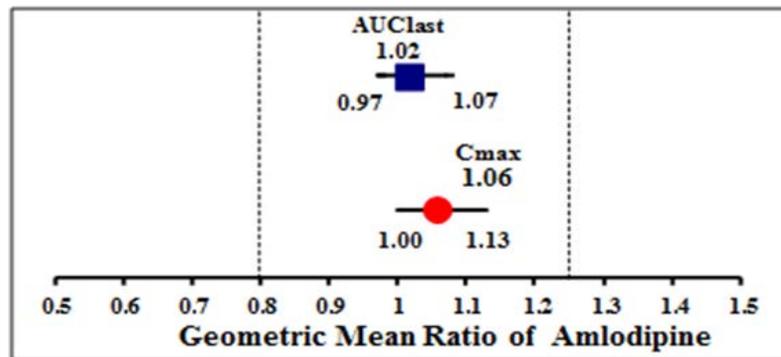
### Study Demonstrating Bioequivalence between the Servier FDC Tablet (PERa/AMLb 10/10 mg) and the Servier Mono-Component Tablets (PERe 8 mg or AMLb 10 mg)

The sponsor performed the in vivo Study PKH05985-001 to demonstrate the bioequivalence of perindopril, perindoprilat and amlodipine between the Servier FDC tablet (PERa/AMLb 10/10 mg) and the Servier mono-component tablets (PERe 8mg or AMLb 10 mg).

The results shown in the below figures indicate bioequivalence of the Servier FDC tablet and the Servier mono-component tablets for perindopril, perindoprilat and amlodipine:

Figure 4. Biocomparability of Perindopril, Perindoprilat and Amlodipine with the Servier FDC Tablet (PERa/AMLb 10/10 mg) and the Servier Monocomponent Tablets Containing PERe 8 mg and AMLb 10 mg)



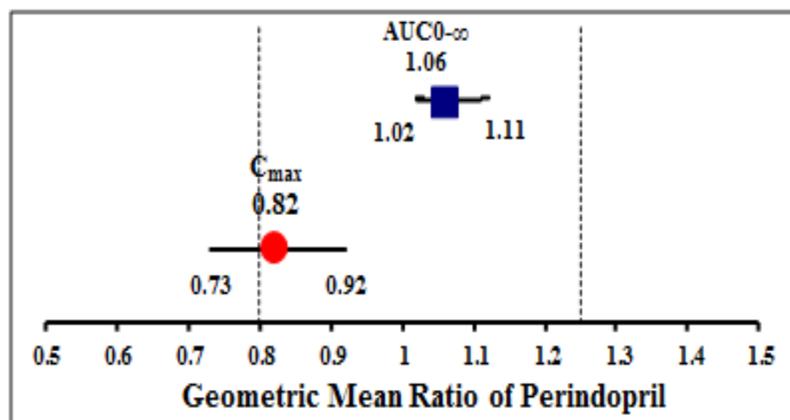


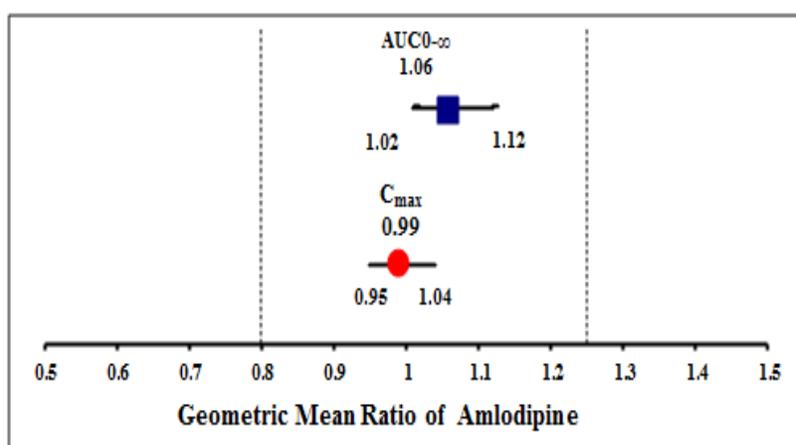
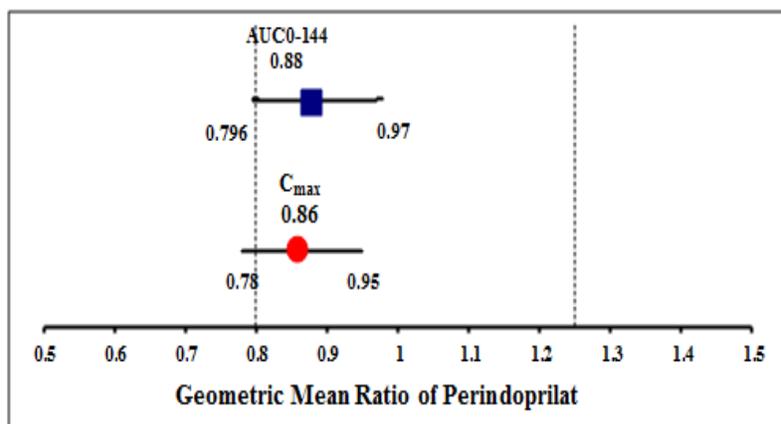
The findings from this study would be of greater value if the bioavailability of PERe from the Servier mono-component relative to ACEON were known.

**2.5.6 What is the effect of food on the bioavailability of the drug from the dosage form?**

Food appears not to have a relevant effect on the exposure measures of perindopril/perindoprilat or amlodipine with to be marketed FDC tablet (PERa/AMLb 14/10 mg) as shown by the below figures:

Fig. 5: Food Effect Study with the XOMA FDC (PERa/AMLb 14/10 mg Tablet





## 2.6 Analytical Section

### 2.6.1 How are the active moieties identified and measured in the plasma?

#### Studies X985401, PKH-05985-001 and PKH05985-009

Perindopril and perindoprilat in plasma were assayed by LC-MS/MS methods. The LC-MS/MS assays for perindopril and perindoprilat were validated in 2001 and 2003 and revalidated in 2007 by the same CRO <sup>(b) (4)</sup> that also analyzed the samples of Studies X985401, PKH-05985-001 and PKH05985-009, for perindopril/perindoprilat.

Amlodipine in plasma was assayed by LC/MS/MS methods. The LC/MS/MS assay used for study X985401 was validated in 2013 by <sup>(b) (4)</sup>.

#### Study MS-193

Perindopril and perindoprilat were measured in plasma by separate capillary GC methods. A validation report for the assay is not available.

#### Publication by Vincent et al. (2000)

Amlodipine in plasma was measured by GC-ECD. A validation report for the assay was not submitted.

**2.6.2 Which metabolites have been selected for analysis and why?**

Perindoprilat has been selected in all studies because it is responsible for the anti-hypertensive effect. No amlodipine metabolite was selected because all pharmacological activity is exerted by amlodipine.

**2.6.3 For all moieties measured, is free, bound, or total measured?**

Total concentrations of perindopril, perindoprilat and amlodipine were measured in all studies

**2.6.4 What bioanalytical methods are used to assess concentrations?**

See Section 2.6.1

**2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is the curve fitting technique?**

**Study X985401**

The range of the standard curve for both, perindopril and perindoprilat was 0.25 to 50.0 ng/mL and covered the therapeutic plasma concentrations range. Linear regressions ( $y = a + b \cdot x$ ) were fitted to the calibration curves for perindopril and perindoprilat using a reciprocal weighting function ( $1/x$ ) resulting in coefficients of determinations  $> 0.99$ . The range of the standard curve for amlodipine was 0.050 to 5.0 ng/mL and covered the therapeutic range. Analyte concentrations were measured using the internal standard method. The standard curves were calculated from the peak area ratio of amlodipine/internal standard using linear regressions ( $y = a + bx$ ) with  $1/x$  weighting

**Study PKH-05985-001**

The range of the standard curve was 0.25 to 50.0 ng/mL for perindopril and perindoprilat and covered the therapeutic range. The standard curves of perindopril and perindoprilat were fitted by linear regression with a mean correlation coefficient of = 0.999 and 0.998, respectively. The span of the standard curve for amlodipine was 0.050 -5 ng/mL which also covered the therapeutic range. The standard curves were fitted by linear regressions with a mean correlation coefficient of = 0.998.

**Study PKH-05985-009**

The span of the standard curve was 0.25 to 50.0 ng/mL for perindopril and perindoprilat and covered the therapeutic range of the plasma concentrations. The standard curves of perindopril and perindoprilat were fitted by linear regression with a mean correlation coefficient of = 0.999 and 0.999, respectively.

The span of the standard curve for amlodipine was 0.050 -5 ng/mL which covered the therapeutic range. The standard curves were fitted by linear regression with a mean correlation coefficient of = 0.997.

**Study MS 193**

The range of the pre-study standard curves for perindopril and perindoprilat ranged between 3-400 ng/mL and 1-80 ng/mL, respectively. This span does not cover the concentrations of perindopril and perindoprilat found after therapeutic doses of the ACEON tablet. The pre-study curves were obtained by linear regression analysis of the concentration vs. peak height ratio generated by assaying 6 seeded plasma samples. Regression analysis of the composite pre-study standard curve data was performed using 1/(y-variance) weighting. The correlation coefficients of the regression were > 0.997 for perindopril and perindoprilat. Duplicate seeded plasma controls at 3 selected concentrations were also assayed in the pre-study standards. During analysis of the study samples standard curves were established each day. Eight seeded controls from the same pools using the pre-study validation phase were run each day.

**Publication by Vincent et al. (2000)**

The LLOQ for Amlodipine was 0.2 ng/mL. The ULOQ was not indicated. The assay measured amlodipine over the entire therapeutic range. No information was provided regarding the curve fitting technique. The correlation coefficients obtained were > 0.998.

**2.6.6 What are the lower and upper limits of quantitation?**

**Study X985401**

The LLOQ and ULOQ were 0.25 ng and 50.0 ng/mL, respectively, for both perindopril and perindoprilat. The LLOQ and ULOQ was 0.050 and 5.0 ng/mL, respectively, for amlodipine.

**Study PKH-05985-001**

The LLOQ and ULOQ were 0.25 ng and 50.0 ng/mL, respectively, for both perindopril and perindoprilat. The LLOQ and ULOQ was 0.050 and 5.0 ng/mL, respectively, for amlodipine.

**Study PKH-05985-009**

The LLOQ and ULOQ were 0.25 ng and 50.0 ng/mL, respectively, for both perindopril and perindoprilat. The LLOQ and ULOQ was 0.050 and 5.0 ng/mL, respectively for amlodipine.

**Study MS 193**

The LLOQ and ULOQ were 0.25 ng and 50.0 ng/mL, respectively, for both perindopril and perindoprilat.

**Publication by Vincent et al. (2000)**

The LLOQ for amlodipine was 0.2 ng/mL. The ULOQ was not indicated.

**2.6.7 What are the accuracy, precision, and selectivity at these limits?**

**Study X985401**

#### Perindopril

The intra-assay accuracy ranged between -3.1 and 7.5%

The intra-assay precision was  $\leq 8.0\%$

The inter-assay accuracy ranged between -2.3 and 7.2%

The inter-assay precision was  $\leq 8.0\%$

#### Perindoprilat

The intra-assay accuracy ranged between -6.5 and 5.3%

The intra-assay precision was  $\leq 7.5\%$

The inter-assay accuracy ranged between -4.8 and 3.0%

The inter-assay precision was  $\leq 6.8\%$

The QC samples met the acceptance criteria.

Chromatograms for perindopril and perindoprilat were free of interfering peaks with blank human plasma from 6 independent sources

For perindopril 68 of 74 incurred samples reached the acceptance criteria (Two thirds of the samples repeated must be within 20% of the mean of original and repeat values). For perindoprilat 74 of 74 samples reached the acceptance criteria

#### Amlodipine

The inter-run accuracy ranged between -3.8 and -6.9%

The inter-run precision was  $\leq 6.6\%$

The intra-run accuracy ranged between -4.1 and -6.9%

The inter-run precision was  $\leq 4.2\%$

Chromatograms were free of interfering peaks with blank plasma from 6 independent sources. Samples spiked with 150 ng/mL perindopril and perindoprilat showed that the assay for amlodipine is selective.

For amlodipine 74 of 76 incurred samples reached the acceptance criteria (Two thirds of the samples repeated must be within  $\pm 20\%$  of the mean of original and repeat values)

### **Study PKH-05985-001**

#### Perindopril

The interassay accuracy ranged between -6.5 and -0.3%

The interassay precision was  $\geq 7.2\%$

#### Perindoprilat

The interassay accuracy ranged between -0.7 and 2.5%

The interassay precision was  $\leq 3.4\%$

#### Amlodipine

The interassay accuracy ranged between -3.1 and -0.1%

The interassay precision was  $\leq 7.3\%$

Chromatograms of perindopril, perindoprilat and amlodipine were free of interfering peaks with blank human plasma

#### **Study PKH-05985-009**

Perindopril

The interassay accuracy ranged between 3.0 and 7.0%

The interassay precision was  $\geq 4.0\%$

Perindoprilat

The interassay accuracy ranged between -2.9 and -1.1%

The interassay precision was  $\leq 3.2\%$

Amlodipine

The interassay accuracy ranged between -6.6 -1.4%

The interassay precision was  $< 6.2\%$

The QC samples met the acceptance criteria.

Chromatograms of perindopril, perindoprilat and amlodipine were free of interfering peaks with blank human plasma.

#### **Study MS 193**

Perindopril and Perindoprilat

For the standard curve at least 6 of the 8 standards were required to calculate to within  $\pm 15\%$  limits of their theoretical value, except at the lowest concentration where  $\pm 25\%$  limits were allowed. On each analysis day at least 6 of the eight seeded controls analyzed had to fall within the  $\pm 15\%$  acceptance criteria. Chromatograms of perindopril and perindoprilat were free of interfering peaks with blank plasma.

#### **Publication by Vincent et al. (2000)**

Amlodipine

The control samples were within  $\pm 10\%$  of the nominal concentrations.

#### **2.6.8 What is the sample stability under conditions used in the study?**

##### **Studies X985401, PKH-05985-001 and PKH-05985-009**

Reports demonstrate sample stability for perindopril, perindoprilat and amlodipine in the relevant matrices for studies X985401, PKH-05985-001 and PKH-05985-009.

Stability under stress conditions was concluded when the relative deviation from the nominal concentration and the first measurement were within  $\pm 15\%$ :

In plasma exposed to room temperature and laboratory light for 24 h

In plasma exposed to 5 ° C for 24 h

In plasma exposed to 6-12 freeze cycles at -20 ( $\pm 5$ ) ° C (freezing time for the first cycle was at least 12 h and thawing was at least 0.5 h)

In plasma exposed to -20 ° C for 1, 3 and 8 months

Extracted samples at autosampler conditions (ca. 10 ° C) and refrigerator conditions 5 ° C ( $\pm 3^\circ$  C)

The stability of perindopril glucuronide and perindoprilat glucuronide, 2 metabolites not measured in the PK studies performed by the sponsor, was also measured. Plasma samples of the glucuronides exposed to room temperature for 6 h are reduced by about 9% (perindopril glucuronide) and about 5% (perindoprilat glucuronide). In vivo the molar concentrations in plasma of perindopril glucuronide are between about 2 to fold greater than those of perindopril. Thus the average increase in perindopril from degraded perindopril glucuronide is about 10% which cannot account for the apparent more than 2 fold increase in perindopril with the XOMA FDC tablet in study X985401 relative to the ACEON tablet in study MS-193.

The stability of amlodipine was demonstrated under the following stress conditions:  
In plasma exposed to room temperature and light for 24 h  
In plasma exposed to -20 °C for 6 years in plasma (Reference study AAI Code EA004)  
In plasma exposed to 3 repeated freeze/thaw cycles  
In prepared samples at autosampler conditions at ~10 °C for 96 h  
In prepared samples at 5 (±3) °C for 96 h  
In extraction solvent at 5 °C for 24 h  
In extraction solvent at room temperature and 5 °C for 24 h  
In blood after storage for 1 h

### **Study MS 193**

No data on the stability of perindopril and perindopril were reported

### **Study by Vincent et al. (2000)**

No data on the stability of amlodipine were reported

### **2.6.9 What is the QC sample plan?**

Studies X985401, PKH-05985-001, PKH-05985-009, MS-193 and Publication by Vincent et al (2000): QC samples were analyzed along the samples with unknown concentrations of the respective analytes.

### **Reference**

1. Vincent J, Harris SI, Foulds G, Dogolo LC, Willavize S, Friedman HL. Lack of Effect of Grapefruit Juice on the Pharmacokinetics and Pharmacodynamics of Amlodipine. Br J Clin Pharmacol 2000, 50:455-463, 2000

## **Appendix 1. Rationale for Recommendation to Use only PK information on Perindopril and Perindoprilat Obtained by the LC-MS/MS Method in the Food Effect Study X985401**

The results of the cross-study comparison between the food effect study X985401 using a LC-MS/MS method and Study MS 193 using a capillary GC method points to the possibility that bioavailability estimates obtained with assays that are not cross-validated may be biased.

It appears that the capillary GC method of Study MS 193, presumably due to its limited sensitivity, was only rarely used in the applications of ACEON. The PK information reported in the label of ACEON must have been obtained with more sensitive assay(s) because terminal  $t_{1/2}$  values for perindopril and perindoprilat are quoted. However, nature, performance and validation of the assays that provided PK information in the ACEON label are not known. In the following this assay(s) is called “label assay”.

Arguments have been presented that the similarity of the respective mean  $t_{1/2}$  values of perindopril and perindoprilat in the label of ACEON (perindopril  $t_{1/2}$ : 0.8-1.0 h, perindoprilat  $t_{1/2}$ =30 -120 h) with those in the food effect study X985401(perindopril  $t_{1/2}$  = 1.3 h, perindoprilat  $t_{1/2}$ = 112 (53) h indicate equivalent performance of the LC-MS/MS and the “label assay” In other words similarity of  $t_{1/2}$  measured by two different assays indicates similarity of PK parameters describing distribution and elimination parameters such as V and CL. Therefore, it is appropriate to import PK information of perindopril and perindoprilat from the label of ACEON into the label of Prestalia. However, this conclusion is incorrect. The LC-MS/MS assay and the “label assay” were not cross-validated. There could be a difference in the accuracy between the two assays resulting in systematic differences in the levels of the analytes measured. If this were the case the respective  $t_{1/2}$  values of perindopril obtained by the LC-MS/MS method and the “label assay” could be similar even though the distribution and elimination parameters, V and CL, are different as shown below:

The  $t_{1/2}$  is defined by:

$$t_{1/2} = \ln 2 / k_e \quad (\text{I})$$

After transformation  $t_{1/2}$  can be redefined as:

$$t_{1/2} = \ln 2 \cdot V / CL \quad (\text{II})$$

Equation (II) indicates that  $t_{1/2}$  is a dependent variable defined by V and CL

In the following example perindopril measured by the LC-MS/MS method is (1) and perindopril measured by the “label assay” is (2). It is assumed that the concentrations of perindopril measured by the LC-MS/MS method are systematically 2 fold greater than with the “label assay”. The bioavailability is assumed to be the same:

$$F_{(1)} = F_{(2)}, CL_{(2)} = 2 \cdot CL_{(1)}, V_{(2)} = 2 \cdot V_{(1)}$$

Using the assumed values for F, CL and V for perindopril in Equation II yields  $t_{1/2(1)} = \ln 2 \cdot V_{(1)}/CL_{(1)}$  and  $t_{1/2(2)} = \ln 2 \cdot 2 \cdot V_{(1)}/[2 \cdot CL_{(1)}]$  which after cancelling terms becomes  $t_{1/2(2)} = \ln 2 \cdot V_{(1)}/CL_{(1)}$ . It follows that  $t_{1/2(1)}$  equals  $t_{1/2(2)}$ .

Thus, the respective  $t_{1/2}$  values for perindopril measured by the LC-MS/MS method and the ‘label assay’ are identical even though V and CL measured by the 2 assays are different.

In contrast, the respective AUCs measured by the LC-MS/MS method and the ‘label assay’ show the expected 2 fold difference in exposure to perindopril:

$$AUC_{(1)}/AUC_{(2)} = [F_{(1)}/F_{(2)}] \cdot D/[0.5 \cdot CL_{(2)}] / D/CL_{(2)} = 2 \quad (IV)$$

Thus, it is incorrect to conclude that a similarity of  $t_{1/2}$  of an analyte measured by 2 different assays implies equivalent assay performance and similarity of the respective distribution- and elimination parameters, V and CL. A cross-validation of the assays is required to support this interpretation.

In conclusion, complete information on the performance is only available for the LC-MS/MS method used in the food effect study X985401. The performance of the LC-MS/MS method measures well against today’s assay standards. Information on relevant PK information on perindopril and perindoprilat measured by the LC-MS/MS method is available from the food effect study X985401 and includes C<sub>max</sub>, t<sub>max</sub>, CL/F and V/F,  $t_{1/2}$  for perindopril and  $t_{1/2}$  for perindoprilat. Only parameters obtained by the LC-MS/MS method should be used for the label of Prestalia. The sponsor should cross-validate the ‘label assay’ with the LC-MS/MS assay so that the PK parameter in the present label of ACEON can be compared to those by the LC-MS/MS assay.

## **Appendix 2. Comparison of Projected and Measured Increments of the Antihypertensive Effect when the Dose of PERa/AMLb is Increased from 3.5/2.5 to 7.5 mg and from 7/5 mg to 14/10 mg**

Using data from Studies CL2-05985-005 and X985400 the increments of the antihypertensive effect were projected when the dose of PERa/AMLb was increased from 3.5/2.5 to 7/5 mg, from 7/5 to 14/10 mg and from 3.5/2.5 to 14/10 mg (see Section 2.2.4.1). Study CL3-05985-006 submitted on November 20, 2014, a Phase 3, multicenter, randomized, double blind study in two parallel groups of hypertensive patients using an

up-titration design actually measured the increments of the antihypertensive effect when the dose of PERa/AMLb was stepwise increased. Thus an abbreviated evaluation of Study CL3-05985-006 appeared to be in order. In that study the patients received during a 9 month treatment period according to their randomization group either PERa/AMLb in 4 possible dose steps (PERa/AMLb 3.5/2.5, 7/5, 14/5, 14/10 mg) or the irbesartan/hydrochlorothiazide combination (IRB/HCTZ) in 4 possible dose steps (IRB 150 mg, IRB/HCTZ 150/12.5, 300/12.5 mg, 300/25 mg) in a fixed titration regimen. In both groups, patients with non-controlled BP were up-titrated monthly step by step to reach BP targets. Included in the randomization set were 3270 patients (1617 in the PERa/AMLb group, 1653 in the IRB/HCTZ group). There was a run-in period with placebo of 2 weeks followed by a randomized treatment over 9 months. Patients were eligible for randomization if  $150 \text{ mm Hg} \leq \text{SBP} < 200 \text{ mm Hg}$  and/or  $95 \text{ mm Hg} \leq \text{DBP} < 115 \text{ mm Hg}$ , with both pressures lower than the upper limits. All patients started the randomized treatment at inclusion (M0 visit), on dose 1. At each monthly visit SBP and DBP were measured at trough: if BP was controlled, patients continued at the same dose as during the previous period; if BP was not controlled, treatments were up-titrated one step. M4 was an optional visit, only for patients up-titrated at M3 and with SBP > 160 mm Hg at M3. If the SBP at M4 or M6 was > 160 mm Hg, patients were withdrawn from the study.

### **Results**

The focus is on the measured increments of the antihypertensive effect of PERa/AMLb when the dose is up-titrated from 3.5/2.5 to 7/5 mg, from 7/5 to 14/10 mg and from 3.5/2.5 to 14/10 mg in Study CL3-05985-006.

Of the 1617 subjects randomized to receive the PERa/AMLb treatment 68.7% completed the study. The rate of withdrawal for adverse events was 22.8% largely due to peripheral leg edema and cough. The mean age of the patients in the randomized set was 62.6 (9.8) years with 41% aged more than 65 years, and were mostly men (63.3%). Overall, 42.3 % of patients presented with isolated systolic hypertension (ISH) which is a high percentage for a hypertensive population. The majority (57.7%) presented with systolic diastolic hypertension (SDH). A total of 8.4% of the patients had a history of leg edema. At baseline mean supine SBP was 163.1 (11.2) mm Hg and mean DBP was 82.9 (5.3) mm Hg in patients with ISH and 97.5 (5.3) mm Hg in patients presenting with SDH.

The below Table I lists the number of patients participating in each step of the up-titration regimen with PERa/AMLb:

Table I. Number (%) of Patients with Isolated Systolic Hypertension or Systolic Diastolic Hypertension Receiving Stepwise Up-titrated Doses of PERa/AMLb

	ISH	SDH
Baseline → PERa/MLb 3.5/2.5 mg	679 (100)	926 (100)
PERa/AMLb 3.5/2.5 mg → 7/5 mg	648 (95)	875 (94)
PERa/AMLb 7/5 mg → 14/5 mg	624 (92)	836 (90)
PERa/AMLb 14/5 → 14/10 mg	593 (87)	789 (85)

The large majority of the subjects was uptitrated to the highest dose level PERa/AMLb so that a comparison of the increments of the antihypertensive effect achieved by the different dose levels of PERa/AMLb is not expected to be significantly compromised.

The next two tables show the mean increments of the antihypertensive effect on DBP with different doses of PERa/AMLb in Study CL3-05985-006 (Table II) and those projected by combining information obtained from Studies X985400 and CL2-05985-005 (Table III):

Table II. Measured Mean Increments of Antihypertensive Effect of PERa/AMLb during Uptitration in Patients with Isolated Systolic Hypertension (ISH) and Systolic Diastolic Hypertension (SDH):

	ISH	SDH
Increase in Dose from → to	Increment in DBP, mm Hg	
PERa/AMLb 3.5/2.5 mg → 7/5 mg	2.1	2.5
PERa/AMLb 7/5 mg → 14/10 mg	1.7	2.6
PERa/AMLb 3.5/2.5 mg → 14/10 mg	3.8	4.8

Table III. Projected Mean Increments of Antihypertensive Effect of PERa/AMLb in Patients with Essential Hypertension

Increase in Dose from → to	Increment in DBP, mm Hg
PERa/AMLb 3.5/2.5 mg → 7/5 mg	2.5
PERa/AMLb 7/5 mg → 14/10 mg	2.5
PERa/AMLb 3.5/2.5 mg → 14/10 mg	5.0

The comparison shows a reasonable agreement between mean projected and measured increments in the antihypertensive effects on trough DBP by PERa/AMLb at corresponding dose levels. The percentage of patients with ISH and SDH in studies CL2-05985-005 and X985400 is not known.

Because there was a significant number of IPE that resulted in premature termination of patients, susceptible subjects were not up-titrated to the next higher dose level of PERa/AMLb resulting in a significantly IPEs. Such IPE values should not be used in

comparisons with studies that used designs that expose equal numbers of subjects to different dose levels of PERa/AMLb.

It conclusion, the measured increments of the antihypertensive effect in study CL2-05985-006 and those projected by combining information obtained from Studies X985400 and CL2-05985-005 are comparable when the dose of PERa/AMLb is increased from 3.5/2.5 to 7/5, from 7/5 to 14/10 or from 3.5/2.5 to 14/10 mg. Thus, the data from Study CL3-05985-006 justify the concerns expressed based on the projectons from Studies CL2-05985-005 and X985400 that the increment of the antihypertensive effect of the middle strength FDC tablets containing PERa/AMLb 7/5 mg is small.. Because of the fixed uptitration design used in study CL3-05985-005, the IPE values at the PERa/AMLb dose levels of 7/5, 14/5 and 14/10 mg represent underestimates and should not be used in comparisons with other studies.

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/s/  
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PETER HINDERLING  
12/06/2014

SUDHARSHAN HARIHARAN  
12/08/2014

Please refer to secondary reviewer memo for perspectives on the clinical utility of the intermediate strength (PERa/AMLb 7/5 mg).

MEHUL U MEHTA  
12/08/2014

I concur with the PMR. For clinical utility of the intermediate strength, please see my comment on the secondary review.

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
<b>NDA/BLA Number</b>	<b>205003</b>	<b>Brand Name</b>	<b>Prestalia®</b>
<b>OCP Division</b>	<b>I</b>	<b>Generic Name</b>	<b>Perindopril arginine/amlodipine fixed dose combination</b>
<b>Medical Division</b>	<b>DCRP</b>	<b>Drug Class</b>	<b>Antihypertensive</b>
<b>OCP Reviewer</b>	<b>Peter H. Hinderling, MD</b>	<b>Indication(s)</b>	<b>Treatment of (b) (4) hypertension</b>
<b>OCP Team Leader</b>	<b>Raj Madabushi, PhD</b>	<b>Dosage Form/Strengths</b>	<b>Fixed dose combination IR tablets, 3.5/2.5, 7/5, 14/10 mg</b>
<b>Pharmacometrics Reviewer</b>	—	<b>Dosing Regimen</b>	<b>3.5/2.5, 7/5, 14/10 mg QD</b>
<b>Date of Submission</b>	<b>3-21-2014</b>	<b>Route of Administration</b>	<b>Oral</b>
<b>Estimated Due Date of OCP Review</b>	<b>10-21-2014</b>	<b>Sponsor</b>	<b>Symplmed Pharmaceuticals</b>
<b>Medical Division Due Date</b>	<b>11-21-2014</b>	<b>Priority Classification</b>	<b>Standard 505(b)(2)</b>
<b>PDUFA Due Date</b>	<b>1-21-2015</b>		

## Summary

The sponsor Symplmed Pharmaceuticals (original sponsor XOMA) intends to market a new fixed dose combination (FDC) immediate release tablet for the treatment of (b) (4) hypertension. Prestalia® contains perindopril arginine (PERa) and amlodipine besylate (AMLb) in 3 strengths: PERa/AMLb 14/10, 7/5, and 3.5/2.5 mg. NDA 205003 is a 505(b) (2) submission relying in part on the efficacy and safety determinations of ACEON® (NDA 20184) and NORVASC® (NDA 19787). The mono-components, perindopril erbumine (PERe) in ACEON®, available in strengths of 2, 4, 8 or 16 mg and amlodipine besylate in NORVASC®, available in strengths of 2.5, 5 or 10 mg, are on the US market by XOMA and Pfizer, respectively. Whereas amlodipine is the active moiety, perindopril after administration is hydrolyzed to the active metabolite perindoprilat.

The sponsor performed 5 clinical studies with FDC tablets PERa/AMLb: 2 randomized, parallel group efficacy and safety studies and 3 pharmacokinetic studies. Also investigated in 4 of the 5 studies were mono-component tablets. Only 2 studies, including a Phase 3 efficacy and safety study and a food interaction study, were conducted in the US and administered to be marketed highest strength FDC tablet and ACEON and NORVASC as mono-components. Three (3) studies, including a Phase 2 efficacy and safety study, were conducted in Europe and used FDC tablets and mono-components manufactured by Servier in Europe.

Both efficacy and safety studies were double-blind, but only the Phase 2 study was placebo controlled. Over-encapsulated tablets were used in both efficacy and safety studies. The Phase 2 study investigated the lowest strength of the FDC tablet PERa/AMLb 2.5/3.5 mg, and the mono-components, 2.5 mg PERa, AMLb 3.5 mg, PERa 5 mg and AMLb 5 mg. The efficacy and safety studies appear to show that the lowest and highest strengths FDC tablets are more potent than the respective individual components. The combined effect is smaller than the sum of the effects of the individual components when administered separately suggesting an infra-additive, synergism. Amlodipine contributes more than perindopril to the antihypertensive activity of the FDC tablet. The absence of a placebo control in the Phase 3 study and the use of FDC tablets and mono-components of unknown relative bioavailability impede the analysis of the dose-effect relationship of the FDC tablets, and assessment of the untested middle strength FDC tablet.

Of the 3 pharmacokinetic studies a bioequivalence study compared the exposure measures for perindopril, perindoprilat and amlodipine after administration of the FDC tablet, PERa/AMLb 10/10 mg, not intended for the market, and after co-administration of the mono-components PERe 8 mg + AMLb 10 mg. A study using the highest strength of the FDC tablet, PERa/AMLb 14/10 mg, and the mono-components PERa 14 mg and AMLb 10 mg, administered on separate occasions, tested a possible pharmacokinetic interaction between perindopril and amlodipine. The third pharmacokinetic study using the highest strength of the FDC tablet, PERa/AMLb 14/10 mg, investigated the impact of food on the exposure measures of perindopril, perindoprilat and amlodipine.

The sponsor's PK studies and cross-study comparisons have not demonstrated bioequivalence

- Between to be marketed FDC tablets and ACEON
- Between to be marketed FDC tablets and FDC tablets manufactured by Servier
- Dose strength proportionality of to be marketed FDC tablets

The sponsor claims that the composition of the 3 strengths of to be marketed FDC tablets and the FDC tablets by Servier are essentially proportionally similar and that process and manufacturing of to be marketed FDC tablets and those by Servier are identical. Further the sponsor asserts that in vitro dissolution data show that amlodipine and perindopril from to be marketed FDC tablets and from the FDC tablets manufactured by Servier show rapid dissolution and/or similar dissolution profiles. Based on the submitted data the sponsor requests granting of 3 Biowaivers for:

- Bridging to be marketed FDC tablets to the marketed mono-components [505(b) (2)]
- Bridging to be marketed FDC tablets to those by Servier
- Bridging the lower strengths to the highest strength of to be marketed FDC tablet

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			Data sets of studies PKH-001 and 009 are missing
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	Can be derived from label of the mono-components

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Sponsor seeks waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	No translation needed

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_Yes\_\_\_\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**Information Request:**

*Please submit subject level pharmacokinetic data sets as SAS transport file (.xpt) for studies PKH-05985-001 and PKH-05985-009*

**Potential Review Issues:**

*The absence of a placebo control in the Phase 3 study and the use of FDC tablets and mono-components of unknown relative bioavailability impede the analysis of the dose-effect relationship of the FDC tablets, and assessment of the untested middle strength FDC tablet.*

*The cross study comparisons indicate that the 90% confidence intervals of the geometric mean ratios of the exposure measures for perindopril and perindoprilat of to be marketed highest strength FDC tablet to the ACEON tablet fall outside of the bioequivalence limits.*

Peter H. Hinderling, MD  
 Reviewing Clinical Pharmacologist

5-6-2014  
 Date

Sudharshan, Hariharan, PhD  
Secondary Reviewer

5-6-2014  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PETER HINDERLING  
05/06/2014

SUDHARSHAN HARIHARAN  
05/06/2014