Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

COVERAM
PERINDOPRIL ARGININE - AMLODIPINE SERVIER
PERINDOPRIL ARGININE – AMLODIPINE BIOPHARMA
5mg/5mg, 5mg/10mg, 10mg/5mg, 10mg/10mg, Tablet

Perindopril arginine – Amlodipine

FR/H/325-326-327/01-04/DC

Applicant: Servier

Date of the PAR: July 2009

Information about the initial procedure:

Application/Legal Basis	10b fixed combination
Active substance	Perindopril arginine – Amlodipine
Pharmaceutical form	tablet
Strength	5mg/5mg, 5mg/10mg, 10mg/5mg, 10mg/10mg
Applicant	Servier
EU-Procedure number	FR/H/325-326-327/01-04/DC
End of procedure	D210: 26/03/2008

1. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Afssaps has granted on August 19, 2008 a marketing authorisation (MA) for **Coveram, Perindopril Arginine – Amlodipine Servier** and **Perindopril Arginine – Amlodipine Biopharma,** tablet, from Les Laboratoires Servier, as a substitution therapy of the mono-components perindopril arginine and amlodipine given separately. Four different formulations are proposed to cover the useful dose range of each product: 5mg/5mg, 5mg/10mg, 10mg/5mg, and 10mg/10mg, in the following indication:

Coveram (and other trade names) is indicated as a substitution therapy for treatment of hypertension and /or stable coronary artery disease in patients already controlled with perindopril and amlodipine given concomitantly at then same dose level.

A comprehensive description of the indication and dosages is given in the SPC.

In support of this application, the applicant has submitted three bioequivalence studies, carried out in agreement with the "*Note for guidance on the investigation of bioavailability and bioequivalence*" (CPMP/EWP/QWP/1401/98). Furthermore, in order to investigate whether a pharmacokinetic interaction exists between the two drug substances, one interaction study was performed with the highest dosage form.

No new pre-clinical or clinical studies were conducted.

During the decentralised procedure, two potential serious risks to public health related to the product information (SPC) were raised by concerned member states (CMS). The first one was related to efficacy and safety data considered as insufficient by one CMS for the claimed indication. This issue was solved as the clinical development of these fixed doses combinations adequately fulfils the Questions and Answers document: CHMP/EWP/19/583/2005, stating that formal bioequivalence studies should be carried out and are sufficient for a fixed combination aiming for a substitution indication. The second issue (raised by other CMS) was related to section 4.6. Pregnancy and lactation;these CMS considered that these fixed combination should be contra-indicated during the first trimester of pregnancy instead of only the second and third trimesters as proposed by the MAH and the RMS. This issue was solved as the Pharmacovigilance Working Party concluded in October 2007 after review and discussion on the teratogenic potential of ACE inhibitors that a contra-indication of ACE inhibitors during the first trimester of pregnancy was not justified

The procedure was ended positively and a marketing authorisation (MA) was granted by all CMS.

2. QUALITY ASPECTS

Introduction

Four fixed combination strengths of perindopril arginine/amlodipine as besilate are described, 5mg/5mg, 10mg/10mg, 5mg/10mg and 10mg/5mg respectively.

Tablets are primary packaged in a polypropylene tube equipped with a low density polyethylene stopper containing desiccant gel.

Drug substance

Perindopril is a prodrug metabolised *in vivo* to perindoprilat, an ACE inhibitor.

The manufacturing process is described in only one step from perindopril *tert*-butylamine salt which has a level quality guarantied by its compliance to the Ph. Eur. Monograph (01/2008:2019). This one step process is described in sufficient details.

The specifications are adequately chosen. Most of them are based on those of the European Pharmacopoeia monograph for perindopril *tert*-butylamine

Regarding the stability studies it can be concluded that the drug substance is stable in the claimed packaging. A retest period of 3 years is acceptable when perindopril arginine is stored in industrial bulk packaging.

Amlodipine is a dihydropyridine calcium-channel blocker active by the oral route which is currently indicated for the treatment of hypertension and prophylaxis of stable angina pectoris.

The Active Substance Master File Procedure (Drug Master File (DMF)) is applied for this drug substance.

The drug substance Amlodipine Besilate is a pharmacopoeial substance (monograph 01/2005:1491).

The Ph. Eur. specifications with additional tests specific of the manufacturing process are used for the control of amlodipine besilate by the Applicant.

The packaging material (industrial bulk packaging) and the claimed retest period are acceptable.

Medicinal product

The submitted dossier-Module 3-describes four strengths: Perindopril arginine/Amlodipine besilate 5/5, 5/10, 10/5, 10/10 mg tablets.

The drug product is a tablet. The association between the two well-known drug substances is new. All excipients are classical for oral solid dosage forms and are described in the current Ph Eur.

The development is sufficiently described in accordance with the relevant European guidelines.

In vitro dissolution profiles comparing the proposed combination formulation and the currently registered and / or marketed tablets containing only one drug substance are similar.

The manufacturing process has been sufficiently described and critical steps identified. It is noted that the applicant commits to validate the manufacturing process for all strengths on full-scale batch sizes at each manufacturing site before marketing.

The proposed specifications for the control of the drug product are adequate. The methods are satisfactorily described and validated. The batch analysis results show that the drug product meet the specifications proposed.

The tablets are packed in a polypropylene, white opaque tube. The stopper is made from polyethylene and includes desiccant gel. The packaging is sufficient to ensure the quality of the tablets.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The data support the shelf life claimed in the SPC, 2 (two) years with the storage precaution “store in the original package”.

3. NON-CLINICAL ASPECTS

Discussion on the non-clinical aspects

No new pre-clinical data have been submitted in the dossier with the combination of perindopril arginine and amlodipine given the human experience of their individual and combined use.

The Applicant has provided data from IMS-Health statistical study to sustain the use of both drugs in

clinical practice and an overview of the toxicological properties of each compound. Perindopril was originally developed as a *tert*-butylamine salt. An arginine salt was then developed to improve the stability of the drug substance. Four-week bridging studies performed in rats and dogs by oral route have shown that the pharmacokinetic parameters and the safety profiles were identical for the two salts. The target organ was the kidney with reversible damage.

No mutagenicity or carcinogenicity has been observed. Reproductive toxicity studies performed for perindopril *tert*-butylamine have not shown sign of embryotoxicity or teratogenicity.

Amlodipine was well tolerated after single or repeated administrations. There was no evidence of teratogenicity or other embryo/foetal toxicity. In a rat study, a prolongation of gestation period and an increased incidence of peri and postnatal mortality were observed. Amlodipine has neither genotoxic nor carcinogenic potential. Section 5.3 of the SPC adequately reflects the pre-clinical data on each compound.

No modification of section 5.3. PreClinical Safety Data of the SPC was necessary; the initial MAH'proposal was endorsed by the RMS and all CMS.

4. CLINICAL ASPECTS

Introduction

As all clinical data concerning both products have already been evaluated, this application consists essentially in the demonstration of the bioequivalence between the free mono-components and the fixed combination of perindopril/amlodipine and in the demonstration of absence of pharmacokinetic interaction between the both products.

Discussion on the clinical aspects

Clinical efficacy

The efficacy of perindopril and amlodipine has already been demonstrated during the clinical development of both substances. Perindopril and amlodipine have both been widely used for several years (more than 15 years) and are registered in all European countries.

Perindopril is an angiotensin converting enzyme (ACE) inhibitor which acts via its active metabolite, perindoprilat. Perindopril is currently indicated for the treatment of hypertension, symptomatic heart failure and the reduction of risk of cardiac events in patients with stable coronary artery disease and a history of myocardial infarction and/or revascularisation (EUROPA study). Perindopril was initially used as tert-butylamine salt. Recently another formulation of perindopril was registered in Europe and other countries worldwide, substituting the tert-butylamine salt by a more stable arginine salt at equimolar dosages (5 and 10 mg corresponding to 4 and 8 mg, respectively). Both perindopril salts have been shown bioequivalent.

Amlodipine is a dihydropyridine calcium-channel blocker active by the oral route. Amlodipine is currently indicated for the treatment of hypertension, prophylaxis of stable angina pectoris and Prinzmetal's angina in some countries. Used in hypertension at a dosage of 5 to 10 mg, amlodipine also reduces coronary morbidity and mortality (ALLHAT study).

Both ACE inhibitors and calcium channel antagonists have demonstrated safety and efficacy profiles. The combination of a calcium channel blocker with an ACE inhibitor is one of the fixed-dose combinations recommended by the medical practice guidelines as being safe and effective (ESC, 2003; ESH/ESC, 2003; JNC7, 2003).

The justification for a combination of perindopril and amlodipine is based on their synergistic effects on several physiopathology mechanisms and on their pharmacokinetics compatibility.

Clinical safety

The safety of perindopril and amlodipine has already been studied during the clinical development of both substances. Moreover, the safety of the combination has been evaluated during the three

bioequivalence study and the pharmacokinetic interaction study. During these four studies, the combination safety profile was well tolerated; and there was no potentiation of adverse effects.

One question related to the potential impact of calcium channel blockers on male fertility was raised. As requested by the RMS, an analysis of literature and a detailed safety review on cases of adverse events on man fertility detailed review were provided by the applicant. As no cases of adverse events of amlodipine on man fertility were described in literature and very few clinical cases were described during the past years withy no clear relationship, in line with the applicant, no specific information was considered necessary in the SPC as it is the case for all others registered products containing amlodipine.

Pharmacovigilance System (PV System) and Risk Management Plan (RMP)

As described, the *PV System* adequately cover all the requested information, including: i) the qualified person responsible for pharmacovigilance (including the backup procedure to apply in the absence of the EUQP) , ii) the documented procedures ; iii) databases ; iv) training and v) the documentation (including the locations of the different types of pharmacovigilance source documents, and archiving arrangements).

As the fixed dose combinations have been extensively used worldwide as free combinations and as these fixed dose combinations are intended for substitution only, a specific RMP is not justified. Routine Pharmacovigilance with adequate Pharmacovigilance System as described and completed by the applicant are sufficient to adequately follow up the safety profile of these new fixed dose combinations of amlodipine and perindopril.

Pharmacokinetics

Four different formulations were proposed to cover the useful dose range of each product: perindopril 5mg/amlodipine 5mg ; perindopril 10mg/amlodipine 5mg ; perindopril 5mg/amlodipine 10mg and perindopril 10mg/amlodipine 10mg. Considering that these drug-products are fixed combinations of two known active ingredients, the applicant performed as required the following investigations:

- The potential PK interaction between the two active components of the fixed combination.

And

- The bioequivalence of the fixed-combination drug-products and the mono-component drug-products when co-administration freely.

Interaction study "PKH-05985-004"

One interaction study was performed with the highest dosage form (P10mg/A10mg) "PKH-05985-004" to investigate whether a pharmacokinetic interaction after single oral administration exists between perindopril arginine 10 mg and amlodipine 10 mg.

This was a phase I, open, randomised, three-period cross-over study, without direct individual benefit. 35 participants completed the study

The three-period cross-over consisted of:

- Period 1 (P1) : single oral administration of one tablet of perindopril arginine 10 mg and one tablet of amlodipine 10 mg in co-administration or one tablet of perindopril arginine 10 mg or one tablet of amlodipine 10 mg depending on the randomisation followed by a 3-week wash-out period,

- Period 2 (P2) : second single oral administration of one of the 2 treatments not received during P1 followed by a 3-week wash-out period ;

- Period 3 (P3): third single oral administration of the treatment not received during P1 and P2.

Treatments:

P + A (co-administration) = test formulations, referred to as treatment "T",

P = formulation of reference, referred to as treatment "R",

A = formulation of reference, referred to as treatment "Q".

Pharmacokinetic analysis: Pharmacokinetic parameters (Cmax, Tmax, AUC and t ½, z) of perindopril, perindoprilat and amlodipine obtained for each treatment based on blood sampling taken before administration and over 240 h after dosing at each treatment period.

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=35)	Geom. Mean (geom. CV%) Treatment R or Q (n=35)	Ratio T/R or T/Q (90% Confidence Interval)
Perindopril			
AUC_t (ng.h/ml)	74 (26%)	74 (27%)	101% (97%, 104%)
AUC (ng.h/ml)	75 (26%), n=34**	74 (27%)	101% (97%, 104%), n=34**
C_{max} (ng/ml)	57 (35%)	62 (36%)	92% (83%, 102%)
$t_{1/2Z}$ (h)	0.60 (0.44 – 0.85)*, n=34	0.61 (0.45 – 2.01)*	-
t_{max} (h)	0.75 (0.5 – 2)*	0.75 (0.5 – 2)*	-
Perindoprilat			
AUC_t (ng.h/ml)	252 (23%)	250 (21%)	101% (97%, 105%)
AUC (ng.h/ml)	332 (17%), n=16**	318 (18%), n=17**	107% (99%, 116%), n=8**
C_{max} (ng/ml)	12 (47%)	12 (46%)	106% (98%, 114%)
$t_{1/2Z}$ (h)	136 (110 – 227)*, n=34	129 (87 – 216)*, n=34	-
t_{max} (h)	4.0 (3 – 8)*	4.0 (3 – 8)*	-
Amlodipine			
AUC_t (ng.h/ml)	253 (30%)	240 (44%)	106% (98%, 114%)
AUC (ng.h/ml)	261 (30%)	248 (44%)	106% (98%, 114%)
C_{max} (ng/ml)	5.30 (29%)	4.97 (36%)	107% (100%, 114%)
$t_{1/2Z}$ (h)	49 (37 – 64)*	48 (36 – 70)*	-
t_{max} (h)	6.0 (3 – 12)*	6.0 (3 – 16)*	-

* : median and range; T : Test (S 6490 + amlodipine); R : Reference (S 6490); Q : Reference (amlodipine)
** : if percentage of AUC extrapolated from AUC_t is greater than 20%, the AUC value is not reported

The absence of pharmacokinetic interaction with respect to the extent and rate of bioavailability was concluded, the 90% confidence intervals for the treatment ratio (perindopril in treatment "T" / perindopril in treatment "R", perindoprilat in treatment "T" / perindoprilat in treatment "R" and amlodipine in treatment "T" / amlodipine in treatment "Q") were fully contained within the same acceptance ranges [80–125%] for perindopril, perindoprilat and amlodipine described for bioequivalence studies.

Bioequivalence studies:

- Study PKH-05985-001: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 10 mg/amlodipine 10 mg versus one tablet of perindopril tert-butylamine 8 mg plus one tablet of amlodipine 10 mg

- Study PKH-05985-002: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 10 mg/amlodipine 5 mg versus one tablet of perindopril tert-butylamine 8 mg plus one tablet of amlodipine 5 mg

- Study PKH-05985-003: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 5 mg/amlodipine 10 mg versus one tablet of perindopril tert-butylamine 4 mg plus one tablet of amlodipine 10 mg

All these three studies were conducted in fast condition and were phase I, open, randomised, two-period cross over studies without direct individual benefit with 36 participants for the two first studies and 35 participants for the third one.

During period 1 (P1) a single oral administration of one tablet of fixed combination perindopril arginine /amlodipine or one tablet of perindopril *tert*-butylamine + one tablet of amlodipine depending

on the randomisation, a 3-week wash-out period, and during period 2 (P2) a second single oral administration of the treatment not received during P1.

In the 3 bioequivalence studies, the fixed combination was compared to perindopril tert-butylamine. As a reminder, perindopril arginine was registered in order to substitute the tert-butylamine salt, as it is a more stable salt and as both perindopril salts have been shown to be bioequivalent (5 and 10 mg corresponding to 4 and 8 mg, respectively).

Treatments:

Treatment "T": the fixed combination of perindopril arginine /amlodipine.

Treatment "R": one tablet of perindopril *tert*-butylamine plus one tablet of amlodipine.

The plasma concentration of perindopril, perindoprilat and amlodipine were monitored in the collected plasma samples by the mean of fully validated analytical technique.

The statistical analysis of the data was conducted according to up to date methods, consisted in an ANOVA analysis and the estimation of 90% Confidence Interval of the ratios T/R for each PK parameter of interest.

The main results of the three studies are tabulated below.

-Study PKH-05985-001: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 10 mg/amlodipine 10 mg versus one tablet of perindopril tert-butylamine 8 mg plus one tablet of amlodipine 10 mg

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=36)	Geom. Mean (geom. CV%) Treatment R (n=36)	Ratio T/R (90% Confidence Interval)
Perindopril			
AUC_t (ng.h/ml)	79.9 (21%)	72.4 (23%)	110% (107%,114%)
AUC (ng.h/ml)	80.7 (21%)	73.1 (23%)	110% (107%,114%)
C_{max} (ng/ml)	63.2 (27%)	58.3 (26%)	109% (100%,118%)
$t_{1/2Z}$ (h)	0.616 (0.47 - 1.31)*	0.619 (0.47 – 0.80)*	-
t_{max} (h)	0.75 (0.5 - 2)*	0.75 (0.5 - 2)*	-
Perindoprilat			
AUC_t (ng.h/ml)	215 (31%)	216 (30%)	99% (96%, 103%)
AUC (ng.h/ml)	280 (22%), n=21**	273 (26%), n=24**	99% (93%, 105%), n=15
C_{max} (ng/ml)	9.8 (44%)	9.1 (46%)	108% (99%, 117%)
$t_{1/2Z}$ (h)	114 (60 – 160)*, n=35	115 (59 – 140)*	-
t_{max} (h)	4 (3 – 8)*	6 (3 – 8)*	-
Amlodipine			
AUC_t (ng.h/ml)	238 (32%)	237 (35%)	100% (97%, 104%)
AUC (ng.h/ml)	245 (31%)	244 (35%)	100% (97%, 104%)
C_{max} (ng/ml)	5.33 (30%)	5.19 (30%)	103% (99%, 107%)
$t_{1/2Z}$ (h)	44.7 (26.2 - 65.3)*	42.9 (27.9 - 71.6)*	-
t_{max} (h)	6 (3 - 10)*	6 (2 - 10)*	-

* : median and range; T : Test (S5985); R : Reference (S 9490 + Amlodipine)
** : if percentage of AUC extrapolated from AUC_t is greater than 20%, the AUC value is not reported

-Study PKH-05985-002: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 10 mg/amlodipine 5 mg versus one tablet of perindopril tert-butylamine 8 mg plus one tablet of amlodipine 5 mg

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=36)	Geom. Mean (geom. CV%) Treatment R (n=36)	Ratio T/R (90% Confidence Interval)
Perindopril			
AUC_t (ng.h/ml)	76 (25%)	71 (24%)	107% (104%, 110%)
AUC (ng.h/ml)	77 (25%)	72 (24%)	107% (104%, 110%)
C_{max} (ng/ml)	68 (27%)	66 (26%)	104% (98%, 110%)
$t_{1/2Z}$ (h)	0.61 (0.44 - 0.84)*	0.60 (0.46 - 0.92)*	-
t_{max} (h)	0.63 (0.25 - 2.0)*	0.75 (0.50 - 1.5)*	-
Perindoprilat			
AUC_t (ng.h/ml)	240 (31%)	238 (27%)	101% (97%, 106%)
AUC (ng.h/ml)	305 (26%), n=26**	290 (26%), n=28**	103% (97%, 110%), n=22**
C_{max} (ng/ml)	12 (43%)	11 (45%)	105% (98%, 112%)
$t_{1/2Z}$ (h)	110 (66 - 139)*	109 (68 - 173)*	-
t_{max} (h)	4.0 (3.0 - 8.0)*	4.0 (3.0 - 10.0)*	-
Amlodipine			
AUC_t (ng.h/ml)	134 (35%)	135 (33%)	99% (95%, 103%)
AUC (ng.h/ml)	139 (35%)	142 (32%)	98% (94%, 102%)
C_{max} (ng/ml)	2.94 (23%)	2.98 (25%)	98% (95%, 103%)
$t_{1/2Z}$ (h)	45 (30 - 65)*	49 (31 - 101)*	-
t_{max} (h)	6.0 (3.0 - 10.0)*	6.0 (3.0 - 10.0)*	-

* : median and range; T : Test (S5985); R : Reference (S 9490 +Amlodipine)
** : if percentage of AUC extrapolated from AUC_t is greater than 20%, the AUC value is not reported

-Study PKH-05985-003: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 5 mg/amlodipine 10 mg versus one tablet of perindopril tert-butylamine 4 mg plus one tablet of amlodipine 10 mg

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=35)	Geom. Mean (geom. CV%) Treatment R (n=35)	Ratio T/R (90% Confidence Interval)
Perindopril			
AUC_t (ng.h/ml)	36.6 (26%)	34.6 (30%)	106% (102%, 110%)
AUC (ng.h/ml)	37.2 (26%)	35.2 (30%)	106% (102%, 110%)
C_{max} (ng/ml)	29.6 (27%)	27.4 (32%)	108% (98%, 118%)
$t_{1/2Z}$ (h)	0.60 (0.45 - 0.88)*	0.61 (0.42 - 0.89)*	-
t_{max} (h)	0.75 (0.50 - 2.00)*	0.75 (0.50 - 2.00)*	-
Perindoprilat			
AUC_t (ng.h/ml)	145 (30%)	144 (31%)	101% (94%, 108%)
AUC (ng.h/ml)	NA	NA	NA
C_{max} (ng/ml)	4.2 (41%)	3.9 (47%)	108% (98%, 119%)
$t_{1/2Z}$ (h)	122 (66 - 188)*, n=32	124 (60 - 296)*, n=31	-
t_{max} (h)	6.0 (3.0 - 10.0)*	6.0 (3.0 - 12.1)*	-
Amlodipine			
AUC_t (ng.h/ml)	283 (30%)	277 (29%)	102% (99%, 106%)
AUC (ng.h/ml)	293 (31%)	286 (30%)	102% (99%, 106%)
C_{max} (ng/ml)	5.72 (22%)	5.45 (20%)	105% (101%, 110%)
$t_{1/2Z}$ (h)	45 (31 - 85)*	46 (32 - 67)*	-
t_{max} (h)	6.0 (3.0 - 8.0)*	6.0 (3.0 - 12.0)*	-

* : median and range; T : Test (S5985); R : Reference (S 9490 + Amlodipine)
NA : Not Available, AUC mean value is not reported since it was available for less than 80% of the subjects

Bioequivalence was demonstrated in whole the three studies with respect to the three components, perindopril, its active metabolite perindoprilat, and amlodipine.

The 90% confidence intervals of the geometric mean ratio (treatment “T” / treatment “R”) were all contained in the generally recognised acceptance range of [80–125%] for AUC, AUCt, and Cmax, for the three components.

The conclusion of the study PKH-05985-001 could be extended to the 5/5 mg dosage form not tested in the development program. Indeed, the bio-waiver claimed for this latter strength is acceptable.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Coveram, Perindopril Arginine – Amlodipine Servier and Perindopril Arginine – Amlodipine Biopharma, tablet (dosages: 5mg/5mg, 5mg/10mg, 10mg/5mg, 10mg/10mg) is demonstrated.

Considering the extensive knowledge on the pre-clinical data for perindopril and amlodipine, and given human experience of their individual and combined use, it can be stated that the new fixed combinations perindopril arginine/amlodipine do not raise any new non-clinical concerns.

Based on the submitted bioequivalence studies, the fixed perindopril arginine/amlodipine combinations are considered bioequivalent with the free mono components given separately at the same dose level.

Following Day 70 and the issues raised by some CMS on the proposed indication (section 4.1.) and the information on pregnancy (section 4.6.), the SPC and PL were amended. Recommendations of the PhVWP on Pregnancy have been included in sections 4.3., 4.4. and 4.6. of the SPC and the corresponding sections of the Package Leaflet. In addition, the new proposed shelf life has been incorporated in section 6.3.

Following Day 120, only one potential serious risk to public health on the proposed indication remained to be solved. Additional efficacy and safety data are not required as only a substitution indication is claimed by the applicant. This is in line with the guideline on substitution products. Some Points for Clarifications were also raised on sections 4.2., 4.6. and 4.8. of the SPC. The applicant adequately solved these questions provided adapted wording in the SPC and the corresponding sections of the Package Leaflet.

In conclusion, all issues being solved, all the CMS recognised the marketing authorisation of Coveram, Perindopril Arginine – Amlodipine Servier and Perindopril Arginine – Amlodipine Biopharma, tablet for the following dosages: 5mg/5mg, 5mg/10mg, 10mg/5mg, 10mg/10mg.

The current SPC, Patient Leaflet (PL) and packaging are in the agreed template.

<u>The following commitments were adopted:</u>

1. The applicant commits to validate the manufacturing process for all strengths on full-scale batch sizes at each manufacturing site before marketing.

2. The applicant commits to provide certificates of analysis for three production scale batches for each strength with results of microbiological purity.

3. When available, Certificates of Analysis for at least two production batches of the medicinal product from all proposed manufacturers will be provided.

4. The applicant commits to submit the stability results from each manufacturing site as soon as available.

5. The applicant commits to review the shelf life specifications at the end of the stability studies.

6. The applicant commits to submit a type II variation in order to implement the recommendation of the PhVWP regarding the use of ACE inhibitors during lactation when available.