Public Assessment Report

Scientific discussion

Name of the Product:
Co-Prenessa 8 mg/2.5 mg tablets

perindopril/indapamide

Procedure number:
HU/H/0150/003/DC

Marketing authorisation holder: Krka d. d.

Date: 19 July 2012

This module reflects the scientific discussion for the approval of Co-Prenessa 8 mg/2.5 mg tablets. The procedure was finalised at 29 November 2011. For information on changes after this date please refer to the module 'Update'.

CONTENT

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Czech Republic, Denmark, Estonia, Finland, Latvia, Lithuania, Poland, Romania, Slovakia) concerned the generic version of a perindopril/indapamide 8mg/2.5mg combination.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The originator product was BiPreterax® tablet from Les Laboratoires Servier, authorised for marketing since November, 1997.

The product containing the active substances ACE inhibitor perindopril erbumine and the non-thiazid diuretic indapamide is indicated as substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril and indapamide given concurrently at the same dose level.

Krka has already had marketing authorisations for its perindopril/indapamide 2 mg/0.625 mg and 4 mg/1.25 mg tablets since 2007 in Hungary.

The three strengths of tablets (the formerly authorised ones and the present 8 mg/2.5 mg) have the same qualitative compositions and are dose-proportional. They are manufactured according to the same manufacturing directions.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Co-Prenessa 8 mg/2.5 mg tablets, from Krka d.d.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The combination product is indicated as substitution therapy for treatment of essential hypertension in patients already controlled with perindopril and indapamide given concurrently at the same dose level.

The tablets contain 8 mg and 2.5 mg of the active substances of perindopril erbumine and indapamide, respectively. They are packed in transparent thermoformed PVC/PE/PVDC//Aluminium foil blisters and box.

II.2 Drug Substances

Perindopril erbumine

The applicant indicated to follow an EDMF-procedure for polymorph form α of perindopril erbumine. Letter of access for the EDMF has been submitted. Perindopril erbumine is described in the European Pharmacopoeia (Ph. Eur).

INN name: perindopril erbumine
Chemical name: 2-Methylpropan-2-amine(2S,3aS,7aS)-1-((S)-2-((S)-1-ethoxy-1-oxopentan-2ylamino)propanoyl)octahydro-1H-indole-2-carboxylate

The active substance is a white or almost white, slightly hygroscopic crystalline powder and is freely soluble in water and in ethanol. It shows polymorphism: perindopril erbumine exists in hydrate forms and in anhydrous polymorphic forms demonstrated as α, β and γ modifications.

The molecule has five asymmetric centres, thus, theoretically 32 stereo isomers can exist. Stereochemical purity is routinely controlled according to the Ph. Eur. method.

The manufacturing process has been adequately described; critical steps and corresponding in-process controls have been defined to ensure adequate quality of the final substance. The in-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, NMR spectra and by FT-IR spectra. Polymorphism is controlled by X-ray powder diffraction test which is routinely performed as an in-process control (IPC 7) to demonstrate the consistency of the manufacturing process.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in respect of their origin and potential carry-over into the final drug substance.

The active pharmaceutical ingredient is specified according to the requirements of the current Ph. Eur. monograph, additional specification have been set for heavy metals and for some residual solvents used in the synthesis (controlled by a GC method).

The substance complies with the requirements of the EMEA guideline on genotoxic impurities.

The Ph. Eur. specification includes the following tests for perindopril erbumine: appearance, solubility, identification (specific optical rotation, IR, TLC), impurity A (TLC), stereochemical purity (HPLC), related substances (HPLC), water content, sulphated ash, assay (titration). The specification is in accordance with the Ph. Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Ph. Eur. are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterized.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

During the stability studies no significant changes in any parameters were observed. The proposed retest period of 2 years is supported by the submitted stability data with the storage condition: “Do not store above 25°C. Store in the original packaging, in order to protect from moisture”.

GMP compliance of the API manufacturer has been demonstrated.

Indapamide

The Applicant has submitted a Ph. Eur. Certificates of Suitability for drug substance indapamide. The CEP indicates that the Ph. Eur. monograph is adequate to control the purity of the substance, provided that it is supplemented with a test for related substances to detect any other detectable impurity by HPLC (not more than 0.10 %) and a test for the residual solvents by GC.

INN name: indapamide
Chemical name: 4-chloro-N-[2’(R,S)-methyl-1’-indolinyl]-3-sulfamoylbenzamide

The active substance is a white or almost white powder and is practically insoluble in water.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents and particle size.

The Ph. Eur. specification includes the following tests for indapamide: appearance, solubility, identification (IR, UV spectrophotometry, TLC), optical rotation, related substances (HPLC), impurity A (HPLC), heavy metals, water content, sulphated ash, assay (HPLC). Residual solvents (GC) and particle size are also controlled. The specification is in accordance with the Ph. Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance.

Residual solvent method not described in the Ph. Eur. is adequately drawn up and sufficiently validated.

The laser diffraction method for particle size determination has been adequately described and validated.

Reference materials used for the control of the substance are adequately characterized

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

The re-test period mentioned in the CEP is five years with no special storage conditions.

GMP compliance of the API manufacturer has been demonstrated by the Applicant.

II.3 Medicinal Product

The drug product is an immediate release tablet containing a fixed combination of perindopril erbumine and indapamide.

The aim of the formulation development was to formulate immediate release tablets with adequate technological and stability properties, and with an in vivo performance comparable to that of BiPreterax® tablets (Servier). This formulation study was based on the development of the single entity Perindopril Erbumine tablets and the Perindopril / Indapamide 2 mg/0.625 mg and Perindopril / Indapamide 4 mg/1.25 mg tablets.

Perindopril/indapamide 2 mg/0.625 mg and 4 mg/1.25 mg of the Krka have already been authorized. These three strengths of tablets (2 mg/0.625 mg, 4 mg/1.25 mg and present developed 8 mg/2.5 mg) have the same qualitative compositions and are dose-proportional. They are manufactured according to the same manufacturing directions.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

The excipients used in the finished product are lactose monohydrate, microcrystalline cellulose, sodium hydrogen carbonate, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. regarding the risk of TSE has been demonstrated by the applicant. The functionality related characteristics of the excipients has been discussed.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The perindopril erbumine/Indapamide 8 mg/ 2.5 mg tablets are presented as white, oval, slightly biconvex, one side scored tablets.

The tablets are packed into PVC/PE/PVDC//Al blisters.

Description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. Validation data on three full scale batches are presented. GMP compliance of the manufacturing sites has been demonstrated

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as detailed in the relevant dosage form monograph of the Ph. Eur. pharmacopoeia and the ICH Q6A guideline. Appropriate control strategy was selected. Certificates of analysis for the batches involved in the bioequivalence study are presented.

Standard pharmacopoeial test methods are used in respect of disintegration, hardness, uniformity of dosage units by content uniformity, water content, and microbiological purity. Validated analytical methods have been presented for assay, test for impurities and degradation products, as well as dissolution test (HPLC method).

IR spectra and certificates of analysis justifying the conformity to the Ph. Eur. monograph 3.1.11. and compliance with European Commissions' regulations (78/142/EEC and 1935/2004/ EC) are provided.

According to dissolution characteristics of the products (including both, batch and stability data) the proposed specification limit is justified and therefore acceptable.

Batch data have been provided and complied with the specification set by the manufacturer. Certificates of analysis were also provided for the working standard used.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the presented results, a shelf-life of 24 months when "stored below 30°C" is approved.

The SPC, PIL and label are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is concluded that the product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the products.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both perindopril and indapamide are well known.

Claiming that both drugs are widely used well-known active substances the Applicant has not performed further studies. The overview is based on literature review.

According to the Guideline on the *Non-Clinical Development of Fixed Combinations of Medicinal Products* (CHMP/EMEA/CHMP/SWP/258498/2005) perindopril/indapamide combination can be considered as stated in "Scenario 1":

"A fixed combination of compounds already approved as free combination therapy."

In this case the Guideline recommends the following:

"When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95)."

Both perindopril and indapamide are widely used antihypertensive medicines, the human experience is vast. As the Applicant has also presented data about significant co-administration of the two compounds the experience on the combination can also be considered sufficient.

III.2 Pharmacology

Perindopril

Perindopril is a prodrug; it exerts its angiotensin converting enzyme (ACE)-inhibitory effect by the main metabolite perindoprilate. By inhibiting ACE it reduces the production of angiotensin II, a potent vasopressor thus dilates blood vessels. Angiotensin II also stimulates aldosterone release consequently increasing plasma volume and excreting potassium. Therefore the lower plasma level of angiotensin II leads to decreased aldosterone secretion as well. Furthermore, as ACE is involved in the metabolism of bradykinin the higher level of bradykinin may also contribute to the vasodilatory effect of perindopril.

In vivo studies show, under various experimental conditions in normotensive, renovascular hypertensive, spontaneously hypertensive animals and experimental models of heart failure, that perindopril inhibits the pressor response to angiotensin II and induces the predicted modifications in the plasma levels of the components of the renin-angiotensin-aldosterone system (RAS): raised plasma renin activity, raised angiotensin I and decreased angiotensin II and aldosterone.

ACE inhibitors may display antidepressant-like properties in rats.

Indapamide

Indapamide belongs to the diuretics and is similar to thiazides both in its structure and mechanism of action. Indapamide inhibits the Na^+ and Cl^- reabsorption in the distal convoluted tubules of the kidney thus reducing the plasma sodium concentration that leads to increased diuresis in the beginning of the treatment. Since sodium loss activates the renin-angiotensin-aldosterone system thiazide diuretics may cause hypokalemia as a consequence of higher aldosterone level. During continuous treatment the diuretic effect, as well as the total body sodium content decreases that may partly be responsible for the antihypertensive effect of thiazides.

Perindopril/indapamide combination

The Applicant has not conducted any combination study in animals. Since there are several other perindopril/indapamide combination products marketed and the toxicological profile of the combination is well-known lack of specific preclinical safety studies on the combination of the two compounds could be considered justified.

III.3 Pharmacokinetics

Perindopril

Perindopril is prodrug and is rapidly absorbed after oral administration. It is extensively metabolised in the liver to the active metabolite perindoprilat and other, inactive, metabolites including glucuronides. Peak plasma concentrations are achieved 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10–20 % bound to plasma proteins in humans. The binding of perindopril and percentage of bound drug or metabolite is below that which would be expected to cause drug interactions.

Perindopril crosses the blood-brain barrier and inhibited brain ACE at high doses. Milk of lactating rats contained radioactivity following administration ^{14}C-perindopril. It is not known whether perindopril is secreted in human milk.

Perindopril is excreted predominantly in urine in humans, but the main excretory route in laboratory species was via the faeces.

Indapamide

In animals (rat and dog) and man, investigated indapamide (10 mg) is rapidly absorbed with maximal plasma levels of 140 ng/ml reached within 0.5–1 hour after administration. In rats the distribution half-life of 1.7 hours and elimination half-lives of 7 and 15 hours. Indapamide is extensively metabolized in animal and human liver with only 7 % or less the dose excreted in the urine as unchanged drug. Similar results were reported in dogs. In humans more than five (as many as 19) metabolites are postulated. Hydroxylation of the indoline ring is believed to result in a major metabolite. This compound shows somewhat less antihypertensive activity than indapamide in animal studies. It is not known whether any of the other metabolites are pharmacologically active. Radioactive tracer studies show that conjugated products represent

approximately 18 % of the excreted radioactivity, with 14% excreted as glucuronides and 4 % as sulfates.

The excretion rate of unchanged indapamide into the urine against the given dose was 3.0 %, 9.1 % and 5.2 % in male rats, female rats and dogs, respectively, showing low values. There was a sex difference for excretion rate of the drug in rats. The major metabolite detected in the bile of rats and dogs was 5-hydroxy-indapamide. It was clarified that the hydroxyl group at the 5-position of indapamide was bound to glucuronic acid or sulfuric acid.

The enterohepatic circulation of the glucuronic acid conjugates and sulfate of 5-hydroxy-indapamide was studied. Both conjugates were absorbed slowly from the intestinal tract compared with indapamide. This suggests that the conjugates are first hydrolyzed in the intestinal tract and reabsorbed subsequently there from. The dominant metabolite of indapamide in faeces of rats and dogs was 5-hydroxy-indapamide which was assumed to be excreted into their faeces through the bile.

The urinary excretion rate-time curves following oral administration of 20 mg indapamide to dogs suggest biphasic elimination with approximate half-life of 2-4 hours and 11–21 hours.

III.4 Toxicology

Since both perindopril and indapamide are widely used medicines and the toxicology profiles are well-known no specific studies were required.

III.5 Ecotoxicity/environmental risk assessment

Since both perindopril and indapamide are widely used medicines and Co-Prenessa 8 mg/2.5 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. Therefore, no environmental risk assessment is deemed necessary.

III.6 Discussion on the non-clinical aspects

The Application is based on Article 10(1) of Directive 2001/83/EC, generic application. Pharmacodynamics, pharmacokinetics and toxicology of both perindopril and indapamide are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The justification for a combination of perindopril and indapamide is based on their synergistic effects. The combination is intended for use as a substitution in patients suffering from hypertension. In this case no specific clinical pharmacological study is needed in agreement with the requirements stated in the documents CHMP/EWP/240/95 Rev. 1 *Guideline on Clinical Development of Fixed Combination Medicinal Products* and CHMP/EWP/191583/2005 *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*.

The Applicant adequately summarized the clinical experience with perindopril and indapamide. The justification of the missing specific pharmacokinetic interaction studies between perindopril and indapamide is acceptable. To support the application the Applicant has submitted one bioequivalence study conducted in accordance with the *Guideline on Bioequivalence* (CHMP/EWP/QWP/1401/98/Rev.1).

IV.2 Pharmacokinetics

Perindopril

Perindopril is rapidly absorbed following oral administration, with peak plasma concentrations occurring at 1 hour post administration. The absolute oral bioavailability has been variously reported as 66% to 95% according to different trials, it is approximately 75%. Perindopril undergoes extensive metabolism after oral administration, resulting in formation of perindoprilat. About 20% of the available parent drug is transformed into this metabolite. The formation of perindoprilat is slow. Mean t_{max} for perindoprilat is generally within 3 to 4 hours, and was at the lower end of this range after repeated administration for 4 weeks. Perindopril is 74% bound in serum at steady state concentrations; the main binders are serum albumin and a1-acid glycoprotein. Perindoprilat is about 15% bound to plasma proteins. Values for volume of distribution for perindopril and free perindoprilat are 0.22 and 0.16 L/kg, respectively, after single oral dose of perindopril 8 mg.

Conversion of perindopril to perindoprilat takes place primarily in the liver although some hydrolysis may also occur in the plasma and the intestinal wall. After absorption perindopril also undergoes first-pass metabolism to form perindopril glucuronide which is subsequently hydrolyzed to perindoprilat glucuronide. Perindoprilat, the active ACE inhibitor, is formed directly from perindopril by hydrolysis. Perindopril and perindoprilat also undergo cyclisation to produce five inactive metabolites, perindopril lactam and perindoprilat lactams. The partial metabolic clearance of perindopril to perindoprilat is 6.12 L/h, with a corresponding value of 3.6 L/h for the partial metabolic clearance perindopril to perindopril glucuronide.

Both perindopril and perindoprilat glucuronide are cleared renally. Mean total body clearance was 31 L/h for perindopril and 41 to 46 L/h for perindoprilat. Mean renal clearance ranged from 3.0 to 3.7 L/h for perindopril, 6.1 to 10.3 L/h for perindoprilat, and 7.0 to 8.5 L/h for

perindoprilat glucuronide. The mean elimination half-life of perindopril is about 1.5 to 2.9 hours; corresponding value for perindoprilat is about 10.9 hours. Elimination profile of perindoprilat is biphasic. Initial half-life is about 1.5 or 2.2 hours (depending on calculation method), the terminal phase of excretion ($t_{1/2}$) is characterized by a half-life of about 20 or 23 hours (range 20 to 120 h). The long terminal half-life represents the strong binding of perindoprilat to ACE.

Indapamide

Indapamide is completely absorbed from gastrointestinal tract with almost 100% bioavailability, regardless of the formulation. The time to peak concentration in sustained release (SR) formulation was 9.8 (fed state) and 12.3 (fasting state) hours after single dose and 11 hours in a steady state after repeated administration. Peak plasma concentration after single dose was 18 and 22 µg/l for the fasted and fed state, respectively, while after 7 days of repeated doses it was 58 µg/L. Indapamide 2.5, 5.0 and 10 mg resulted in dose proportional C_{max} and AUC values indicating dose- proportional bioavailability.

Indapamide is approximately 76-79 % bound to plasma proteins12. The blood/ plasma radioactivity ratio in a study with human volunteers was 5.7:1, indicating that indapamide preferentially binds to red blood cells12, 17. The volume of distribution has been estimated from blood concentration to be 25 to 27 L, and 110 L when estimated from plasma concentration.

Indapamide is extensively metabolised in the liver and excreted as metabolic products. Only up to 7 % of the administered dose is excreted unchanged in urine. Hydroxylation of the indoline ring is believed to result in a major metabolite. At least 5 and up to 19 metabolites were detected in the urine of human volunteers. According to molecular weight of metabolites, they are conjugates; glucuronides and sulphates. The pharmacological activity of the metabolites has not been reported.

Indapamide is eliminated predominantly in the urine, where 60 to 70 % of an orally administered dose is excreted, predominantly as metabolites. Human faecal elimination of indapamide accounts for 16 to 23 % of an orally administered dose. After repeated oral administration of Indapamide SR, $t_{1/2}$ was 19.2 hours.

Total systemic clearance of indapamide was estimated to be 20-23.4 ml/min. Renal clearance is low, accounting for less than 10 % of total systemic clearance of unchanged indapamide. Indapamide is extensively reabsorbed in proximal renal tubules. Hepatic clearance, metabolism and biliary excretion play major role in the total systemic clearance of indapamide.

Perindopril/indapamide combination

According to the literature data the two compounds do not interact in the pharmacokinetic processes.

Bioequivalence study

In order to demonstrate pharmacokinetics of the fixed dose combination and to establish bioequivalence with the free combination of the monocomponents, a comparative, randomised, single-dose, 2-way crossover bioavailability study of the present perindopril erbumine/indapamide 8 mg/2.5 mg tablets in healthy adult male volunteers under fasting conditions was performed. The objective of this study was to assess the single-dose relative bioavailability of this fixed combination of KRKA to co-administration of Prexanil® 8 mg tablet (perindopril erbumine) and Natrilix® 2.5 mg film-coated tablet (indapamide) under fasting conditions.

Design
This was an open-label, randomised, 2-way, 2-sequence, single-dose comparative bioavailability study performed on adult non-tobacco using male volunteers. Single 8 mg/2.5 mg perindopril erbumine/indapamide oral doses were separated by a washout period of 42 days.

Blood sampling
*B*lood samples were collected before dosing and at the following times thereafter: 0.167, 0.333, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 12, 16, 24, 36, 48, and 72 hours. Samples were assayed for perindopril, perindoprilat and indapamide.

The wash-out period between the treatment periods was 42 days.

Bioanalytics

Perindopril

Plasma concentrations of perindopril and perindoprilate were determined in plasma samples of volunteers using a High Performance Liquid Chromatography / Tandem Mass Spectrometry Method (HPLC-MS/MS).

Indapamide

Whole blood concentrations of indapamide were determined in blood samples of volunteers using a High Performance Liquid Chromatography / Tandem Mass Spectrometry Method (HPLC-MS/MS).

Statistics
Arithmetic means, standard deviations (SD), coefficients of variation (CV), number of observations (n), geometric means, median, minimum, and maximum values were calculated for the plasma concentration and PK parameter data.

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, AUC_{inf}, and C_{max} for perindopril and indapamide and on the ln-transformed AUC_{0-72} and C_{max} for perindoprilat. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term at a 10% level of significance. Each ANOVA included calculation of least squares means (LSM), the difference between formulation LSM, and the standard error associated with this difference. The above statistical analyses were done using the SAS® GLM procedure.

The following standards were used to determine bioequivalence in this comparative bioavailability study:

- for perindopril and indapamide:
  the 90% CI of the ratios of LSM of AUC_{0-t}, AUC_{inf}, and C_{max} of the test to reference formulation were to be within 80.00 – 125.00%;
- for perindoprilat:
  the 90% CI of the ratios of LSM of AUC_{0-72} and C_{max} of the test to reference formulation were to be within 80.00 – 125.00%..

This statistical methodology is adequate. The predefined confidence interval for the test/reference ratios of the means of AUC0-∞, AUC_{0-t} and C_{max} parameters are between 80% and 125%.

Results
The results are summarised in the following tablets.

Table 1. Pharmacokinetic parameters of **perindopril**:

	AUC_{0-t} (ng h/mL)	AUC_{0-inf} (ng h/mL)	C_{max} (ng/mL)	t_{max} (h)	$T_{1/2\ el}$ (h)	K_{el} (1/h)
KRKA d.d (A)						
Mean	73.023	73.529	65.9504	0.6132	0.7274	0.9762
CV	25.4	25.5	26.5	29.5	18.1	14.1
Servier (B)						
Mean	71.075	72.032	61.5861	0.7674	0.7807	0.9266
CV	27.0	26.5	39.5	59.2	23.5	19.3

Perindopril in Plasma KRKA, d.d., Novo mesto (A) vs. Les Laboratoires Servier (Prexanil® and Natrilix®) (B) (N = 39)			
PK Parameter	**Ratio of LSM (A/B)**	**90% CI**	**CV (%)**
AUC 0-t	102.8%	98.64 – 107.14%	10.8
AUCinf	102.4%	98.27 – 106.70%	10.6
Cmax	107.2%	97.80 – 117.53%	24.4

Table 2. Pharmacokinetic parameters of **perindoprilat:**

	AUC_{0-72h} (ng h/mL)	AUC_{0-t} (ng h/mL)	C_{max} (ng/mL)	t_{max} (h)
KRKA d.d (A)				
Mean	177.504	177.504	11.7887	4.4497
CV	30.2	30.2	53.3	32.7
Servier (B)				
Mean	172.351	166.618	10.7290	5.2330
CV	32.5	33.6	60.6	36.2

Perindoprilat in Plasma KRKA, d.d., Novo mesto (A) vs. Les Laboratoires Servier (Prexanil® and Natrilix®) (B) (N = 39)			
PK Parameter	**Ratio of LSM (A/B)**	**90% CI**	**CV (%)**
AUC 0-72	105.3%	99.38 – 111.50%	14.3
AUC 0-t	106.6%	101.08 – 112.39%	13.9
Cmax	110.1%	98.21 – 123.38%	30.5

Table 3. Pharmacokinetic parameters of **indapamide**:

	AUC_{0-t} (ng h/mL)	AUC_{0-inf} (ng h/mL)	C_{max} (ng/mL)	t_{max} (h)	$T_{1/2\ el}$ (h)	K_{el} (1/h)
KRKA d.d (A)						
Mean	1998.68	2077.77	100.0964	1.9993	15.18	0.04643
CV	19.3	20.6	15.6	47.7	12.8	13.3
Servier (B)						
Mean	1967.48	2045.12	104.2431	1.5434	14.96	0.04714
CV	19.7	20.6	15.6	85.6	13.2	13.4

Indapamide in Whole Blood KRKA, d.d., Novo mesto (A) vs. Les Laboratoires Servier (Prexanil® and Natrilix®) (B) (N = 39)			
PK Parameter	**Ratio of LSM (A/B)**	**90% CI**	**CV (%)**
AUC 0-t	101.6%	99.06 – 104.22%	6.7
AUCinf	101.6%	98.90 – 104.44%	7.1
Cmax	96.0%	93.10 – 98.91%	7.9

The calculated confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max} of perindopril, perindoprilate and indapamide are within the 0.80-1.25 acceptance range for bioequivalence. The other pharmacokinetic variables were comparable between the test product and the reference products.

The safety profiles of both the test product and the combination of the monocomponent originators were comparable. There were no deaths, serious AEs, or other significant AEs in this study. The most common adverse reactions were headache (7) and dizziness (4).

Conclusion
Based on the submitted bioequivalence study, the applied formulations of perindopril/indapamide 8mg/2.5mg tablets are considered bioequivalent with the concomitantly given originator reference products Prexanil® 8mg tablets and Natrilix® 2.5mg film-coated tablets.

IV.3 Pharmacodynamics

Perindopril

Perindopril belongs to the angiotensin converting enzyme (ACE) inhibitors. It inhibits the renin-angiotensin system by preventing the conversion of angiotensin I to angiotensin II. Furthermore, it inhibits the degradation of bradykinin. Since angiotensin II is on one hand a potent vasoconstrictor ACE-inhibitors have an indirect significant vasodilatory effect. On the other hand, angiotensin II is responsible for aldosterone secretion therefore ACE-inhibitors reduce the aldosterone level consequently decreasing the circulating volume and increasing serum potassium level. ACE-inhibitors also inhibit the trophic effects of angiotensin II such as remodelling of the heart muscle in case of congestive heart failure where the activity of rennin-angiotensin-aldosterone system is high.

Perindopril has a gradual onset of action and low risk for first-dose hypotension, absence of unwanted effects on blood pressure (BP) in normotensive patients when delivered at low doses, maintained effectiveness with missed doses, positive hemodynamic effects, and the ability to reverse some of the vascular abnormalities associated with hypertension, including arterial stiffness and left ventricular hypertrophy.

Indapamide

Indapamide belongs to the diuretics and is similar to thiazides both in its structure and mechanism of action. Indapamide inhibits the Na^+ and Cl^- reabsorption in the distal convoluted tubules of the kidney thus reducing the plasma sodium concentration that leads to increased diuresis in the beginning of the treatment. Since sodium loss activates the renin-angiotensin-aldosterone system thiazide diuretics may cause hypokalemia as a consequence of higher aldosterone level. During continuous treatment the diuretic effect, as well as the total body sodium content decreases that may partly be responsible for the antihypertensive effect of thiazides. The antihypertensive effect of thiazides can be observed with lower doses than those indicated in congestive heart failure.

Indapamide has a better safety profile than other thiazides. It does not cause severe metabolic changes such as impaired glycemic control and hypercholesterinemia.

Perindopril/indapamide combination

When the two active substances are combined there can be a synergistic effect observed in the antihypertensive effect. Perindopril counteracts with the higher renin level caused by indapamide and may reduce the risk of hypokalemia thus possessing a better safety profile than the drugs given individually. This combination in different doses is already approved as a first line, second line and substitution treatment of hypertension.

IV.4 Clinical efficacy

No specific clinical studies have been performed. The substitution therapy in hypertension is fully justified by the amended Clinical Overview both by the literature and the co-prescription data.

IV.5 Clinical safety

The applicant has submitted one bioequivalence study.

It was a single dose crossover comparative bioequivalence study of perindopril/indapamide 8mg/2.5 mg combination tablets vs. perindopril 8 mg tablets and indapamide 2.5 mg tablets given concomitantly in healthy male volunteers

The safety profiles of both the test product and the combination of the monocomponent originators were comparable. There were no deaths, serious AEs, or other significant AEs in this study. The most common adverse reactions were headache (7) and dizziness (4).

No new safety problem emerged from the study.

IV.6 Discussion on the clinical aspects

The application concerns a generic combination of perindopril and indapamide. The suggested indication is substitution therapy for patients suffering from hypertension already adequately controlled with monocomponent-containing tablets given concurrently. To support the application the Applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time. For further justification the Applicant has provided co-prescription data from the markets of the concerned member states.
There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application concerns a generic combination of perindopril and indapamide. The suggested indication is substitution therapy for patients suffering from hypertension already adequately controlled with monocomponent-containing tablets given concurrently. The active substances are widely and safely used in combinations, the application of the present product does not pose any new risk.

The submitted documentation is formally adequate and scientifically sound. The benefit/risk assessment is positive, there is nothing against granting the marketing authorisation.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The Applicant/MAH submitted detailed description of The Pharmacovigilance System of KRKA, which fulfils the requirements and provides adequate evidence that the KRKA has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V.1.3 Risk Management Plan

No Risk Management Plan, as per the provisions of Volume 9A of The Rules Governing Medicinal Products in the European Union (September 2008) needs not to be submitted, given that the application has concerned a generic product with no safety concerns identified for the reference product.

V.1.4. Periodic Safety Update Report (PSUR)

KRKA has an already approved product of similar combination of active ingredients on the market. According to Volume 9A it is recommended that all formulations of the same active ingredient are included in the same PSUR. Therefore, the first PSUR including the new formulation will have the data lock point what is the same as is already in place for other formulation.

V.1.5 Legal status

Prescription-only medicine.

V. 2 Summary of Product Characteristics (SmPC)

The SmPC of the Co-Prenessa 8mg/2.5mg tablets is in line with that of Parateraxl/Noliterax/Teraxan, the product licensed during the decentralized procedure FR/H/343/01/DC and the final approved SmPC of procedures HU/H/0230-0231-0232/03/DC. The SmPC is acceptable.

V.3 Package Leaflet and user testing

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 language used for the purpose of user testing the patient information leaflet was Hungarian.

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*.

National Institute of Pharmacy
Directorate of GYEMSZI
Budapest, Hungary

Public Assessment Report Number:
HU/H/0150/003/DC

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Y/N (version)						