IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Perindopril arginine/Indapamide/Amlodipine Krka 5 mg/1.25 mg/5 mg tablets
Perindopril arginine
Indapamide
Amlodipine besilate
PA1347/112/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet from KRKA d.d., Novo mesto on 10th May 2024 indicated as substitution therapy for treatment of essential hypertension, in adult patients already controlled with perindopril/indapamide fixed dose combination and amlodipine, taken at the same dose level.

This application for a marketing authorisation was submitted via a decentralised procedure in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.

Ireland was the Reference Member State (RMS), and the Concerned Member States (CMSs) were Belgium, Bulgaria, Croatia, Czechia, Cyprus, Estonia, Germany, Greece, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia and Slovenia.

This is a prescription-only medicinal product.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Perindopril arginine/ Indapamide/ Amlodipine Krka 5/1.25/5 mg Tablet
Name(s) of the active substance(s) (INN)	Perindopril arginine/ Indapamide/ Amlodipine
Pharmacotherapeutic classification (ATC code)	Agents acting on the renin-angiotensin system, ACE inhibitors, other combinations, ATC code: C09BX01
Pharmaceutical form and strength(s)	5/1.25/5 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA1347/112/001
Marketing Authorisation Holder	KRKA,D.D., Novo mesto
MRP/DCP No.	IE/H/1240/001
Reference Member State	Ireland
Concerned Member State	Belgium, Bulgaria, Croatia, Czechia, Cyprus, Estonia, Germany, Greece, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia and Slovenia.

II. QUALITY ASPECTS

II.1. Introduction

This application is for Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg tablets.

II.2 Drug substance

The active substances are perindopril arginine, indapamide and amlodipine besilate. Indapamide and amlodipine besilate are established active substances described in the European Pharmacopoeia, whereas perindopril arginine is an established active substance supported by an ASMF. All the active substances are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with each specification has been provided.

II.3 Medicinal product

P.1 Composition

The finished drug products are tablets containing 5 or 10 mg of perindopril arginine, 1.25 mg or 2.5 mg of indapamide and amlodipine besilate equivalent to 5 mg or 10 g of amlodipine.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

These active substances are a generic formulation of TRIPLIXAM 5/1.25/5 mg film-coated tablets on the European market. No new preclinical data have been submitted.

III.2 Ecotoxicity/environmental risk assessment

Since Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg, 10/2.5/5 mg 10/2.5/10 mg Tablets is a generic product, it 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

Pharmacodynamic, pharmacokinetic and toxicological properties of perindopril arginine, indapamide and amlodipine are well known. As perindopril arginine, indapamide and amlodipine are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under Article 10(1) of Directive 2001/83/EC.

The active substances (perindopril arginine, indapamide and amlodipine) are well-known with established efficacy and tolerability when used as monotherapy or in combination together.

The content of the SmPCs approved during the national procedure are in accordance with those accepted for the reference product TRIPLIXAM 5/1.25/5 mg (perindopril/ indapamide/ amlodipine) by Les Laboratoires Serviers registered in Malta since 13/01/2014 via procedure NL/H/2636/002/DC.

This application concerned three strengths - Perindopril arginine/Indapamide/Amlodipine 5/1.25/5 mg, 10/2.5/5 mg 10/2.5/10 mg Tablets.
To support the application, the applicant submitted the report of a bioequivalence study with the highest strength and a justification for waiver of a bioequivalence study with the two lower strengths.

The bioequivalence study was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study, designed to evaluate the bioequivalence of the Test Product (perindopril/indapamide/amlodipine) 10mg/2.5mg/10mg tablets) versus the Reference Product (Triplixam (perindopril/indapamide/amlodipine) 10mg/2.5mg/10mg film-coated tablets) after a single-dose in healthy subjects under fasted conditions. The results of this study indicated based on the pharmacokinetic parameters of active substances, that the Reference tablet and Test tablet are bioequivalent.

To support a biowaiver for the two lower strengths, the Applicant established that:

1. All dosage strengths of the pharmaceutical products are manufactured by the same manufacturer and process;
2. The qualitative compositions of the different strengths is the same;
3. The amount of all active substances is less than 5% weight of tablet core in all strengths.

Furthermore, the ratio between the amount of excipients is the same between BE dose (10 mg /2.5mg/10mg) and 5 mg/1.25 mg/5 mg dose. For dose 10 mg/2.5 mg/5 mg the differences in amount of cellulose accounts for differences in amounts of active substances amlodipine;
4. All active substances (perindopril, amlodipine and indapamide) express linear pharmacokinetics over the therapeutic dose range;
5. The dissolution profiles are similar under identical conditions for batch used in bioequivalence study and batches of the additional strengths at pHs 1.2, 4.5 and 6.8.

Based on the fact that bioequivalence was shown with the highest strength (10 mg /2.5mg/10mg) and biowaiver criteria as per the EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** were fulfilled, a waiver for a bioequivalence study with the Perindopril arginine/Indapamide /Amlodipine 5/1.25/5 mg and Perindopril arginine/Indapamide/Amlodipine 10/2.5/5 mg strengths was considered to be acceptable.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The co-administration of perindopril/indapamide and amlodipine does not change their pharmacokinetic properties by comparison to separate administration.

Perindopril:

Absorption and bioavailability
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour (perindopril is a prodrug and perindoprilat the active metabolite). The plasma half-life of perindopril is equal to 1 hour. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Distribution
The volume of distribution is approximately 0.2 L/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Biotransformation
Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

Elimination
Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Linearity/non-linearity
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Indapamide:

Absorption
Indapamide is rapidly and completely absorbed from the digestive tract.
The peak plasma level is reached in humans approximately one hour after oral administration of the product.

Distribution
Plasma protein binding is 79 %.

Metabolism and elimination
The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation.

Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Amlodipine:

Absorption and bioavailability
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not affected by food intake.

Distribution
The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Metabolism
Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elimination
The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

IV.3 Pharmacodynamics

Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/10 mg Tablet is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. Perindopril arginine salt is an angiotensin converting enzyme inhibitor, indapamide, a chlorosulphamoyl diuretic and amlodipine, a calcium ion flux inhibitor of the dihydropyridine group.

The pharmacological properties of Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/10 mg Tablet are derived from those of each of the components taken separately. In addition, the combination of perindopril/ indapamide produces an additive synergy of the antihypertensive effects of the two components.

IV.4 Clinical Efficacy

The clinical efficacy of this combination of perindopril/indapamide/amlodipine is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application. The summary of product characteristics for the Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/10 mg Tablet are in line with those of the reference product TRIPLIXAM 5/1.25/5 mg, 10/2.5/5 mg 10/2.5/10 mg Tablets (perindopril/ indapamide/ amlodipine) by Les Laboratoires Serviers.

IV.5 Clinical Safety

The clinical safety of this combination of perindopril/indapamide/amlodipine is well established. No additional safety clinical studies to demonstrate safety have been included in the application. The summary of product characteristics for the Perindopril arginine/ Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet, Perindopril arginine/Indapamide/ Amlodipine Krka 10/2.5/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/10 mg Tablet are in line with those of the reference product TRIPLIXAM 5/1.25/5 mg, 10/2.5/5 mg 10/2.5/10 mg Tablets (perindopril/ indapamide/ amlodipine) by Les Laboratoires Serviers. Hence there are no differences from the reference product in the undesirable effects, contraindications, precautions and warnings. The results of the bioequivalence study did not indicate any safety concern related to the test product.

Risk Management Plan
A risk management plan was submitted, 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 Perindopril arginine/Indapamide/Amlodipine Krka 5 mg/1.25 mg/5 mg, 10 mg/2.5 mg/5 mg & 10 mg/2.5 mg/10 mg Tablets.

Routine pharmacovigilance and risk minimisation activities are appropriate to manage risks relating to the product.

Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test products against the reference products, in accordance with the relevant guidance.
No additional tests are required for this application.
The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet is a generic form of TRIPLIXAM 5/1.25/5 mg (perindopril/ indapamide/ amlodipine) by Les Laboratoires Serviers. TRIPLIXAM 5/1.25/5 mg (perindopril/ indapamide/ amlodipine) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown for the 10/2.5/10 mg strength and a biowaiver for the 5/1.25/5 mg and 10/2.5/5 mg strengths has been accepted in accordance with CHMP bioequivalence guidance documents.
The SmPCs are consistent with those of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

From a quality, non-clinical and clinical perspective, the overall assessment outcome of Perindopril arginine/Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/5 mg Tablet, Perindopril arginine/Indapamide/Amlodipine Krka 10/2.5/10 mg Tablet, is positive.

The HPRA, on the basis of the data submitted considered that Perindopril arginine/ Indapamide/Amlodipine Krka 5/1.25/5 mg Tablet demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New DCP as RMS	IE/H/1240/001/DC	SmPC, PAR	10th May 2024	9th May 2029