CBG MEB

Public Assessment Report

Scientific discussion

Tricorlix 7 mg/5 mg/2.5 mg film-coated tablets

(perindopril arginine/amlodipine/indapamide)

NL/H/3968/001/DC

Date: 21 August 2019

This module reflects the scientific discussion for the approval of Tricorlix. The procedure was finalised on 15 February 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ACE	Angiotensin Converting Enzyme
ARA	Angiotensin Receptor Antagonist
BP	Blood Pressure
CCB	Calcium Channel Blockers
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DBP	Diastolic Blood Pressure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FDC	Fixed Dose Combination
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
MRP	Mutual Recognition Procedure
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QSAR	Quantitative Structure-Activity Relation
RH	Relative Humidity
RMP	Risk Management Plan
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SR	Slow Release
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of Toxicological Concern

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tricorlix 7 mg/5 mg/2.5 mg film-coated tablets from Les Laboratoires Servier.

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

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

This decentralised procedure concerns a FDC. These contain active substances from medicinal products already authorised in the EEA. Tricorlix contains three of such active substances. Hence, perindopril, amlodipine, and indapamide are already in widespread use alone, and in free or fixed-dose combination to treat hypertensive patients. Products containing one of the active substances have been approved in the EU for more than 25 years. The originator products are the following:

- 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 (MRP) in September 2005 (FR/H/0265/001-003).
- The innovator product containing indapamide, Fludex SR 1.5 mg tablets (NL license 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 MRP (FR/H/0100/001).
- The Dutch amlodipine innovator product Norvasc 5 mg and 10 tablets (NL license 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 MAH has several registrations with FDCs of these three products (Triplixam, NL/H/2636/001-005/DC and Arplexam, NL/H/2638/001-005/DC), both since 18 March 2014. Furthermore, the combination perindopril and indapamide and the combination perindopril arginine and amlodipine have already been approved through several procedures by the same MAH. However, Tricorlix is the first combination with 7 mg perindopril arginine, 5 mg amlodipine and 2.5 mg indapamide.

The concerned member states (CMS) involved in this procedure were Bulgaria, Germany, Spain, France, Italy, Latvia, Portugal and Romania.

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

Rationale for the combination of perindopril, amlodipine, and indapamide
The European practice guidelines underline that no less than 15-20% of the patients need more than two antihypertensive drugs to achieve an effective blood pressure reduction and the combination of a blocker of the renin-angiotensin system, a calcium antagonist and a thiazide diuretic is the most effective three-drug combination (Mancia, 2009; Mancia, 2013; NICE, 2011).
Furthermore, the current FDC will simplify therapy for patients, as the number of individual dose units to be taken will decrease. This may lead to improved compliance to long-term therapy.

II. QUALITY ASPECTS

II.1 Introduction

Tricorlix is a white, oblong, film-coated tablet, engraved with  on one face.

One film-coated tablet contains 4.75 mg perindopril equivalent to 7 mg perindopril arginine, 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine and 2.5 mg indapamide.

The film-coated tablets are packed in a polypropylene tablet container equipped with a low density polyethylene flow reducer and cap, containing a desiccant or in a high density polyethylene bottle equipped with a polypropylene screw cap containing a desiccant.

The excipients are:
Tablet core
- Calcium carbonate starch compound: calcium carbonate 90%, pregelatinised maize starch 10%
- Cellulose, microcrystalline (E460)
- Croscarmellose sodium (E468)
- Magnesium stearate (E470b)
- Colloidal anhydrous silica
- Pregelatinised starch

Tablet film-coating
- Glycerol (E422)
- Hypromellose 6 mPa.s (E464)
- Macrogol 6000
- Magnesium stearate (E470b)
- Titanium dioxide (E171)

II.2 Drug Substances

The active substance perindopril arginine is an established active substance that is not described in a pharmacopoeia. Perindopril arginine is a powder that is freely soluble in water, and slightly soluble in ethanol (96%).
The active substances indapamide and amlodipine are established active substances described in the European Pharmacopoeia (Ph.Eur.) and/or the US Pharmacopoeia (USP). Indapamide is a white or almost white powder, which is practically insoluble in water and soluble in ethanol (96%). It has one asymmetric carbon, it is used in the racemic form. 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 Ph.Eur.

Manufacturing process
The manufacturing processes for indapamide and amlodipine besilate have been assessed by EDQM as part of the CEP application procedure.
The manufacturing process of perindopril arginine has been adequately described. Synthesis of a perindopril tertbutylamine intermediate has been assessed by EDQM as part of the CEP application for perindopril tertbutylamine.

Quality control of drug substances
The active substance specifications of indapamide and amlodipine besilate are considered adequate to control the quality and meet the requirements of their monograph in the Ph.Eur. They include additional requirements.
The active substance specification of perindopril arginine is considered adequate to control the quality. It includes additional tests for particle size and intermediates.
Batch analytical data demonstrating compliance with this specification have been provided for three batches of each manufacturer.

Stability of drug substances
For perindopril arginine, stability data is provided, they are 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. No special storage condition is required.

Indapamide is stable for three years and amlodipine is stable for five years 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
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. For the pharmaceutical development the Quality by Design (QbD) approach is applied. The MAH performed factorial design studies as a screening tool to determine the most compatible excipients. It is used as a support in the choice of the excipients as well as showing the robustness of the manufacturing process. In general 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. Drug load is low for the active substances. Overall, the pharmaceutical development data is considered sufficient.

Manufacturing process
The manufacturing process includes mixing, compression and coating. Because of the low drug load the manufacturing process is considered a non-standard manufacturing process. Based on the extended knowledge of this type of manufacturing, the MAH referred to the process validation of the different strengths of the same FDC for which it currently holds a marketing authorisation.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two production scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. except for calcium carbonate starch compound for which in-house monograph is applied. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dimension characteristics, average mass, identification of perindopril arginine, amlodipine and indapamide, content of the drug substances, degradation products, uniformity of dosage units, dissolution of the drug substances, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for two production scaled batches stored at 25°C/60% RH (6 months), 30°C/65% or 75% RH (6 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. No specific changes were observed. A photostability study was conducted, the results demonstrate that the product is photostable.

On the basis of the data submitted, a shelf life was granted of 24 months without special storage conditions.

Stability data have been provided demonstrating that the product remains stable for up to 100 days depending on the size of the container following first opening of the container.

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 Tricorlix has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Toxicology

The MAH performed an extra study to demonstrate the lack of interaction between perindopril and amlodipine (13-week toxicity study in rats; GLP-compliant). The results confirmed that no relevant toxicity occurs at medium doses and no new target organs nor relevant additive effects were identified with the combination of perindopril and amlodipine. Also, the toxico-kinetic data demonstrated no interaction between perindopril and amlodipine.

Impurities
Three perindopril impurities are qualified by Ames test, mouse lymphoma test and 4-week rat toxicity test. Seven other potential and/or specified impurities were subjected to a Quantitative Structure-Activity Relation (QSAR) analysis using two complementary methodologies (DEREK and Leadscope software) and found negative.
For amlodipine, seventeen potential and/or specified impurities were subjected to a QSAR analysis using DEREK and Leadscope software. Only one exhibited an alert for mutagenicity. However, the maximal exposure to this impurity would be well below the threshold of toxicological concern (TTC) of 1.5 µg/day.
One indapamide impurity was qualified by Ames test, mouse lymphoma test and a 4-week rat toxicity test. A second impurity was found negative in the Ames test, but positive in the QSAR analysis and in an *in vivo* micronucleus test in male rats for the very high oral dose. However, the exposure is well below the TTC. A third impurity was positive in the QSAR analysis and the Ames test, but at a specification of 0.06% (1.5 µg/day) the exposure is not above the TTC level. Another impurity has an alert for mutagenicity in the QSAR analysis, however, this impurity is extremely unstable and leads spontaneously by hydrolysis to a specified impurity, which has no QSAR alert. Two other impurities were also negative in the QSAR analysis.

All detected impurities are qualified or below the qualification threshold of 1.0% of the product, except one specified impurity from perindopril, which shelf-life specification is ≤1.5%. However, this impurity is the active metabolite of perindopril, perindoprilat, which is not of toxicological concern.
The drug substance specifications of two impurities from perindopril and one impurity from amlodipine are slightly above the qualification threshold and only tested by QSAR and thus not fully qualified. However, because of the low exceedance of the substance threshold, the lack of an alert in the QSARs and the compliance with the product threshold, a toxicological risk is not expected, and therefore, the substance specifications can be accepted.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Tricorlix is intended for substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. In addition an extra study was submitted demonstrating no interaction between perindopril and amlodipine. The data justify why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The MAH submitted an overview of the established use of all components of the proposed FDC: perindopril, indapamide and amlodipine. Justification for the triple combination has been provided and discussed.

IV.2 Pharmacokinetics

The clinical programme of the FDC of perindopril, indapamide and amlodipine consists of one pharmacokinetic bioequivalence study (PKH-05170-001) and one interaction study (PKH-06593-004). The interaction study was previously submitted and assessed for the application of Triplixam (NL/H/2636/005) and associated names.

Bioequivalence study PKH-05170-001
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tricorlix 7 mg/5 mg/2.5 mg tablets (Les Laboratoires Servier, France) is compared with the pharmacokinetic profile of the reference products Viacoram 7 mg perindopril/5 mg amlodipine tablets (Servier Ireland Industrie, Ireland) and Fludex 2.5 mg indapamide tablets (Les Laboratoires Servier Industrie, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A randomised, single dose, laboratory-blinded, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 18-45 years. Each subject received a single treatment (7 mg/5 mg/2.5 mg) of one of the two FDC formulations.

- Treatment 1: Test product administered alone
- Treatment 2: Viacoram and Fludex taken concomitantly

There were two dosing periods, separated by a washout period of three weeks.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
46 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindopril, amlodipine and indapamide under fasted conditions.

	Geom. Mean (geom. CV%) or #median (range)	
	Treatment-1 (Test) (n=46)	**Treatment-2 (Reference) (n=46)**
Perindopril		
AUC_{0-t} (ng.h/ml)	61.486 (30.6%)	63.382 (27.8%)
$AUC_{0-\infty}$ (ng.h/ml)	62.310 (30.2%)	64.262 (27.4%)
C_{max} (ng/ml)	50.665 (30.4%)	51.308 (30.2%)
$t_{1/2}$ (h)	0.674 (10.5%)	0.688 (14.0%)
t_{max} (h)	0.667 (0.33 – 1.75)#	0.667 (0.50 – 2.50)#
Perindoprilat (for infomation only)		
AUC_{0-t} (ng.h/ml)	155.018 (24.8%)	153.699 (25.0%)
C_{max} (ng/ml)	7.842 (45.1%)	7.741 (39.1%)
t_{max} (h)	6.0 (4.00 – 8.00) #	5.5 (3.00 – 8.07)#
Amlodipine		
AUC_{0-72} (pg.h/ml)	114,679.679 (24.9%)	114,123.970 (24.4%)
C_{max} (pg/ml)	2,894.824 (22.3%)	2,872.339 (23.8%)
t_{max} (h)	6.000 (5.00 – 14.03)#	6.000 (5.00 – 14.00)#
Indapamide		
AUC_{0-t} (ng.h/ml)	1,776.480 (22.0%)	1,823.503 (20.8%)
$AUC_{0-\infty}$ (ng.h/ml)	1,853.785 (24.7%)	1,908.403 (23.4%)
C_{max} (ng/ml)	105.205 (17.0%)	95.208 (18.1%)
$t_{1/2}$ (h)	15.271 (19.4%)	15.448 (18.8%)
t_{max} (h)	1.392 (0.667 – 3.0)#	1.750 (0.667 – 12.1)#

T: One tablet of S 05170: perindopril arginine 7 mg/amlodipine 5 mg/ indapamide 2.5 mg
R: One tablet of Viacoram® 7mg/5 mg (perindopril arginine/amlodipine) plus one tablet of Fludex® 2.5 mg (indapamide)

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

Table 2. Geometric mean ratio (treatment T/treatment R) and 90% Confidence Intervals of pharmacokinetic parameters for perindopril, amlodipine and indapamide

Analyte	Ratio T/R (90% CI)
Perindopril	
AUC_{0-t} (ng.h/ml)	97.01% (94.12%, 99.98%)
C_{max} (ng/ml)	98.75% (91.54%, 106.52%)
Amlodipine	
AUC_{0-72} (pg.h/ml)	100.49% (98.22%, 102.81%)
C_{max} (pg/ml)	100.78% (97.65%, 104.01%)
Indapamide	
AUC_{0-t} (ng.h/ml)	97.43% (95.80%, 99.08%)
C_{max} (ng/ml)	110.50% (106.68%, 114.46%)

T: One tablet of S 05170: perindopril arginine 7 mg/amlodipine 5 mg/ indapamide 2.5 mg
R: One tablet of Viacoram 7mg/5 mg (perindopril arginine/amlodipine) plus one tablet of Fludex 2.5 mg (indapamide)

Conclusion on bioequivalence study PKH-05170-001
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tricorlix is considered bioequivalent with the co-administration of one tablet of Viacoram 7 mg/5 mg (perindopril arginine/ amlodipine) FDC plus one tablet of Fludex 2.5 mg (indapamide).

Interaction study PKH-06593-004

Design

The goal of the interaction study was to investigate a potential pharmacokinetic interaction between the fixed combination of 10 mg perindopril/2.5 mg indapamide and 10 mg amlodipine within the fixed combination Triplixam 10 mg/2.5 mg/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 Triplixam 10 mg/2.5 mg/10 mg (Les Laboratoires Servier, the Netherlands)
- Reference: one tablet of BiPreterax, 10 mg perindopril/2.5 mg indapamide (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 three weeks.

Results

As three subjects were withdrawn due to non-medical reasons, two due to an adverse event (AE) and two 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) Treatment T (n=30)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV) Treatment R (n=30)
AUC	ng*h/mL	380.5 (27.9 %) 394.5 ± 109.8 (27.8 %)	342.9 (26.5 %) 354.6 ± 96.1 (27.1 %)
AUC_{last}	ng*h/mL	357.7 (27.8 %) 370.8 ± 102.0 (27.5 %)	319.7 (27.2 %) 331.1 ± 92.3 (27.9 %)
C_{max}	ng/mL	23.302 (19.6 %) 23.747 ± 4.905 (20.7 %)	21.733 (17.3 %) 22.043 ± 3.772 (17.1 %)
t_{max}	h	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) Treatment T (n=30)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV) Treatment S (n=30)
AUC	ng*h/mL	228.9 (36.2 %) 242.5 ± 81.5 (33.6 %)	213.2 (30.3 %) n=28 222.0 ± 62.3 (28.1 %) n=28
AUC_{last}	ng*h/mL	220.0 (34.5 %) 231.9 ± 74.8 (32.3 %)	201.5 (28.0 %) 208.8 ± 55.7 (26.7 %)
C_{max}	ng/mL	5.227 (25.8 %) 5.396 ± 1.421 (26.3 %)	4.813 (24.0 %) 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) Treatment T (n=30)	Geom. Mean (geom. %CV), Arithm. Mean ± SD (%CV) Treatment R (n=30)
AUC	ng*h/mL	63.8 (19.6 %) 65.0 ± 13.2 (20.3 %)	62.2 (21.4 %) n=29 63.5 ± 13.1 (20.6 %) n=29
AUC_{last}	ng*h/mL	63.0 (19.9 %) 64.2 ± 13.2 (20.5 %)	61.2 (21.7 %) 62.5 ± 13.1 (21.0 %)
C_{max}	ng/mL	50.671 (38.5 %) 54.100 ± 19.799 (36.6 %)	48.124 (39.5 %) 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

	Least Squares Geometric Mean Ratio T/R (90% CI)	Least Squares Geometric Mean Ratio T/S (90% CI)
Parameter	**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

	Least Squares Geometric Mean Ratio T/R (90% CI)	
Parameter	**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%-125% range.

Overall conclusion pharmacokinetics
The bioequivalence of Tricorlix 7 mg/5 mg/2.5 mg tablets has been demonstrated to the individually marketed products perindopril/amlodipine (Viacoram 7 mg/5 mg) and indapamide (Fludex). No pharmacokinetic bridges were built between Tricorlix and the individual originator mono-components. In this case no justification needs to be provided why 'drifting' of bioavailability is not considered relevant as it concerns a substitution indication for patients already on a perindopril/amlodipine fixed dose and mono-component indapamide.

Study PKH-06593-004 indicated the absence of an interaction when perindopril, indapamide and amlodipine are co-administered, as demonstrated with the already marketed perindopril/ indapamide FDC and the amlodipine formulation. Also in literature no relevant pharmacokinetic interactions between the individual components are described.

IV.3 Pharmacodynamics

The pharmacodynamics of perindopril, amlodipine and indapamide are well known and well-established. Perindopril, amlodipine, and indapamide have different mechanisms of action which are complementary when the components are combined.

IV.4 Clinical efficacy

The rationale for the development of a perindopril/amlodipine/indapamide 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, 2013),
- 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).

The MAH provided the following data:

CL3-05985-018 study
A 6-month, multicentre, randomised, double-blind, active-controlled study, in which 1,774 patients with mild to moderate hypertension received either perindopril 3.5 mg/amlodipine 2.5 mg, uptitrated to 7 mg/5 mg, and 14 mg/10 mg, then to 14 mg/10 mg combined with 1.5 mg indapamide sustained release (SR), or a valsartan-amlodipine strategy (80 mg valsartan up-titrated to 160 mg and to 160 mg/5 mg valsartan/amlodipine, then to 160 mg/10 mg valsartan/amlodipine). The addition of 1.5 mg indapamide SR in patients not controlled with 14 mg perindopril+10 mg amlodipine showed an additional clinical and statistical significant decrease in SBP and DBP.

ADVANCE sub-study
The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation) trial was a factorial randomised controlled trial to determine the effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes mellitus (Chalmers, 2014).
A total of 11,140 patients with type 2 diabetes mellitus were randomly assigned to fixed combination of perindopril-indapamide (4 mg/1.25 mg) or placebo. Effects of randomised treatment on mortality and major cardiovascular outcomes were examined in subgroups defined by baseline use of CCBs. Patients on CCB at baseline (n=3,427) constituted a higher risk group compared with those not on CCB (n=7,713), with more extensive use of antihypertensive and other protective therapies. Active treatment reduced the relative risk of death by 28% (95% confidence interval, 10%-43%) among patients with CCB at baseline compared with 5% (-12%-20%) among those without CCB (P homogeneity=0.02) and 14% (2%-25%) for the whole population. Similarly, the relative risk reduction for major cardiovascular events was 12% (-8%-28%) versus 6% (-10%-19%) for those with and without CCB at baseline although the difference was not statistically significant (P homogeneity=0.38).
The combination of perindopril and indapamide with CCBs seems to provide further protection against mortality in patients with type 2 diabetes mellitus.

PAINT study
A 4-month, multicentre, prospective, observational, open-label PAINT study (perindopril/amlodipine plus indapamide combination for controlled hypertension Non-intervention Trial) in which the efficacy of triple therapy with perindopril, amlodipine, and indapamide SR was evaluated in patients with uncontrolled hypertension on previous antihypertensive therapy (Páll, 2014). BP was found to decrease significantly in patients already treated with the dual combination of perindopril/amlodipine (5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, or 10 mg/10 mg) by the addition of indapamide SR 1.5 mg (all p <0.0001). The office BP (OBP) target was achieved after four months' treatment with perindopril/amlodipine/indapamide by ≥70%, regardless of dose.

Sirenko
A phase 4 study conducted in 4.424 hypertensive patients receiving the FDC of 5 mg or 10 mg perindopril/5 mg or 10 mg amlodipine for a 2-month follow-up. 1.5 mg indapamide SR was added if target blood pressure was not achieved after one month, according to physician decision (Sirenko, 2013a). Among the patients receiving indapamide, 39.9% achieved the target blood pressure and benefited from an additional 16.4±9.3/7.6±7.2 mm Hg decrease in blood pressure. The highest frequency of using indapamide was observed in patients receiving the higher dose of amlodipine/perindopril. Effectiveness did not depend significantly on previous therapy, but on baseline BP.

PIANIST study
In this multicentre, prospective observational open-label study of four months, the antihypertensive and metabolic effects of perindopril 10 mg/indapamide 2.5 mg plus amlodipine 5 mg or 10 mg triple combination were assessed in 4,731 uncontrolled essential hypertensive patients at high to very-high risk (Tóth, 2014). Baseline BP in the overall population was 160.5±13.3/93.8±8.7 mm Hg which decreased by 28.3±13.5/13.8±9.4 mm Hg after 4-month therapy to 132.2±8.6/80.0±6.6 mm Hg (p <0.0001). According to the severity of hypertension, BP significantly decreased by 18.7/9.7 mm Hg in Grade I, 30.4/14.7 mm Hg in Grade II, and 45.4/20.7 mm Hg in Grade III (all, p <0.0001). In the overall population, most patients 72% (n=3,408) achieved BP control (<140/90 mm Hg) under treatment, divided up as follows: 85.7% in Grade I, 69.5% in Grade II and 53.7% in Grade III.

PRACTIC sub-study
The PRACTIC sub-study, a prospective open trial, evaluated the efficacy of adding amlodipine to perindopril/indapamide in uncontrolled hypertensive patients treated on perindopril 10 mg/indapamide 2.5 mg FDC in clinical practice (Sirenko, 2013b).
Amlodipine given to 185 (24.3%) patients (mean age 59.8±0.6, mean baseline SBP/DBP - 177.9±0.8/101.6±0.7 mm Hg) further reduced SBP/DBP from the 1st to 3rd month by a mean 19.3±0.6/9.4±0.5 mm Hg, and achievement of target BP was significantly (p <0.001) improved from 7% (1st month) to 64.3% (3rd month). Administration of perindopril 10 mg + indapamide 2.5 mg plus amlodipine 5-10 mg lowered SBP/DBP by 45.3/20.5 mm Hg from baseline to the 3rd month.

In addition, the MAH provided results from post-hoc analyses of clinical studies (SYMBIO, PICASSO, CONFIDENCE II, PROTECT I, SHAKE THE HABIT I, and SHAKE THE HABIT II, SHIFT, BEAUTIFUL, SIGNIFY, PERFORM) involving use of the triple combination perindopril/amlodipine/indapamide.

IV.5 Clinical safety

The safety of perindopril, indapamide and amlodipine has already been established during the clinical development of each substance. These active substances have been marketed since many years as mono-therapies or combination therapies. The dosages proposed for the current FDC correspond to approved doses of the FDC perindopril/amlodipine (Viacoram and associated names) and the mono-component indapamide.

Substitution indication is claimed for the triple FDC. For this reason, the following sections focus on the safety of the combination perindopril/amlodipine, indapamide and the combination perindopril/amlodipine/indapamide, respectively.

Perindopril/Amlodipine

The expected adverse events of the fixed combination are similar to those known from perindopril and amlodipine, respectively. Since 2008 (first EU MA granted for Coveram (and associated names), as substitution therapy), no unexpected adverse event has been considered in the SmPC of the fixed combination perindopril/amlodipine (Coveram, Viacoram and associated names) as compared to the monocomponents. Furthermore, it should be noted that each of the mono components perindopril and amlodipine, respectively, are in clinical use within the EU since decades with well-known safety profile.

Indapamide

The expected adverse events of the fixed combination are similar to those known from indapamide. There is no restriction for use in elderly or very elderly patients. In the large trial in very elderly patients (> 80 years old), indapamide showed an excellent tolerability of use.

Combination Perindopril/Amlodipine/Indapamide

Safety results from clinical studies performed with perindopril, amlodipine and indapamide

CL3-05985-018 study

The safety data of CL3-05985-018 focused on the addition of indapamide (1.5 mg SR) to patients already treated with perindopril/amlodipine 14 mg/10 mg. The rate of patients reporting at least one EAE following the addition of indapamide 1.5 mg SR is very similar to the rate in previous step titration (per 7 mg + amlodipine 5 mg to per 14 mg+ amlodipine 10 mg) (25% vs 24%) and similar to the comparative group with valsartan 160 mg and amlodipine 10 mg (25% each) (Table 3).

In terms of preferred term, especially when comparing the effect of adding indapamide 1.5 mg to the previous step (step 4 versus step 3), no additional major events appear except those related to thiazide-like properties: hyperuricaemia and hypokalaemia (Table 4). The repartition of intensity is not changed after adding indapamide 1.5 mg (Table 5).

Table 3. Rate of patients reporting at least one EAE within each step.

		N patients exposed	N patients with EAE	% patients with EAE	N EAE
Step 1	**Per 3.5 mg + Aml 2.5 mg**	887	165	18.6%	264
	Val 80 mg	884	153	17.3%	224
Step 2	**Per 7 mg + Aml 5 mg**	718	125	17.4%	181
	Val 160 mg	741	129	17.4%	187
Step 3	**Per 14 mg + Aml 10 mg**	495	119	24.0%	180
	Val 160 mg + Aml 5mg	564	130	23.0%	185
Step 4	**Per 14mg + Aml 10mg + Ind 1.5mg**	202	51	25.2%	76
	Val 160 mg + Aml 10 mg	273	69	25.3%	100

Table 4. Most frequently reported EAEs in step 4 as compared to step 3 in at least 1% of patients in any group – Safety Set.

Preferred term	**Step 4 (Per 14 + Aml 10 + Ind 1.5) (N = 202)**			**Step 3 (Per 14 + Aml 10) (N = 495)**		
	NEAE	n	%	NEAE	n	%
All	**76**	**51**	**25.2**	**180**	**119**	**24.0**
Oedema peripheral	9	9	4.5	28	28	5.7
Type 2 diabetes mellitus	3	3	1.5	4	4	0.8
Blood glucose increased	3	3	1.5	3	3	0.6
Hyperuricaemia	3	3	1.5	-	-	-
Hypokalaemia	3	3	1.5	-	-	-
Nasopharyngitis	2	2	1.0	8	8	1.6
Cough	2	2	1.0	7	7	1.4
Hypertriglyceridaemia	2	2	1.0	7	7	1.4
Hypercholesterolaemia	2	2	1.0	6	6	1.2
Dizziness	2	2	1.0	3	3	0.6
Erectile dysfunction	2	2	1.0	1	1	0.2
Asthenia	2	2	1.0	-	-	-
Headache	0	0	0.0	1	1	0.2

Table 5. Analysis of EAE by intensity and according to the last step of dose at the time of onset - Safety Set.

Intensity	Step 4				Step 3			
	Per 14 + Aml 10 + Ind 1.5 (N = 202)		Val 160 + Aml 10 (N = 273)		Per 14 + Aml 10 (N = 495)		Val 160 + Aml 5 (N = 564)	
	NEAE	%	NEAE	%	NEAE	%	NEAE	%
All	**76**	**100**	**100**	**100**	**180**	**100**	**185**	**100**
Severe	2	2.6	5	5.0	9	5.0	12	6.5
Moderate	24	31.6	45	45.0	68	37.8	70	37.8
Mild	50	65.8	50	50.0	103	57.2	103	55.7
Missing	-	-	-	-	-	-	-	-

In the clinical studies and literature data mentioned, no new safety concerns were raised.
Safety data from pharmacokinetic studies showed that this treatment is well tolerated and safe.
The AEs reported with the free or FDC perindopril/ indapamide/ amlodipine (Triplixam and associated names, marketed in Europe since 2014, containing higher doses of perindopril and amlodipine for several dose strengths of the FDC, as compared to Tricorlix), did not show any new safety information compared to the monocomponents and are in line with their well-known safety profiles.

IV.6 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 Tricorlix.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypotension • Hyperkalaemia • Angioedema • Neutropenia/Agranulocytosis/Thrombocytopenia • Foetotoxicity/Use during second and third trimesters of pregnancy • Increased risk of hypotension, hyperkalaemia and acute renal failure when combining RAS-agents • Hypokalaemia • Renal failure • Severe hepatic impairment (hepatic encephalopathy, fulminant hepatitis) • Photosensitivity
Important potential risks	• Use during first trimester of pregnancy
Missing information	• Children and adolescents (<18 years old) • Lactating women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The combined use of perindopril arginine, amlodipine and indapamide is well established. The literature data submitted by the MAH support the use of the combination. The pharmacokinetic studies investigating bioequivalence and interaction potential show satisfactory results: a single tablet of the FDC can be used instead of co-administration of the separate products. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has (PL) 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 three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tricorlix 7 mg/5 mg/2.5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are considered an approvable FDC. The active substances are well known, established substances, which are used as a combination in clinical practice.

A pharmacokinetic study showed that there is no pharmacokinetic interaction between the individual compounds of this FDC product. The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products. The clinical data are considered sufficient to support the use of the FDC as substitution therapy for treatment of essential hypertension, in adult patients already controlled with perindopril/amlodipine FDC and indapamide, taken at the same dose level.

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 the benefit-risk balance for this FDC is positive, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 February 2018.

VII. REFERENCES

Chalmers et al., Effects of Combination of Perindopril, Indapamide, and Calcium Channel Blockers in Patients With Type 2 Diabetes Mellitus, Results From the Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) Trial, Hypertension (2014);63:259-264

Dahlöf et al., Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial, Lancet (2005); 366: 895–906

Hatala et al., Optimization of Blood Pressure Treatment with Fixed-Combination Perindopril/ Amlodipine in Patients with Arterial Hypertension, Clin Drug Investig 2012; 32 (9): 603-612

Mancia et al., Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document, Journal of Hypertension (2009), 27:2121–2158

Mancia et al., The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), European Heart Journal (2013) 34, 2159–2219

Páll et al., Triple Combination Therapy in Hypertension: The Antihypertensive Efficacy of Treatment with Perindopril, Amlodipine, and Indapamide SR, Clin Drug Investig (2014) 34:701–708

Progress Collaborative Group, Randomised trial of a perindopril-based blood-pressure-loweringregimen among 6105 individuals with previous stroke or transientischaemic attack, Lancet (2001);358:1033–41

Sirenko Y, Radchenko A, et al. Antihypertensive effectiveness of indapamide-retard adding to fixed-dose combination perindopril/amlodipine in a hypertensive population. Abstract submitted to ESC 2013 by Y. Sirenko (a) . J Hypertens. 2013; 31(e-Supplement A):e334

Sirenko Y, MankovskiyB, Radchenko A, Kushnir S, et al. Effectiveness of adding amlodipine to fixed-dose perindopril/indapamide treatment in patients with uncontrolled arterial hypertension and diabetes mellitus (results of the PRACTIC trial). Abtract submitted to ESC 2013 (b). J Hypertens. 2013; 31(e-Supplement A):e334

Tóth et al., Antihypertensive Efficacy of Triple Combination Perindopril/ Indapamide Plus Amlodipine in High-Risk Hypertensives: Results of the PIANIST Study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients), Am J Cardiovasc Drugs (2014) 14:137–145

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse