

Public Assessment Report

Scientific discussion

Arplexam 2.5 mg/0.625 mg/5 mg

Arplexam 5 mg/1.25 mg/5 mg

Arplexam 5 mg/1.25 mg/10 mg

Arplexam 10 mg/2.5 mg/5 mg

**Arplexam 10 mg/2.5 mg/10 mg,
film-coated tablets**

(perindopril arginine/indapamide/amlodipine)

NL/H/2638/001-005/DC

Date: 2 July 2014

This module reflects the scientific discussion for the approval of Arplexam film-coated tablets. The procedure was finalised on 17 December 2013. For information on changes after this date please refer to the module 'Update'.

A list of abbreviations and literature references is given on pages 21-23.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Arplexam film-coated tablets, registered by Les Laboratoires Servier.

The product is indicated as substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril/indapamide fixed dose combination and amlodipine, taken at the same dose level.

A comprehensive description of the indication and posology is given in the SmPC.

The five different strengths cover the dose range of each product with five different dose-strength combinations as follows:

perindopril arginine 2.5 mg, indapamide 0.625 mg and amlodipine 5 mg,
perindopril arginine 5 mg, indapamide 1.25 mg and amlodipine 5 mg,
perindopril arginine 10 mg, indapamide 1.25 mg and amlodipine 10 mg,
perindopril arginine 5 mg, indapamide 2.5 mg and amlodipine 5 mg,
perindopril arginine 10 mg, indapamide 2.5 mg and amlodipine 10 mg.

This decentralised procedure concerns a fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposes. In these kinds of applications pre-clinical and clinical data relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovakia and Spain.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

Perindopril arginine is registered in the Netherlands by Les Laboratoires Servier, for the indication hypertension under the name Coversyl arg 2.5 mg, 5 mg and 10 mg tablets (NL License RVG 31957-31959). The product was approved through a Mutual Recognition Procedure in September 2005 (FR/H/0265/001-003).

The innovator product containing indapamide, Fludex SR 1.5 mg tablets (NL RVG 19206), was first registered in the Netherlands by Les Laboratoires Servier in December 1995 for the indication essential hypertension. The product was approved through a Mutual Recognition Procedure (FR/H/0100/001).

The Dutch amlodipine innovator product Norvasc 5 mg and 10 tablets (NL RVG 13348-13349) has been registered by Pfizer since June 1990 for the indications hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal's) angina.

The combination perindopril and indapamide for the indication hypertension has already been approved in several DCP and MRP procedures, including Coversyl Plus arg 5 mg/1.25 mg and 10 mg/2.5 mg (procedures FR/H/0130/004 and FR/H/0345/001), and Preterax (FR/H/0130/001-002). These marketing authorisations are held by Les Laboratoires Servier. The MAH makes reference to these dossiers for Arplexam.

The combination perindopril arginine and amlodipine for the indication hypertension has already been approved through several procedures, including Coveram (5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg). This product was registered by Les Laboratoires Servier in 2008 through procedure FR/H/0325/001-004/DC.

The MAH gave the following argumentation for this fixed dose combination:

In line with the requirements stated in the document CHMP/EWP/191583/2005 entitled *Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention*:

- perindopril, indapamide and amlodipine are well known (therapeutic experience of more than 15 years),

- the joint application of the components is already in widespread use in the proposed dosage strengths, and has proven to be efficacious and safe and thus clinically useful,
- the pharmacological rationale for the use of perindopril/indapamide and amlodipine in combination is adequately justified in literature. The MAH presented a bibliographical data analysis.
- the present application is based on pharmacokinetic data, *i.e.* interaction and bioequivalence studies.

No dedicated studies in the target population have been performed with this product on blood pressure, or with respect to increased compliance in a target population with possible comorbid disease or using co-medication. This is however not necessary taking into account the substitution indication.



New non-clinical studies were performed for the characterization of impurities.



A total of 5 studies have been performed which were designed to compare bioavailability to the reference formulations and to assess a possible pharmacokinetic interaction between the 3 compounds. One study investigated a potential interaction between the co-administered components of the fixed dose combination containing indapamide, amlodipine and perindopril. In the other 4 studies, for the bioequivalence assessment, a comparison was made with one tablet of the proposed fixed dose combination to the reference products, administered as one tablet of perindopril/indapamide plus one tablet of amlodipine. The studies have been performed with the 3 higher strengths. For the lower strengths a biowaiver has been granted. The study results are briefly presented in this report under section IV 'Clinical aspects'.



The RMS checked Paediatric Investigation Plan (PIP) compliance. On 21 January 2011 the EMA adopted a product-specific waiver for perindopril/indapamide/amlodipine besilate for all subsets of the paediatric population from birth to less than 18 years of age (EMEA-001048-PIP01-1).



II. QUALITY ASPECTS



II.1 Introduction

Arplexam 2.5 mg/0.625 mg/5 mg is a white, oblong, film-coated tablet, engraved with  on one face and  on the other face.

Arplexam 5 mg/1.25 mg/5 mg is a white, oblong, film-coated tablet, engraved with  on one face and  on the other face.

Arplexam 5 mg/1.25 mg/10 mg is a white, oblong, film-coated tablet, engraved with  on one face and  on the other face.

Arplexam 10 mg/2.5 mg/5 mg is a white, oblong, film-coated tablet, engraved with  on one face and  on the other face.

Arplexam 10 mg/2.5 mg/10 mg is a white, oblong, film-coated tablet, engraved with  on one face and  on the other face.

The tablets are packed in a polypropylene tablet container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing desiccant, or in a high density polyethylene tablet container equipped with a polypropylene stopper containing desiccant as hospital pack.

The excipients are:

Tablet core - calcium carbonate starch compound: calcium carbonate 90%, pregelatinised maize starch 10%; cellulose microcrystalline (E460); croscarmellose sodium (E468); magnesium stearate (E572); colloidal anhydrous silica; pregelatinised starch

Film-coating - glycerol (E422), hypromellose 6mPa.s (E464), macrogol 6000, magnesium stearate (E572), titanium dioxide (E 171).

The core tablet formulation of the 5 mg/1.25 mg/10 mg strength was designed with the same drug/excipients ratio as the 2.5 mg/0.625 mg/5 mg strength and a core tablet finished mass of 200 mg instead of 100 mg. These two formulations are proportionally similar in active and inactive ingredients. The core tablet formulation for the 5 mg/1.25 mg/5 mg strength was designed with a core tablet finished mass of 150 mg. The dilution of the 3 drug substances was thus slightly modified.

The core tablet formulation of the 10 mg/2.5 mg/10 mg strength was chosen to be proportionally similar in active and inactive ingredients to the 5 mg/1.25 mg/5 mg strength and thus with a core tablet finished mass of 300 mg.

Finally, the core tablet formulation of the 10 mg/2.5 mg/5 mg strength was designed with a core tablet finished mass of 250 mg.

II.2 Drug Substances

The active substance perindopril arginine is an established active substance, however not described in a pharmacopoeia. Perindopril arginine is a white or almost white hygroscopic powder, which is freely soluble in water and slightly soluble in ethanol (96%). The substance exhibits polymorphism. A consistent, stable form is produced.

The active substances indapamide and amlodipine are established active substances described in the Pharmacopoeias of Europe and/or the USA (Ph.Eur. and/or USP). Indapamide is a white or almost white powder, which is practically insoluble in water and soluble in ethanol (96%). Amlodipine is a white or almost white powder, which is freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in purified water and 2-propanol.

The CEP procedure is used for the active substances indapamide and amlodipine besilate. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

An appropriate description of the manufacturing process of perindopril arginine has been provided. For the other two active substances, reference is made to the information included in the CEP.

Quality control of drug substances

The specification of perindopril arginine is mostly in line with the Ph.Eur. monograph on perindopril tert-butylamine. However, some additional requirements specific for perindopril arginine are added.

For indapamide and amlodipine limits and tests as per proposed specification are in line with the respective Ph.Eur. monographs. For indapamide the additional requirements of the CEP are adopted and additional tests are included. The specification is acceptable in view of the route of synthesis and the various European guidelines. For amlodipine, requirements of the CEP are adopted. Appropriate additional tests are included. The specification is acceptable as well.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of each supplier.

Stability of drug substances

For perindopril arginine, stability data have been provided of studies performed in line with ICH guidance. Results show no specific changes or trends on any of the parameters at any of the tested conditions. Based on this data, the proposed re-test period of 36 months is considered acceptable.

The retest periods for indapamide and amlodipine are 3 years and 5 years respectively, when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

For the pharmaceutical development the Quality by Design (QbD) approach was applied. It is used as a support in the choice of the excipients as well as showing the robustness of the manufacturing process. The development of the product has been adequately described, the choice of excipients is justified and their functions explained. The development of the process is supported by the QbD data. In the bioequivalence studies, the MAH uses two single products for comparison, *i.e.* perindopril/indapamide from the MAH itself (BiPreterax®) and amlodipine from Pfizer (Norvasc® 5/10, tablets). Drug load is low for both active substances (<4% for perindopril arginine, <2% for indapamide and <5% for amlodipine). The different strengths of Arplexam are not dose proportional.

A biowaiver could however be granted for the 2.5/0.625/5 mg based on the bioequivalence studies with the 5/1.25/10 mg strength. For the 5/1.25/5 mg tablet reference is made to the bioequivalence

study with the 10/2.5/10 mg strength. These biowaivers for the lowest strengths are acceptable. Overall, the pharmaceutical development data is considered sufficient.

Manufacturing process

The manufacturing process is a standard process. It contains mixing, compression and coating. The MAH has provided data on the manufacturing of all tablet strengths on several batches produced at different sites. Results are in line with the acceptance criteria. A process validation scheme is included and is considered acceptable. The provided data is regarded as sufficient.

Control of excipients

The excipients comply with the Ph.Eur. except for calcium carbonate starch compound and dry premix for white colour coating, which are controlled according to an in-house monograph. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, average mass, dissolution of all active substances, identification of perindopril arginine, amlodipine and indapamide, assay of the active substances, uniformity of dosage units, purity and microbiological quality. The proposed tests in the specification are acceptable. The analytical methods have been adequately validated. Batch analytical data from the proposed production sites have been provided on three pilot-scale and one full-scale batch of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for several pilot-scale batches stored at 25°C/60% RH (18 months), 30°/65% or 75%RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the stability guideline. The batches were stored in PP tablet containers and HDPE bottles (hospital pack). No specific changes were observed.

A photostability study was conducted. The results demonstrate that the product is photostable.

The claimed shelf-life of 2 years for the product in the PP tablet container and the hospital pack can be granted given the data available. The claimed storage condition 'none' is considered acceptable. The in-use storage data for the open bottle showed that the product remains stable for 90 days. The proposed pack size (30 tablets and 100 tablets) are considered to be covered by these results. No specific information has to be stated for the in-use storage. The proposed stability after first opening of the tablet container (30 days for the 30 tablet container and 100 days for the 100 tablet container) is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Arplexam film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology and pharmacokinetics

For this fixed dose application, no new data regarding pharmacology or pharmacokinetics have been provided. No new studies have been performed and none are considered necessary. This is acceptable, as all three active substances are well known.

III.2 Toxicology

The toxicological profile of perindopril, indapamide and amlodipine is also well known, and the substances have been used in combination for many years. There are therefore no safety concerns.

New studies have been performed on several impurities. The established specification limits are considered qualified.

III.3 Ecotoxicity/environmental risk assessment (ERA)

No environmental risk assessment was performed for perindopril, indapamide and amlodipine. This is not considered necessary since no increased environmental exposure is expected. Arplexam is prescribed as substitution to patients already controlled with a combination of existing perindopril/indapamide and amlodipine formulations.

III.4 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical data. Therefore, the Member States agreed that no further non-clinical studies are required. The limits for impurities have been adequately justified.

IV. CLINICAL ASPECTS

IV.1 Introduction

The MAH submitted an overview of the established use of all components of the proposed fixed dose combination: perindopril, indapamide and amlodipine. Justification for the triple combination, also referring to the ESC guideline, has been provided and discussed. An overview has been provided of studies performed with the monocomponents comprising blood pressure lowering studies, outcome studies using the monocomponents and an overview of prescribing figures of the triple combination across some countries in Europe. Overall, the overview justified why no further studies are required.

The only studies performed were pharmacokinetic studies, which are discussed below.

IV.2 Pharmacokinetics

The pharmacokinetic properties of perindopril, indapamide and amlodipine are well known. A total of 5 pharmacokinetic studies have been performed. Three studies (no. PKH-06593-001, PKH-06593-002 and PKH-06593-003) were conducted to demonstrate bioequivalence of the applied triple combination product perindopril/indapamide/amlodipine to the individually marketed products perindopril/indapamide and amlodipine for several strengths. During the decentralised procedure the results of an additional, fourth bioequivalence study were provided, study PKH-06593-007, in support of Arplexam 5/1.25/10 mg tablets, because bioequivalence was not shown in PKH-06593-001. Study PKH-06593-004 investigated a potential pharmacokinetic interaction between the individual components of the fixed combination.

For all studies the design is acceptable. The analytical methods have been described and pharmacokinetic and statistical analyses were appropriate. The studies were conducted under fasted conditions, which is in accordance with the applicable guidelines.

The choice of the reference products used in the bioequivalence studies has been justified. The formula of the bioequivalence batches is identical to the formula proposed for marketing.

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

Biowaiver

The pharmacokinetic studies have been performed using the higher strengths: perindopril/indapamide/amlodipine 5/1.25/10 mg, 10/2.5/5 mg and 10/2.5/10 mg. The application also includes two lower strengths: Arplexam 2.5/0.625/5 mg and 5/1.25/5 mg. For the lower strengths a biowaiver has been requested. The biowaiver for the 2.5/0.625/5 mg strength is based on the bioequivalence

study with the 5/1.25/10 mg strength. For the 5/1.25/5 mg tablet bioequivalence is based on the bioequivalence study with the 10/2.5/10 mg strength. All conditions as described in the guideline have been met, regarding tablet composition, manufacturing process and comparative dissolution. All 3 compounds demonstrate linear pharmacokinetic dose proportionality. In conclusion, the biowaivers requested for the two lower strengths of Arplexam can be accepted.

Bioequivalence studies

Study PKH-06593-001 - 5/1.25/10 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-40 years.

The following treatments were administered:

- Test: one tablet of Arplexam 5/1.25/10 mg (Les Laboratoires Servier, the Netherlands)
- Reference: one tablet of BiPreterax®, perindopril 5 mg/indapamide 1.25 mg (Les Laboratoires Servier Industrie, France) plus one tablet of Norvasc amlodipine 10 mg (Pfizer, the Netherlands).

There were 2 dosing periods, separated by a washout period of 3 weeks.

Results

A total of 36 subjects were included in the study. Thirty-one subjects completed both periods and were included in the analysis.

Indapamide pharmacokinetic parameters

Indapamide			
Parameter	Unit	Geom. Mean (geom. %CV) Treatment T (n=31)	Geom. Mean (geom. %CV) Treatment R (n=31)
AUC ₇₂	ng*h/mL	195.9 (17.9 %)	199.2 (18.1 %)
AUC _{last}	ng*h/mL	183.4 (18.1 %)	186.8 (19.1 %)
C _{max}	ng/mL	12.14 (15.0 %)	11.72 (17.3 %)
t _{max}	h	1.5 (0.75 – 4.00)#	2.0 (0.75 – 4.00)#

: median and range

T: One tablet of S 06593: perindopril 5 mg/indapamide 1.25 mg/amlodipine 10 mg

R: One tablet of S 06590: perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg

Amlodipine pharmacokinetic parameters

Amlodipine			
Parameter	Unit	Geom. Mean (geom. %CV) Treatment T (n=31)	Geom. Mean (geom. %CV) Treatment R (n=31)
AUC ₇₂	ng*h/mL	218.1 (23.1 %)	218.8 (19.3 %)
AUC _{last}	ng*h/mL	217.2 (22.4 %)	216.1 (19.2 %)
C _{max}	ng/mL	6.640 (24.3 %)	6.424 (23.1 %)
t _{max}	h	6.0 (3.0 – 10.0)#	6.0 (3.0 – 8.0)#

: median and range

T: One tablet of S 06593: perindopril 5 mg/indapamide 1.25 mg/amlodipine 10 mg

R: One tablet of S 06590: perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg

Perindopril pharmacokinetic parameters

Perindopril			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=31)	Treatment R (n=31)
AUC ₇₂	ng*h/mL	32.8 (26.5 %)	32.6 (25.8 %)
AUC _{last}	ng*h/mL	32.0 (26.9 %)	32.0 (26.1 %)
C _{max}	ng/mL	24.69 (33.8 %)	28.67 (34.3 %)
t _{max}	h	1.0 (0.50 – 2.22)#	0.75 (0.42 – 2.00)#

: median and range

T: One tablet of S 06593: perindopril 5 mg/indapamide 1.25 mg/amlodipine 10 mg

R: One tablet of S 06590: perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Indapamide (n=31)	Amlodipine (n=31)
AUC ₇₂	98.34 % (93.98 %, 102.90 %)	99.62 % (96.33 %, 103.02 %)
AUC _{last}	98.14 % (93.75 %, 102.72 %)	100.43 % (96.55 %, 104.45 %)
C _{max}	103.51 (98.55 %, 108.71 %)	103.28 % (98.72 %, 108.04 %)

T: One tablet of S 06593: perindopril 5 mg/indapamide 1.25 mg/amlodipine 10 mg

R: One tablet of S 06590: perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of perindopril and perindoprilat

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Perindopril (n=31)	Perindoprilat (n=31)
AUC ₇₂	100.86 % (97.01 %, 104.86 %)	102.34 % (98.92 %, 105.86 %)
AUC _{last}	100.46 % (96.59 %, 104.48 %)	102.62 % (98.88 %, 106.50 %)
C _{max}	86.40 % (78.50 %, 95.07 %)	102.35 % (93.35 %, 112.21 %)

T: One tablet of S 06593: perindopril 5 mg/indapamide 1.25 mg/amlodipine 10 mg

R: One tablet of S 06590: perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg

Study PKH-06593-002 - 10/2.5/5 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 33 healthy male subjects, aged 19-46 years.

The following treatments were administered:

- Test: one tablet of Arplexam 10/2.5/5 mg (Les Laboratoires Servier, the Netherlands).
- Reference: one tablet of BiPreterax®, perindopril 10 mg/indapamide 2.5 mg (Servier Industries, Ireland) plus one tablet of Norvasc amlodipine 5 mg (Pfizer, the Netherlands).

There were 2 dosing periods, separated by a washout period of at least 3 weeks.

Results

A total of 33 subjects were included in the study. Two subjects were withdrawn due to non-medical reasons. The remaining 31 subjects completed the study and were included in the pharmacokinetic analysis.

Indapamide pharmacokinetic parameters

Indapamide			
Parameter	Unit	Geom. Mean (geom. %CV) Treatment T (n=31)	Geom. Mean (geom. %CV) Treatment R (n=31)
AUC ₇₂	ng*h/mL	423.6 (29.6 %)	419.3 (28.7 %)
AUC _{last}	ng*h/mL	410.4 (32.3 %)	408.6 (31.0 %)
C _{max}	ng/mL	26.91 (22.8 %)	25.79 (20.3 %)
t _{max}	h	1.5 (0.75 – 3.00)#	2.0 (0.75 – 4.00)#

: median and range

T: One tablet of S 06593: perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 mg

R: One tablet of S 06597: perindopril 10 mg/indapamide 2.5 mg plus one tablet of amlodipine 5 mg

Amlodipine pharmacokinetic parameters

Amlodipine			
Parameter	Unit	Geom. Mean (geom. %CV) Treatment T (n=31)	Geom. Mean (geom. %CV) Treatment R (n=31)
AUC ₇₂	ng*h/mL	93.52 (29.4 %)	93.16 (25.0 %)
AUC _{last}	ng*h/mL	92.78 (29.4 %)	93.16 (25.0 %)
C _{max}	ng/mL	2.893 (26.9 %)	2.887 (23.1 %)
t _{max}	h	6.0 (3.0 – 10.0)#	6.0 (2.0 – 12.0)#

: median and range

T: One tablet of S 06593: perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 mg

R: One tablet of S 06597: perindopril 10 mg/indapamide 2.5 mg plus one tablet of amlodipine 5 mg

Perindopril pharmacokinetic parameters

Perindopril			
Parameter	Unit	Geom. Mean (geom. %CV) Treatment T (n=31)	Geom. Mean (geom. %CV) Treatment R (n=31)
AUC ₇₂	ng*h/mL	63.83 (17.5 %)	62.03 (19.8 %)
AUC _{last}	ng*h/mL	63.23 (17.6 %)	61.34 (20.4 %)
C _{max}	ng/mL	51.14 (40.2 %)	48.86 (34.0 %)
t _{max}	h	0.75 (0.50 – 2.00)#	1.00 (0.50 – 2.00)#

: median and range

T: One tablet of S 06593: perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 mg

R: One tablet of S 06597: perindopril 10 mg/indapamide 2.5 mg plus one tablet of amlodipine 5 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Indapamide (n=31)	Amlodipine (n=31)
AUC ₇₂	101.02 % (95.37 %, 106.99 %)	100.47 % (97.09 %, 103.96 %)
AUC _{last}	100.44 % (94.49 %, 106.75 %)	99.64 % (96.06 %, 103.34 %)
C _{max}	104.38 % (98.89%, 110.17 %)	100.16 % (95.46 %, 105.08 %)

T: One tablet of S 06593: perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 mg

R: One tablet of S 06597: perindopril 10 mg/indapamide 2.5 mg plus one tablet of amlodipine 5 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of perindopril and perindoprilat

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Perindopril (n=31)	Perindoprilat (n=31)
AUC ₇₂	102.85 % (99.43 %, 106.37 %)	102.27 % (98.57 %, 106.10 %)
AUC _{last}	103.04 % (99.52 %, 106.67 %)	102.04 % (98.26 %, 105.95 %)
C _{max}	104.12 % (95.93 %, 112.99 %)	104.27 % (97.14 %, 111.91 %)

T: One tablet of S 06593: perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 mg

R: One tablet of S 06597: perindopril 10 mg/indapamide 2.5 mg plus one tablet of amlodipine 5 mg

Study PKH-06593-003 - 10/2.5/10 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 35 healthy male subjects, aged 18-42 years.

The following treatments were administered:

- Test: one tablet of Arplexam 10/2.5/10 mg (Les Laboratoires Servier, the Netherlands)
- Reference: one tablet of BiPreterax®, perindopril 10 mg/indapamide 2.5 mg (Servier Industries, Ireland) plus one tablet of Norvasc amlodipine 10 mg (Pfizer, the Netherlands).

There were 2 dosing periods, separated by a washout period of 3 weeks.

Results

A total of 35 subjects were included in the study. As 3 subjects were withdrawn due to non-medical reasons, 32 subjects were included in pharmacokinetic analysis

Indapamide pharmacokinetic parameters

Parameter	Unit	Indapamide	
		Geom. Mean (geom. %CV) Treatment T (n=32)	Geom. Mean (geom. %CV) Treatment R (n=32)
AUC ₇₂	ng*h/mL	332.3 (19.2 %)	337.2 (18.9 %)
AUC _{last}	ng*h/mL	319.6 (21.3 %)	327.9 (20.7 %)
C _{max}	ng/mL	21.04 (20.3 %)	21.00 (19.5 %)
t _{max}	h	1.50 (0.75 – 3.0)#	1.50 (0.75 – 6.0)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg (fixed combination) plus one tablet of amlodipine 10 mg

Amlodipine pharmacokinetic parameters

Parameter	Unit	Amlodipine	
		Geom. Mean (geom. %CV) Treatment T (n=32)	Geom. Mean (geom. %CV) Treatment R (n=32)
AUC ₇₂	ng*h/mL	191.5 (23.5 %)	186.4 (24.4 %)
AUC _{last}	ng*h/mL	191.6 (23.5 %)	186.4 (24.4 %)
C _{max}	Ng/mL	5.716 (21.8 %)	5.624 (22.6 %)
t _{max}	H	6.0 (3.0 – 10.0)#	6.0 (3.0 – 10.0)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg (fixed combination) plus one tablet of amlodipine 10 mg

Perindopril pharmacokinetic parameters

Perindopril			
Parameter	Unit	Geom. Mean (geom. %CV)	Geom. Mean (geom. %CV)
		Treatment T (n=32)	Treatment R (n=32)
AUC ₇₂	ng*h/mL	68.92 (25.3 %)	65.78 (25.0 %)
AUC _{last}	ng*h/mL	68.26 (25.6 %)	64.99 (25.4 %)
C _{max}	Ng/mL	58.90 (36.2 %)	55.09 (32.2 %)
t _{max}	h	0.75 (0.50 – 1.50)#	0.75 (0.42 – 3.00)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg (fixed combination) plus one tablet of amlodipine 10 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Indapamide	Amlodipine
	(n=32)	(n=32)
AUC ₇₂	98.53 % (95.18 %, 101.98 %)	102.77 % (99.50 %, 106.13 %)
AUC _{last}	97.45 % (93.66 %, 101.38 %)	-
C _{max}	100.21 % (95.41 %, 105.25 %)	101.65 % (97.14 %, 106.36 %)

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg (fixed combination) plus one tablet of amlodipine 10 mg

All plasma concentrations of amlodipine were quantifiable at 72 h, therefore, AUC_{last} values correspond to AUC₇₂ values.

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of perindopril and perindoprilat

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Perindopril	Perindoprilat
	(n=32)	(n=32)
AUC ₇₂	104.78 % (101.05 %, 108.64 %)	102.47 % (98.52 %, 106.57 %)
AUC _{last}	105.04 % (101.25 %, 108.96 %)	-
C _{max}	106.92 % (94.69 %, 120.71 %)	96.90 % (88.09 %, 106.57 %)

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg (fixed combination) plus one tablet of amlodipine 10 mg

All plasma concentrations of perindoprilat were quantifiable at 72 h, therefore, AUC_{last} values correspond to AUC₇₂ values.

Study PKH-06593-007 - 5/1.25/10 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 53 healthy male subjects, aged 20-44 years.

The following treatments were administered:

- Test: one tablet of Arplexam 5/1.25/10 mg (Les Laboratoires Servier, the Netherlands)
- Reference: one tablet of BiPreterax®, perindopril 5 mg/indapamide 1.25 mg (Les Laboratoires Servier Industrie, France) plus one tablet of Norvasc amlodipine 10 mg (Pfizer, the Netherlands).

There were 2 dosing periods, separated by a washout period of 3 weeks.

Results

A total of 53 subjects were included in the study. There was 1 drop-out due to a positive urine screen for cannabis. Fifty-two subjects completed both periods and were included in the analysis.

Indapamide			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=52)	Treatment R (n=52)
AUC ₇₂	ng*h/mL	252.3 (23.0 %)*	250.7 (22.7 %)
AUC _{last}	ng*h/mL	237.5 (24.8 %)	237.5 (24.4 %)
C _{max}	ng/mL	14.4 (23.8 %)	13.9 (22.6 %)
t _{max}	h	1.5 (0.75 – 3.00)#	2.0 (0.75 – 4.00)#

: median and range

*n=51

Amlodipine			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=52)	Treatment R (n=52)
AUC ₇₂	ng*h/mL	178.9 (21.4 %)	170.8 (25.5 %)
AUC _{last}	ng*h/mL	178.9 (21.5 %)	170.8 (25.5 %)
C _{max}	ng/mL	4.947 (22.7 %)	4.784 (24.5 %)
t _{max}	h	6.01 (3.0 – 16.0)#	6.0 (6.0 – 12.0)#

: median and range

Perindopril			
Parameter	Unit	Geom. Mean (geom. %CV)	
		Treatment T (n=52)	Treatment R (n=52)
AUC ₇₂	ng*h/mL	36.6 (24.8 %)	36.0 (25.7 %)
AUC _{last}	ng*h/mL	35.9 (25.1 %)	35.3 (25.9 %)
C _{max}	ng/mL	28.67 (29.1 %)	28.1 (32.2 %)
t _{max}	h	0.75 (0.50 – 1.50)#	0.75 (0.50 – 2.02)#

: median and range

Least Squares Geometric Mean Ratio T/R (90% CI)		
Parameter	Indapamide (n=52)	Amlodipine (n=52)
AUC ₇₂	100.63 % (97.51 %, 103.85 %)*	104.79 % (102.14 %, 107.49 %)
AUC _{last}	99.98 % (96.90 %, 103.14 %)	104.75 % (102.10 %, 107.46 %)
C _{max}	103.73 (99.72 %, 107.90 %)	103.41 % (99.14 %, 107.85 %)

*n=51

Least Squares Geometric Mean Ratio T/R (90% CI)		
Parameter	Perindopril (n=52)	Perindoprilat (n=52)
AUC ₇₂	101.88 % (98.54 %, 105.33 %)	102.71 % (100.50 %, 104.96 %)*
AUC _{last}	101.86 % (98.50 %, 105.32 %)	102.53 % (100.33 %, 104.76 %)
C _{max}	102.11 % (95.49 %, 109.18 %)	105.23 % (99.88 %, 110.85 %)

*n=51

Conclusion on bioequivalence studies PKH-06593-001, PKH-06593-002, PKH-06593-003 and PKH-06593-007

In studies PKH-06593-002 and PKH-06593-003 bioequivalence of the applied triple combination product has been demonstrated to the individually marketed products amlodipine and perindopril/indapamide. Bioequivalence has been investigated with the higher strengths perindopril/indapamide/

amlodipine 10/2.5/5 mg and 10/2.5/10 mg. The 90% confidence intervals calculated for AUC_{0-72} , AUC_{last} and C_{max} are within the bioequivalence acceptance range of 80% – 125%.

The bioequivalence study with the 5/1.25/10 mg strength (study PKH-06593-001) was not acceptable since the 90% confidence interval of the perindopril C_{max} is outside (below) the acceptance interval. However, a new bioequivalence study has been performed, PKH-06593-007, demonstrating bioequivalence between one tablet of the 5/1.25/10 mg strength versus one tablet of the fixed combination perindopril 5 mg/indapamide 1.25 mg plus one tablet of amlodipine 10 mg. The results of the new bioequivalence study overrule results of the first study as the design of the study was improved. Therefore perindopril/indapamide/amlodipine 5/1.25/10 mg is acceptable from a pharmacokinetic point of view.

Interactions

Study PKH-06593-004

Design

The goal of this study was to investigate a potential pharmacokinetic interaction between the fixed combination of perindopril 10 mg/indapamide 2.5 mg and amlodipine 10 mg within the fixed combination Arplexam 10/2.5/10 mg after a single oral dose. The study had an open-label randomised three-period, six-way crossover design and was carried out under fasted conditions in 37 healthy male participants aged 18-42 years.

The following treatments were administered:

- Test: one tablet of Arplexam 5/2.5/10 mg (Les Laboratoires Servier, the Netherlands)
- Reference: one tablet of BiPreterax®, perindopril 10 mg/indapamide 2.5 mg (Les Laboratoires Servier Ireland) plus one tablet of Norvasc amlodipine 10 mg (Pfizer, the Netherlands).

The dosing periods were separated by a washout period of 3 weeks.

Results

As 3 subjects were withdrawn due to non-medical reasons, 2 due to an adverse event and 2 due to a protocol deviation, a total of 30 subjects were included in pharmacokinetic analysis.

Indapamide pharmacokinetic parameters

Indapamide			
Parameter	Unit	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)
		Treatment T (n=30)	Treatment R (n=30)
AUC	ng*h/mL	380.5 (27.9 %)	342.9 (26.5 %)
AUC_{last}	ng*h/mL	394.5 ± 109.8 (27.8 %)	354.6 ± 96.1 (27.1 %)
		357.7 (27.8 %)	319.7 (27.2 %)
C_{max}	ng/mL	370.8 ± 102.0 (27.5 %)	331.1 ± 92.3 (27.9 %)
		23.302 (19.6 %)	21.733 (17.3 %)
t_{max}	h	23.747 ± 4.905 (20.7 %)	22.043 ± 3.772 (17.1 %)
		1.50 (1.0 – 3.0)#	2.00 (1.0 – 4.0)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg

Amlodipine pharmacokinetic parameters

Amlodipine			
Parameter	Unit	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)
		Treatment T (n=30)	Treatment S (n=30)
AUC	ng*h/mL	228.9 (36.2 %)	213.2 (30.3 %) n=28
		242.5 ± 81.5 (33.6 %)	222.0 ± 62.3 (28.1 %) n=28
AUC _{last}	ng*h/mL	220.0 (34.5 %)	201.5 (28.0 %)
		231.9 ± 74.8 (32.3 %)	208.8 ± 55.7 (26.7 %)
C _{max}	ng/mL	5.227 (25.8 %)	4.813 (24.0 %)
		5.396 ± 1.421 (26.3 %)	4.946 ± 1.207 (24.4 %)
t _{max}	h	6.0 (3.0 – 10.0)#	6.0 (2.0 – 10.1)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

S: Amlodipine 10 mg

Perindopril pharmacokinetic parameters

Perindopril			
Parameter	Unit	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV)
		Treatment T (n=30)	Treatment R (n=30)
AUC	ng*h/mL	63.8 (19.6 %)	62.2 (21.4 %) n=29
		65.0 ± 13.2 (20.3 %)	63.5 ± 13.1 (20.6 %) n=29
AUC _{last}	ng*h/mL	63.0 (19.9 %)	61.2 (21.7 %)
		64.2 ± 13.2 (20.5 %)	62.5 ± 13.1 (21.0 %)
C _{max}	ng/mL	50.671 (38.5 %)	48.124 (39.5 %)
		54.100 ± 19.799 (36.6 %)	51.480 ± 18.685 (36.3 %)
t _{max}	h	0.75 (0.50 – 1.98)#	1.00 (0.48 – 2.00)#

: median and range

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg

Geometric mean ratios (treatment T / treatment R resp. treatment S) and 90 % Confidence Intervals for pharmacokinetic parameters of indapamide and amlodipine

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	Least Squares Geometric Mean Ratio T/S (90% CI)
	Indapamide (n=30)	Amlodipine (n=30)
AUC	111.25 % (105.11 %, 117.73 %)	106.48 % (100.56 %, 112.75 %), n=28
AUC _{last}	112.23 % (105.84 %, 118.99 %)	108.87 % (102.64 %, 115.47 %)
C _{max}	107.24 % (101.47 %, 113.33 %)	109.01 % (102.76 %, 115.64 %)

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg

R: S 06597: perindopril 10 mg/ indapamide 2.5 mg

S: amlodipine 10 mg

Geometric mean ratios (treatment T / treatment R) and 90 % Confidence Intervals for pharmacokinetic parameters of perindopril and perindoprilat

Parameter	Least Squares Geometric Mean Ratio T/R (90% CI)	
	Perindopril (n=30)	Perindoprilat (n=30)
AUC	103.44 % (98.23 %, 108.93 %), n=29	101.02 % (92.39 %, 110.44 %), n=15
AUC _{last}	103.02 % (97.96 %, 108.33 %)	105.11 % (100.42 %, 110.01 %)
C _{max}	105.16 % (92.71 %, 119.26 %)	113.37 % (102.33 %, 125.58 %)

T: S 06593: perindopril 10 mg/ indapamide 2.5 mg/ amlodipine 10 mg
R: S 06597: perindopril 10 mg/ indapamide 2.5 mg

Conclusion on study PKH-06593-004

The results of study PKH-06593-004 demonstrate the absence of a significant interaction between the co-administered components of the applied combination product containing indapamide, amlodipine and perindopril. For all three compounds pharmacokinetic parameters are comparable and 90% confidence intervals are within the 80 to 125% range.

IV.3 Clinical efficacy

The rationale for the development of a perindopril/indapamide/amlodipine fixed dose combination is based on:

- the fact that these substances belong to the major three antihypertensive classes recommended for the management of hypertension by the most recent European guidelines, and that the interest of their combination is recognized (Mancia, 2009),
- the efficacy in blood pressure lowering of each component is supported by the demonstration of their clinical benefit from large programs of clinical trials performed with each of them administered alone or in combination,
- their beneficial effect in terms of mortality and morbidity, and on the protection of the hypertensive target organs such as the heart, kidney, brain and vessels in addition to their blood pressure reduction,
- the synergy of the mono-components effects,
- their favourable acceptability and safety profile,
- the long-term experience with these 3 agents, all have been marketed for more than 20 years and are freely associated by practitioners in the treatment of hypertension,
- and finally, their compatibility from a pharmacokinetic point of view (one administration per day in the morning).

Need for 3 different drugs

The blood pressure lowering agents perindopril, indapamide and amlodipine fulfil the criteria for the choice of antihypertensive drugs, according to current European guidelines on hypertension management (Mancia, 2009). This European Society of Hypertension (ESH) guideline (current at the time of submission) stresses that no less than 15-20% of the patients need more than two antihypertensive drugs to achieve an effective BP reduction and the combination of a blocker of the renin-angiotensin system, a calcium antagonist and a thiazide diuretic is the most rational three-drug combination (Mancia, 2009). This combination of a blocker of the renin-angiotensin system, a calcium antagonist and a thiazide diuretic is also recommended by the guidelines of the National Institute for Health and Clinical Excellence (NICE, 2011).

Compliance

As antihypertensive therapy should in general be maintained indefinitely, and guidelines of the European Society of Cardiology (ESC) pointed out "increasing compliance with antihypertensive treatment and achieving a wide blood pressure control in the population thus represents a major challenge for clinical practice in the future". Beyond their own efficacy, the triple therapy within a single pill will favour long-term compliance to the treatment. A review (Gupta, 2010) of the potential advantage of fixed dose combination formulations over their corresponding free drug components given separately showed that the use of a fixed dose combination of antihypertensive agents was associated with a 29% significant increase in compliance and a non-significant persistence with therapy [OR:1.29 (95%CI, 1.11-1.50)]. Similarly, in a meta-analysis of nine studies comparing the

administration of fixed dose combinations with their separate components, the adherence rate was improved by 26% in patients receiving the fixed dose combinations (Bangalore, 2007).

Efficacy studies

Among the trials assessing intermediate end-points in hypertensive patients, perindopril and indapamide are effective in reducing left ventricular hypertrophy (PICXEL, REASON: Asmar, 2001; LIVE: Gosse, 2000) and microalbuminuria (PREMIER: Mogensen, 2003; NESTOR: Marre, 2004) and amlodipine in slowing down progression of carotid artery atherosclerosis (PREVENT: Pitt, 2000).

Their clinical benefit is demonstrated in specific conditions: in the very elderly, indapamide and perindopril decreased cardiovascular morbid events and mortality (HYVET: Beckett, 2008, 2012), in diabetes mellitus indapamide and perindopril decreased macro- and microvascular complication of diabetes, renal outcomes and total mortality (ADVANCE, 2007), in cerebrovascular diseases, indapamide and perindopril decreased cerebrovascular events and mortality (PROGRESS, 2001; PATS, 1995; Liu, 2009; HYVET: Beckett 2008, 2012), in coronary heart disease, perindopril (EUROPA, 2003) decreased composite cardio-vascular events and amlodipine (CAMELOT: Nissen, 2004) decreased the number of hospitalisation for angina and revascularisation procedures.

The MAH provided results from observational studies involving use of the proposed triple combination, a subgroup analysis of the ADVANCE study with the proposed triple combination, as well as data from a active-controlled double blind trial in which some patients used the proposed combination.

Existing combinations

Two fixed triple-combination therapies are already registered and marketed in Europe: valsartan/amlodipine/HCTZ and olmesartan/amlodipine/HCTZ. A third one is registered in USA: aliskiren/amlodipine/HCTZ. In clinical trials, triple-combination therapy (amlodipine/valsartan/HCTZ) showed its efficacy with a reduction in SBP/DBP down to 39.7/24.7 mmHg, and up to 75% of patients achieving BP goal. The occurrence of peripheral oedema was less frequent than with dual-component therapy with amlodipine, and hypotension-related adverse events were infrequent (Gradman, 2010).

IV.4 Clinical safety

Monocomponents

Perindopril

Reported side effects are rare and mostly benign. Most of them occurred on initiating treatment and were transient. Cough, headache, asthenia, dizziness, vertigo, paraesthesia, vision disturbances, tinnitus, hypotension, dyspnea, nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhea, constipation, localised skin rash, pruritus and muscle cramps have been commonly reported with perindopril. Cough occurs with an incidence of around 8%. Angioneurotic oedema has been uncommonly reported with perindopril as with other ACE inhibitors. No restriction nor precaution of use especially in elderly are mentioned in the SmPC except those in relation with renal impairment.

Five studies were conducted with perindopril tert-butylamine administered for several days at dosage up to 16 mg/day (Claessens, 1987; Boissel, 1987; Reid, 1987; Myers, 1996; Chrysant, 1993) which corresponds to 20 mg of perindopril-arginine. The clinical and biological acceptability was satisfactory at all dosages. The frequency and nature of symptoms were not related to the dose.

Indapamide

Reported side effects are rare and mostly benign. Most of them occurred on initiating treatment and were transient.

Thiazide-related diuretics, including indapamide, may cause undesirable effects, the most common being maculopapular rashes, and uncommon, vomiting, and purpura.

During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/L) was seen in 10% of patients and <3.2 mmol/L in 4% of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/L. The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent. There is no restriction for use in elderly or very elderly patients. In the large trial in very elderly patients (>80 years old) HYVET (Beckett, 2008, 2012), indapamide showed a very good tolerability of use.

Amlodipine

Vasodilator adverse events such as oedema, headache, and flushing are commonly observed with amlodipine. Somnolence, dizziness, abdominal pain and nausea have also been commonly reported. Oedema, dizziness, flushing and palpitations have been reported to be dose related.

Treatment with amlodipine was well tolerated at doses up to 10 mg daily. In controlled clinical trials directly comparing amlodipine (N=1,730) in doses up to 10 mg to placebo (N=1,250), discontinuation of amlodipine due to adverse reactions was required in about 1.5% of patients and was not

significantly different from placebo (about 1%). The most common side effects are headache and oedema. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. Amlodipine should be used with caution in patients with severe congestive heart failure or with hepatic impairment.

No restriction in dosage is mentioned for the elderly or in case of combination with an ACE inhibitor or a diuretic and no phenomenon of rebound is noticed.

Combination

All three agents have been marketed since many years as monotherapies or bi-therapies and are freely associated by practitioners in the treatment of hypertension. The expected adverse events are those reported with perindopril/indapamide and amlodipine with a possible reduction in frequency and/or severity of peripheral oedema in comparison with amlodipine alone, due to the counter-action between components, when they are taken together.

Safety data from pharmacokinetic studies performed in 140 healthy volunteers showed that this treatment is well tolerated and safe, regardless of the dosage. Headache, flushing and orthostatic hypotension are the most frequently observed adverse events. In the efficacy studies mentioned above, no new safety concerns were raised.

Pharmacovigilance

In order to assess the prescription and co-prescription of the combination of an ACE inhibitor, a diuretic and a calcium antagonist, and more precisely of perindopril, indapamide and amlodipine in Europe, a prescription study survey was performed in 2010 using CEGEDIM¹ longitudinal patient databases (LPD). During the decentralised procedure the MAH added prescription data from 12 additional Member States, although these were not used in the pharmacovigilance analysis below.

LPD data are used for marketing and epidemiological studies, as well as by local health authorities, as a means of determining reimbursement schemes for specified drugs. The samples are constant and nationally representative. The production of all multi-country studies is carried out by a dedicated LPD team, ensuring comparable analyses across all studies. A total of five longitudinal patient databases (LPD) were analysed: Belgium, France, Italy, Germany and the UK.

The participating physicians used a CSD-provided electronic medical records (EMR) software to record patient's information including all medicinal prescriptions allowing the LPD data to come directly from the patient's medical records. Data were collected from general practitioners (GPs), and in addition from cardiologists in France.

In general practice, within the group of patients receiving a tritherapy with an ACE inhibitor and diuretic and calcium antagonist, the percentage of patients receiving the combination perindopril + indapamide + amlodipine was different, depending on the country and the registration status of the fixed combination perindopril/indapamide, and was most frequently prescribed in Belgium and France (12.6% and 9.9% respectively) as compared to Germany (1.0%). The results obtained in France show that the same proportion is observed whether prescriptions were provided from GPs or cardiologists.

The pharmacovigilance database included all reports received from worldwide sources, that is:

- Spontaneous reports: all individual case-reports sent spontaneously (including affiliates, subsidiaries and licensees) by healthcare professionals, including those received from Regulatory Authorities and those published in the medical literature as well as those sent by non-healthcare professionals.
- Clinical studies: all serious suspected adverse drug reactions, which have been observed in clinical investigations monitored by Servier's Departments or licensees involved in clinical research, including clinical trials, named patient/compassionate use, post-authorisation studies and registries.

From 25 November 1997 up to 14 May 2012, 1819 cases-reports were reported with the fixed combination of perindopril-indapamide (P-I). The worldwide unit sales of P-I during this period represented approximately 192,444,547 patient months of treatment.

Out of these 1819 cases-reports, 91 patients were treated concomitantly with amlodipine (P-I/A).

Although the analysis should be interpreted cautiously taking into account the low number of patients receiving P-I/A, the data do not suggest a difference in the safety profile of patients receiving either P-I or P-I/A.

The most frequently reported reactions for both groups (P-I and P-I/A) belong to the following System Organ Classes:

¹Cegedim is a global technology and services company specializing in the healthcare field

- Metabolism and nutrition disorders: mainly hyponatraemia and hypokalaemia
- Skin and subcutaneous tissue disorders: mainly angioedema
- General disorders and administration site conditions: mainly malaise (P-I) and pyrexia (P-I/A)
- Gastrointestinal disorders: mainly nausea and vomiting

Based on the reports collected in the pharmacovigilance database, these data do not suggest a difference in the safety profile when amlodipine is associated with perindopril-indapamide.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Arplexam tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Hypotension • Renal failure • Hypokalaemia • Hyperkalaemia • Neutropenia/agranulocytosis/ thrombocytopenia • Angioedema • Anaphylactoid reactions • Photosensitivity • Hepatic encephalopathy • Foetotoxicity/use during second and third trimesters of pregnancy
Important potential risks	<ul style="list-style-type: none"> • Use during first trimester of pregnancy
Missing or limited information	<ul style="list-style-type: none"> • Children and adolescents • Lactating women • Patients with hepatic impairment • Patients with renal impairment • Ethnic differences

The Member States agree that routine pharmacovigilance and risk minimization activities are considered sufficient.

IV.6 Discussion on the clinical aspects

The pharmacokinetic studies were designed to demonstrate bioequivalence between the recognized reference formulations of the individual mono-components with the proposed fixed-dose combination as well as to investigate a possible pharmacokinetic interaction of the components. Results were satisfactory: the fixed dose combination can be used instead of the separate mono-components. Overall, the provided clinical overview is considered sufficient to justify the rationale of this particular triple combination when used to substitute patients already on stable doses of the separate agents. Data from clinical practice do not suggest any substantial different safety profile from that which is known for the mono-components.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The PL did not need to be adapted based on the results of the tests. For each question more than 90% of the participants was able to find the section and answer the question correctly. The results show that the package leaflet meets the

criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Arplexam film-coated tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Perindopril arginine, indapamide and amlodipine are well known, established substances, which are used as a combination in clinical practice.

Bioequivalence was demonstrated for Arplexam compared to BiPreterax® (perindopril/indapamide) plus one tablet of Norvasc® (amlodipine).

The results of an interaction study demonstrate that there is no significant pharmacokinetic interaction between the co-administered components of the applied combination product indapamide, amlodipine and perindopril.

The efficacy and safety profile of Arplexam is considered the same as for the monocomponents.

The content of the SmPC approved during the decentralised procedure is acceptable, as it contains all relevant information for each of the active substances. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The Member States, on the basis of the data submitted, considered that this fixed dose combination is approvable, since bioequivalence has been demonstrated with the innovator products of the individual components. The decentralised procedure was finalised with a positive outcome on 17 December 2013.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the number of units (e.g. tablets, ampoules, etc.) in a pack.	NL/H/2638/001-005/IB/001	IB	14-5-2014	13-6-2014	Approval	No

List of abbreviations

ACE	Angiotensin-Converting Enzyme
AUC	Area under the plasma concentration-time curve from time 0 (time of drug administration) to infinity
AUClast	Area under the plasma concentration-time curve from time 0 (time of drug administration) to t_{last}
AUC72	Area under the plasma concentration-time curve from time 0 (time of drug administration) to t_{72h}
BP	Blood Pressure
CEGEDIM	Cegedim is a global technology and services company specializing in the healthcare field
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
C_{max}	Maximum observed plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CSD	CEGEDIM Strategic Data
DBP	Diastolic Blood Pressure
EDQM	European Directorate for the Quality of Medicines
e.g.	<i>exempli gratia</i> , for example
EU	European Union
EMA	European Medicines Agency
EMR	Electronic Medical Record
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GP	General Practitioner
HCTZ	Hydrochlorothiazide
HDPE	High-density Polyethylene
HQ	Headquarter
ICH	International Conference of Harmonisation
i.e.	<i>id est</i> , that is
LPD	Longitudinal Patient Database
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package Leaflet
PP	Polypropylene
QbD	Quality by Design
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SR	Slow Release
t_{max}	Time corresponding to maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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