Agence française de sécurité sanitaire des produits de santé

**Direction de l'Evaluation**
**des Médicaments et des Produits Biologiques**

# PUBLIC ASSESSMENT REPORT
# Scientific Discussion

# Preterian 2.5mg/0.625mg
# Preterian 5mg/1.25mg
# Preterval 5mg/1.25mg
# Film-coated tablets

# (perindopril arginine/indapamide)

# FR/H/130/03-04/E/01
# FR/H/131/04/E/01
# Applicant: Servier

**Date of the PAR: April 2009**

**Information about the initial procedure:**

| | |
|---|---|
| **Application/Legal Basis** | Full Dossier Art 8.3 Dir 2001/83/EC |
| **Active substance** | perindopril arginine/indapamide |
| **Pharmaceutical form** | film-coated tablets |
| **Strength** | 5mg/1.25mg and 2.5mg/0.625mg |
| **Applicant** | Servier |
| **EU-Procedure number** | FR/H/130/03-04/E/01 and FR/H/131/04/E/01 |
| **End of procedure** | 17/12/2007 |

## 1. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for **Preterian 2.5mg/0.625mg, Preterian 5mg/1.25 mg, and Preterval 5mg/1.25mg film-coated tablets** from Laboratoires Servier on February 13th, 2007; in the treatment of "*Essential hypertension*".

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

This application is a Repeat Use of another already validated marketing authorisation for the medicinal product: **Preterian 2.5mg/0.625mg, Preterian/Preterval 5mg/1.25 mg, film-coated tablet**. These former products were registered through a decentralised procedure finalised in October 2006. They were new formulations of already marketed fixed doses combinations of perindopril /indapamide, resulting from a change of the perindopril salt (replacement of the tert-butylamine by the arginine salt). No other modification of neither active substance nor dose was performed.

As a reminder, perindopril tert-butylamine/indapamide has been marketed since 1999 and registered in 109 countries for the treatment of hypertension, with a low dose of each of the two constituents (Preterax 2 mg/0.625 mg) allowing first-line treatment to be started and a higher dose (Bipreterax 4mg/1.25 mg) for use in case of insufficient efficacy.

In support of this application, the applicant has submitted the same quality, efficacy and safety data than for the previous procedures. This is justified as this is a Repeat Use.

During the decentralised procedure, no potential serious risk to public health concerns was raised on the quality, preclinical efficacy and safety data.

The procedure was ended positively and a marketing authorisation (MA) was granted by all CMS for **Preterian 2.5mg/0.625mg Preterian 5mg/1.25 mg, and Preterval 5mg/1.25mg**, film-coated tablet.

## 2. QUALITY ASPECTS

### Introduction

Two dosage combinations of perindopril/indapamide are proposed:
- a tablet containing 2.5 mg of perindopril arginine and 0.625 mg of indapamide and finished to a mass of 93 mg.
- a tablet containing 5 mg of perindopril arginine and 1.25 mg of indapamide and finished to a mass of 93 mg.

The primary packaging is a polypropylene white container equipped with a low density polyethylene flow reducer and a low density polyethylene white opaque stopper containing a white desiccant gel.

### Drug substance

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

The process is described in only one step from perindopril *tert*-butylamine salt which has a level quality guaranteed by its compliance to the Ph. Eur. Monograph. 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 double polyethylene bag overwrapped in a sealed complex bag made of LDPE/alu/polyester and placed in cardboard drums.

Indapamide is a non-thiazide sulphonamide diuretic drug. Indapamide is a stable compound and its level quality is guaranteed by its compliance to the Ph. Eur. Monograph.

The CEP procedure is followed. Therefore the manufacturing procedure has been assessed at the EDQM.

The Ph. Eur. specifications are used except for the residual solvents (isopropanol) and the particle size. The in-house method of determination of isopropanol by GC has been assessed by EDQM and is presented in an Annex of the CoS. The in house method for particle size performed on a skip testing basis is described and validated.

The packaging material (double polyethylene bags closed with a plastic tie placed inside a cardboard drum with a metal lid secured by a zinc-plated band) and the retest period (3 years) are included on the CoS and are therefore acceptable.

**Medicinal product**

**Drug Product**

The qualitative and quantitative compositions of both strengths are identical with the exception of the amount of filler (lactose monohydrate) used to compensate the differences in weight of active substances.
Both strengths are white rod-shaped film coated tablets with a theoretical mass of 93mg. In order to differentiate them, the applicant has agreed to emboss a line on both faces of the tablet containing 2.5 mg/0.625 mg.
The development is sufficiently described in accordance with the relevant European guidelines.
The description of the manufacturing process and manufacturing flow chart highlighting the in process controls, are provided for each of the two manufacturing sites. Equipments are presented.
For the two manufacturing sites proposed, the operating parameters are specified in the description of the manufacturing process. The critical parameters have been identified and optimised during the development section.
A process validation scheme is provided in section 3.2.R.1. and a commitment is made to perform the validation before marketing the tablets.

The product specifications cover appropriate parameters for this dosage form. Adequate analytical methods and validations are proposed for the control of the drug product. The batch analysis results show that the drug products meet the specifications proposed.

The container closure system is a white opaque 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 data support the shelf life claimed in the SPC, 30 months with the following storage precaution “Keep the container tightly closed to protect from the moisture”.

## 3. NON-CLINICAL ASPECTS

### Discussion on the non-clinical aspects

No new preclinical studies were performed with the combination of perindopril arginine and indapamide. The preclinical expert report is based on : i) the expert report on the toxicological and pharmacological documentation already submitted for the registration of Preterax; ii) the Common Technical Document submitted for the registration of perindopril arginine salt (S 6490, Biocoversyl), in which preclinical comparative studies between perindopril tert-butylamine and arginine salts are described.

Perindopril and indapamide pharmacology has been largely studied in the animal, separately and in combination. Given that perindopril both tert-butylamine salt or arginine salt pharmacokinetics was studied in animals (rat and dog) and as both perindopril salts are bioequivalent in human volunteers, it is acceptable that no pharmacological study to compare blood pressure lowering effects of the two salts was performed.

Previously submitted pharmacokinetic and toxicokinetic studies performed in rats and dogs after repeated oral administration of equimolar doses of either perindopril salt showed that both salts have similar pharmacokinetic profile. As the perindopril tert-butylamine salt and the perindopril arginine salt were shown to be bioequivalent in human volunteers, it is acceptable that no new studies in animals for the development of the combination perindopril arginine with indapamide were performed.

The aim of the evaluation of perindopril arginine salt was to compare the general toxicity for single dose toxicity in rats and mice (perindopril arginine is devoid of acute toxicity and comparable to perindopril tert-butylamine) and for repeated dose toxicity in rats and dogs in performing four-week bridging studies in rats and dogs by oral route. The pharmacokinetic parameters and the safety profiles were identical for the two salts irrespective of the animal species and the dose level. The potential genotoxicity of perindopril arginine was also investigated with a battery of tests including in vitro and in vivo tests and confirming the absence of genotoxicity of the new salt arginine, previously demonstrated for perindopril tert-butylamine. A qualification of two impurities generated from the synthesis pathway was also performed.

Considering the extensive knowledge on the non-clinical data for the combination perindopril tert-butylamine with indapamide and the identical safety profile of the two salts perindopril tertbutylamine and perindopril arginine, it can be stated that the new fixed combination perindopril arginine/indapamide does not raise any new non-clinical concerns. Section 5.3 of the SPC adequately reflects the preclinical data.

## 4. CLINICAL ASPECTS

### 4.1. Introduction

The fixed combinations Preterian (perindopril arginine/Indapamide) are pharmaceutical alternatives of the already approved fixed combinations perindopril tert-butylamine salt/indapamide.

### 4.2. Discussion on the clinical aspects

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC.

### 4.3. Pharmacokinetics

The clinical pharmacokinetics (PK) of both active ingredients of the fixed combination (indapamide and perindopril) has already been studied and fully characterized during the previous development of the monocomponent drug products: Fludex (indapamide), Coversyl (perindopril *ter*-butylamine), Biocoversyl (perindopril arginine) and the fixed combination Preterax and Bi-Preterax (perindopril

*ter*-butylamine and indapamide). Additionally to the characterization of the PK behaviour of each active ingredient, the most relevant findings of the previous PK development were:

- Lack of significant PK interaction potential between both components of the fixed combination.

- Similar PK behavior of both perindopril salts: *ter*-butylamine and arginine.

To support the application, the MAH has submitted as report a bioequivalence study investigating the highest strengths: perindopril arginine salt 5 mg/indapamide 1.25 mg versus perindopril tert-butylamine salt 4 mg/indapamide 1.25 mg. A biowaiver was claimed and accepted for the lower strength 2.5/0.625 mg. All criteria for biowaiver were fulfilled consistently with the CHMP NfG on the investigation of Bioavailability and Bioequivalence.

The study was conducted according to an open-label, two-treatment, two-period, two-sequence, single-dose (5 mg-equivalent perindopril arginine salt 5 mg/indapamide 1.25 mg) cross-over design. Thirty-four (34) adult healthy male and female volunteers were enrolled and randomized. All of them finished the study and were analyzed as per protocol according to the statistical plan.
Plasma concentrations of perindopril, perindoprilat and indapamide were monitored in the collected plasma samples by the means of fully validated analytical techniques. The primary PK parameters investigated in the study were: AUC0-t, AUC0-inf, Cmax and Tmax. The findings of the study are tabulated below.

Perindopril: Pharmacokinetic parameters (geometric mean ± CV %, $T_{max}$ median, range).

| **Treatment** | **$AUC_{0-t}$** **ng/ml/h** | **$AUC_{0-\infty}$** **ng/ml/h** | **$C_{max}$** **ng/ml** | **$t_{max}$** **h** |
|---|---|---|---|---|
| **Test** | 38 (26%) | 38 (26%) | 31 (37%) | 0.75 [0.5-2.0] |
| **Reference** | 37 (29%) | 38 (28%) | 29 (36%) | 0.75 [0.5-1.5] |

Perindoprilat: Pharmacokinetic parameters (Geometric mean ± CV %, $T_{max}$ median, range).

| **Treatment** | **$AUC_{0-t}$** **ng/ml/h** | **$C_{max}$** **ng/ml** | **$t_{max}$** **h** |
|---|---|---|---|
| **Test** | 140 (27%) | 3.4 (48%) | 8.0 [4.0-12] |
| **Reference** | 144 (22%) | 3.4 (43%) | 8.0 [4.0-12] |

Indapamide: Pharmacokinetic parameters (geometric mean ± CV %, $T_{max}$ median, range).

| **Treatment** | **$AUC_{0-t}$** **ng/ml/h** | **$AUC_{0-\infty}$** **ng/ml/h** | **$C_{max}$** **ng/ml** | **$t_{max}$** **h** |
|---|---|---|---|---|
| **Test** | 259 (25%) | 280 (24%) | 16 (26%) | 1.5 [0.75-6.0] |
| **Reference** | 257 (27%) | 278 (26%) | 16 (29%) | 3 [1.0-6.0] |

Perindoprilat pre-dose concentrations values slightly above the LLOQ were detected at period 2 in 3 subjects for test treatment and 3 subjects in reference treatment. In order to demonstrate that such observations could not bias the conclusions of the study, the investigators performed a re-analysis of the data, based on baseline-corrected plasma concentrations of perindoprilat. The outcome of this analysis (not reported here) confirmed the conclusions of the initial analysis.
Conclusively, the bioequivalence of the new fixed combination tablet 5 mg perindopril arginine/1.25 mg indapamide and the current 4 mg tert-butylamine perindopril/1.25 mg indapamide tablets could be considered demonstrated.

Waiver from bioequivalence study for the 2.5/0.625 mg strength was claimed by the applicant and accepted as all the requirements for biowaiver were fulfilled.

## 5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Considering the extensive knowledge on the preclinical data for the combination perindopril *tert*-butylamine/indapamide and the identical safety profile of the two salts perindopril *tert*-butylamine and perindopril arginine, it can be stated that the new fixed combination perindopril arginine salt/indapamide does not raise any new preclinical concerns.

Based on the submitted bioequivalence study, Preterian/Preterval 5mg/1.25 mg, film-coated tablets (arginine salt) is bioequivalent with Bipreterax (tert-butylamine salt) 4 mg/1.25 mg. Results of study CL1-06590-001 with 5 mg/1.25 mg formulation can be extrapolated to the other strength 2.5 mg/0.625 mg, according to the conditions of the Note for Guidance on "the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.". As both Preterian 2.5mg/0.625mg and Preterian/Preterval 5mg/1.25 mg, film-coated tablets are similar to Preterax Arginine 2 mg/0,625 mg and BiPreterax Arginine 4 mg/1,25 mg, a marketing authorisation can be recommended.

Bioequivalence between both salts has been shown to be in compliance with the European Guidance documents.

The SPC is consistent with the efficacy and safety profile of both components.

The SPC, Package Leaflet and labelling are in the agreed template.

The Member States mutually recognised the French evaluation of the marketing authorisation.