Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

Noliterax 10 mg/2.5 mg, film-coated tablet
Perindopril/Indapamide Servier 10 mg/2.5 mg, film-coated tablet

(Perindopril arginine / Indapamide)

FR/H/345/01/DC
FR/H/346/01/DC

Applicant: Les Laboratoires SERVIER

Date of the PAR: December 2009

Information about the initial procedure:

Application/Legal Basis	article 10 b
Active substance	**Perindopril arginine / Indapamide**
Pharmaceutical form	**film-coated tablet**
Strength	**10 mg/ 2.5 mg**
Applicant	**Les Laboratoires SERVIER**
EU-Procedure number	**FR/H/345-346/01/DC**
End of procedure	January 14th, 2009 – D183

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) on March 4th, 2009, for Noliterax 10 mg/ 2.5 mg and Perindopril arginine/Indapamide 10 mg/2.5 mg Servier, film-coated tablet, from Laboratoires Servier, as a substitution therapy of the mono-components perindopril arginine and indapamide given separately.

Note: Noliterax is used throughout the PAR also to indicate the associated name Perindopril/Indapamide 10 mg/2.5 mg Servier.

Noliterax is indicated in the following indication:

- *Substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril and indapamide given concurrently at the same dose level.*

A comprehensive description of the indications and doses is given in the SmPC.

These decentralised procedure applications concern a fixed combination application according to article 10b of directive 2001/83/EC.

This application is a substitution based on the "Note for Guidance on fixed combination medicinal products" (CPMP/EWP/240/95) and on the document CHMP/EWP/191583/2005 "*Questions and answers one the clinical development of fixed combinations of drugs belonging to therapeutic classes in the field of cardiovascular treatment and prevention*".

In support of this application, the applicant has submitted one bioequivalence study, 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, which is acceptable for this kind of application.

During the procedure, a potential serious risk to public health concerns was raised by one CMS regarding the interaction study but this issue was resolved by adequate responses of the applicant at D106.

The procedure was ended positively on January 14th, 2009.

2. QUALITY ASPECTS

2.1 Introduction

A new strength for the combination of perindopril arginine/indapamide is proposed: a film-coated tablet containing 10 mg of perindopril arginine and 2.5 mg of indapamide.

The drug product is a white and round tablet packaged in polypropylene tube closed with polyethylene stopper.

The qualitative and quantitative composition of this new strength is homothetic to the existing 5 mg/1.25 mg film-coated tablet currently authorised in Europe (FR/H/130/004/DC). The same manufacturing process is performed using the same blend whereas the final mass of tablets is proportional to the strength.

2.2 Drug substances

PERINDOPRIL ARGININE

Perindopril is a prodrug metabolised *in vivo* to perindoprilat, an ACE inhibitor which can treat certain cardiovascular conditions by lowering blood pressure.

- Manufacture

The process was 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.

- Specification

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

- Stability

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.

INDAPAMIDE

Indapamide is a non-thiazide sulphonamide diuretic drug, generally used in the treatment of hypertension and edema caused by congestive heart failure. Indapamide is a stable compound and its level quality is guarantied by its compliance to the Ph. Eur. Monograph (01/2008:1108, corrected 6.0).

The CEP procedure is followed.

- Manufacture

The manufacturing procedure has been assessed at the EDQM.

- Specification

The Ph. Eur. specifications are used except for the residual solvents and the particle size. The in-house method of determination of residual solvents by GC has been assessed by EDQM and is presented in an Annex of the CoS. The in house method for particle size is described and validated.

- Stability

A retest period of 3 years is included in the CoS for indapamide stored in industrial bulk packaging.

2.3 Medicinal product

The medicinal product Perindopril arginine/ Indapamide 10 mg/2.5 mg, film-coated tablet is formulated using excipients described in the current Ph. Eur.

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

The applicant demonstrated that the kinetics of dissolution of both drug substances from the new strength and the currently marketed strength are similar.

Additionally, a bioequivalence study was conducted comparing the proposed formulation (combination 10 mg/2.5 mg film-coated tablet) and two co-administered formulations marketed in France (perindopril arginine 10 mg film-coated tablet plus indapamide 2.5 mg film-coated tablet).

The description of the manufacturing process and manufacturing flow-chart are provided for each of the manufacturing sites. Equipments are presented, operating parameters are specified and critical steps have been identified.

No validation data is presented for 10 mg/2.5 mg tablets batches. However, validation of the content homogeneity of the final blend is demonstrated on full-scale batches of 5 mg/1.25 mg formulation and five certificates of analysis of the 5 mg/1.25 mg tablets issued from the declared sites are presented as supportive data. Considering that the manufacture of the 10 mg/2.5 mg tablets is the same as the manufacture of the 5 mg/1.25 mg tablets (final mass only differing), the manufacturing sites may be accepted without formal process validation results. The applicant's commitment to validating the manufacturing process at industrial scale, at each production site, before marketing and according to the protocol submitted in section 3.2.R.1 is noted. Meanwhile, the batch size accepted is limited to the pilot batch size.

The product specifications cover appropriate parameters for this dosage form. Adequate analytical methods are proposed for the control of the drug product. Their validations have been presented.

Certificates of analysis have been provided on industrial scale batches produced by all manufacturing site. The results show that the drug products meet the specifications proposed.

The container closure system for the drug product to be marketed is a tube made of polypropylene equipped with a flow reducer made of polyethylene and a stopper made of polyethylene containing desiccant gel. The packaging chosen is appropriate for the storage 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 shelf-life accepted for the drug product is 2 years.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Since this product is a combination of two widely used and well known substances based on a full application with regard to preclinical data, no further data have been submitted or are considered necessary, which is adequate. Pharmacodynamic, pharmacokinetic and toxicological properties of perindopril and indapamide are well known.

Extended non-clinical studies were carried out during the development of the first two dosages of the fixed combination perindopril *tert*-butylamine/indapamide: perindopril 2 mg/indapamide 0.625 mg (Preterax®) and perindopril 4 mg/indapamide 1.25 mg (Bipreterax®). The animal exposure, in the toxicology studies previously carried out, was superior to the human exposure at therapeutic doses and largely covers the perindopril 8 mg/indapamide 2.5 mg dosage. Moreover, Preterax® and Bipreterax® have the same proportions of perindopril *tert*-butylamine and indapamide (76% / 24%).

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 have been observed. Reproductive toxicity studies performed for perindopril *tert*-butylamine have not shown sign of embryotoxicity or teratogenicity.

Non-clinical data contained in this expert report on the toxicological and pharmacological documentation (Claude JR, 1996) submitted for the registration of perindopril 2 mg/indapamide 0.625 mg and perindopril 4 mg/indapamide 1.25 mg are summarized in the non-clinical overview.

No modification of Section 5.3. PreClinical Safety Data of the SmPC was necessary; the initial

MAH'proposal was endorsed by the RMS and all CMS.

Environmental risk

The product is intended as a substitute for identical products on the European market.

Evaluation of the potential environmental risk posed by the medicinal product has not been provided. As perindopril and indapamide are a well-known substance, generic and authorise, such an evaluation is deemed unnecessary. Approval of this product will not result in an increase in the total quantity of the active substance released into the environment, since it is intended as a substitute for other identical products on the market.

4. CLINICAL ASPECTS

4.1 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/indapamide and in the demonstration of absence of pharmacokinetic interaction between the both products.

4.2 Discussion on the clinical aspects

The efficacy of perindopril and indapamide has already been demonstrated during the clinical development of both substances. Perindopril and indapamide 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 inhibitor (ACEI) approved worldwide in more than 100 countries, including Europe (1st approval in France in 1988). It is a prodrug that is hydrolysed to the active metabolite, perindoprilat. Both perindoprilat and to lesser extent perindopril are glucuronised into their respective glucuronides, which are inactive. Perindoprilat also facilitates vasodilatation by preventing breakdown of bradykinin. Perindoprilat is *in vitro* about 1000 fold more potent than perindopril. The pharmacokinetics and pharmacodynamics of perindopril and perindoprilat are well known. Perindopril has been used in the proposed indications of hypertension and heart failure for many years and in stable coronary heart disease recently. Perindopril arginine is available as 2.5 mg, 5 mg and 10 mg. The advantage of this salt is to be more stable than perindopril *tert*-butylamine.

- Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. Indapamide has been used in the proposed indications of hypertension. Indapamide is an antihypertensive diuretic agent used by 2,300,000 hypertensive patients every day. Indapamide immediate release (IR) 2.5 mg and 1.5 SR have been registered in more than 100 countries since 1974 and 1996 respectively, including Europe.

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

Clinical safety

The safety of perindopril and indapamide 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 potentialisation of adverse effects.

Perindopril was approved for the first time in 1988; Indapamide was approved since 1974 i.e. there is more than 10 years post-authorisation experience with the active substance.

The safety profile of both perindopril arginine and indapamide can be considered well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SmPC.

No new safety concerns have been identified with the reference medicinal product.

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

Provided that pharmacovigilance system issues are resolved, routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

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

RMP. As the fixed dose combinations have been extensively used worldwide as free combinations and as these fixed dose combinations are only 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 indapamide and perindopril.

4.3 Pharmacokinetics

Considering that Noliterax is a new fixed combination of two already approved and largely used active substances: perindopril arginine and indapamide, 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-05597-002"

One interaction study was performed with the dosage form (P 8mg/I 2.5mg) "PKH-05597-002" to investigate whether a pharmacokinetic interaction after single oral administration exists between perindopril tert-butylamine 8 mg and indapamide 2.5 mg.

The study was designed as a randomised cross-over open level study, with three single administrations. 36 healthy volunteers were included and only 34 participants completed the study. The three-period cross-over consisted of:

- Period 1 (P1) : single oral administration of one tablet of perindopril tert-butylamine 8 mg and one tablet of indapamide 2.5 mg in co-administration or one tablet of perindopril tert-butylamine 8 mg or one tablet of indapamide 2.5 mg depending on the randomisation.

- Period 2 (P2): second single oral administration of one of the 2 treatments not received during P1 ;

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

Treatments:

Test product:

One tablet of S9490 (perindopril *tert*-butylamine 8 mg) co-administered with one tablet of S1520 (indapamide 2.5 mg).

Reference product:

S9490: tablet (Coversyl®) containing 8 mg of perindopril *tert*-butylamine, administered *po*.

Batch: L0011163, packaging batch: Q01008, expiry date: 01/12/2007.

S1520: tablet (Fludex®) containing 2.5 mg of indapamide, administered *po*.

Batch: L0014847, packaging batch: Q01008, expiry date: 01/12/2007.

Pharmacokinetic analysis: Pharmacokinetic parameters (Cmax, Tmax, AUC) of perindopril *tert*-butylamine, perindoprilat and indapamide.

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=34)	Geom. Mean (geom. CV%) Treatment R (n=34)	Ratio T/R (90% Confidence Interval)
Perindopril			
AUC_{last} (ng.h/ml)	85.0 (22%)	84.2 (25%)	101% (97%, 105%)
AUC (ng.h/ml)	85.7 (22%)	84.9 (25%)	101% (97%, 105%)
C_{max} (ng/ml)	73.4 (22%)	67.0 (29%)	110% (101%, 119%)
t_{max} (h)	0.75 (0.25 – 2.00)*	0.75 (0.50 – 2.00)*	-
Perindoprilat			
AUC_{last} (ng.h/ml)	201 (26%)	210 (26%)	96% (93%, 99%)
AUC (ng.h/ml)	244 (27%), n=22**	247 (29%), n=19**	94% (90%, 99%), n=15
C_{max} (ng/ml)	9.8 (50%)	10.7 (50%)	92% (85%, 99%)
t_{max} (h)	4.04 (3.00 – 8.00)*	4.00 (3.00 – 8.00)*	-

* : median and range; T : Test (S9490+S1520); R : Reference (S9490).

** : if percentage of AUC extrapolated from AUC_t is greater than 20%, the AUC value is not reported.

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=34)	Geom. Mean (geom. CV%) Treatment Q (n=34)	Ratio T/Q (90% Confidence Interval)
Indapamide			
AUC_{last} (ng.h/ml)	665.1 (25%)	661.5 (28%)	100% (96%, 105%)
AUC (ng.h/ml)	684.6 (25%)	681.2 (27%)	101% (96%, 105%)
C_{max} (ng/ml)	30.5 (28%)	29.9 (24%)	102% (97%, 107%)
t_{max} (h)	2.50 (0.83 – 8.00)*	3.00 (0.75 – 8.00)*	-

* : median and range; T : Test (S9490+S1520); Q : Reference (S1520)

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 *tert*-butylamine in treatment "T" / perindopril *tert*-butylamine in treatment "R", perindoprilat in treatment "T" / perindoprilat in treatment "R" and indapamide in treatment "T" / indapamide in treatment "Q") were fully contained within the same acceptance ranges [80–125%] for perindopril *tert*-butylamine, perindoprilat and indapamide described for bioequivalence studies.

Bioequivalence study:

Study PKH-6597-001: Bioequivalence study of one tablet of the fixed combination of perindopril arginine 10 mg/indapamide 2.5 mg versus one tablet of perindopril arginine 10 mg plus one tablet of

indapamide 2.5 mg : Bioequivalence of Noliterax to the current Coversyl and Fludex when co-administred freely.

This was a randomised open level study, with a two-period cross-over, 37 subjects included and 36 healthy volunteers completed the study.

Treatment 1: one tablet of the fixed combination of perindopril arginine (10 mg)/indapamide (2.5 mg)

Treatment 2: one tablet of perindopril arginine 10 mg + one tablet of indapamide 2.5 mg.

The plasma concentration of perindopril, perindoprilat and indapamide 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 this study are tabulated below.

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_{last} (ng.h/mL)	81.5 (25%)	80.3 (25%)	102% (98%, 105%)
AUC4 (ng.h/mL)	82.1 (25%)	80.9 (24 %)	102% (98%, 105%)
C_{max} (ng/mL)	68.3 (37%)	71.0 (32%)	96% (88%, 105%)
t_{max} (h)	0.75 (0.50 – 3.00)*	0.75 (0.50 – 1.50)*	-

* : median and range; T : Test (S6597); R : Reference (S6490+S1520)

Parameter (unit)	Geom. Mean (geom. CV%) Treatment T (n=36)	Geom. Mean (geom. CV%) Treatment R (n= 36)	Ratio T/R (90% Confidence Interval)
Perindoprilat			
AUC_{last} (ng.h/ml)	232.4 (26%)	221.9 (25%)	105% (102%, 108%)
AUC4 (ng.h/ml)	277.4 (25%), n=31**	264.3 (27%), n=27**	103% (100%, 107%), n=26
C_{max} (ng/ml)	11.9 (44%)	10.9 (43%)	109% (103%, 116%)
t_{max} (h)	4.00 (3.00 – 8.00)*	4.00 (3.00 – 8.00)*	-
Indapamide			
AUC_{last} (ng.h/ml)	516.4 (27%)	554.5 (29%)	93% (89%, 97%)
AUC4 (ng.h/ml)	537.7 (26%)	572.4 (28%)	94% (90%, 98%)
C_{max} (ng/ml)	29.9 (22%)	28.3 (22%)	106% (101%, 110%)
t_{max} (h)	2.00 (0.75 – 4.0)*	2.00 (0.5 – 4.02)*	-

*: median and range; T: Test (S6597); R: Reference (S6490+S1520).

**: if percentage of AUC extrapolated from AUCt is greater than 20%, the AUC value is not reported.

The bioequivalence of Noliterax to Coversyl 10 mg and Fludex 2.5 mg coadministered freely was demonstrated in this study with respect to the three components, perindopril, its active metabolite perindoprilat, and indapamide.

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.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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

Following Day 70, the SmPC and PL were amended to implement information of the use of ACE inhibitors during pregnancy and lactation according to the recommendations of the PhVWP. Indeed, a contra indication of the use of ACE inhibitors during the second and third trimesters of pregnancy has been maintained in Section 4.3. (Contra Indications) of the SmPC. The use of ACE inhibitors remains however not recommended during the first trimester of pregnancy. Regarding lactation, as no information is available, the use of ACE inhibitors is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. Sections 4.4. (Special warnings and precautions for use) and 4.6. (Pregnancy and lactation) of the SmPC and the corresponding sections of the Package Leaflet have also been amended accordingly.

In conclusion, all issues being solved, all the CMS considered that Noliterax 10 mg/2.5 mg and Perindopril arginine/Indapamide Servier 10 mg/2.5 mg, film-coated tablets are approvable.

The current SmPC, Package Leaflet (PL) and packaging are in the agreed template.