IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dalnecombi 7 mg/5 mg/2.5 mg tablets
Perindopril arginine
Amlodipine besilate
Indapamide
PA1347/117/001

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 Dalnecombi 7 mg/5 mg/2.5 mg tablets, from KRKA, d.d., on 31st January 2025 as substitution therapy for treatment of essential hypertension, in adult patients already controlled with perindopril/amlodipine fixed dose combination and indapamide, taken at the same dose level.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. With Ireland as the Reference Member State in this decentralised procedure, KRKA, d.d. applied for a marketing authorisation for Dalnecombi 7 mg/5 mg/2.5 mg tablets in Ireland, Germany, Spain, Cyprus, Lithuania, Latvia, Poland and Slovenia. The reference medicinal product for data exclusivity is Triplixam 5 mg/1.25 mg/5 mg film-coated tablets by Les Laboratoires Servier, registered in Malta since 13/01/2014. A European Reference Product is used in the RMS: Tricorlix (also referred to as Viacorlix/Viacorind in other member states) 7 mg/5 mg/2.5 mg film-coated tablets, by Les Laboratoires Servier, registered in Latvia.

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). Indapamide is a non-thiazide sulfonamide with an indole ring, belonging to the diuretic family.
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The legal status for this marketing authorisation is subject to medical prescription, which may be renewed.

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	Dalnecombi 7 mg/5 mg/2.5 mg tablets
Name(s) of the active substance(s) (INN)	Perindopril arginine, Amlodipine besilate, Indapamide
Pharmacotherapeutic classification (ATC code)	C09BX01
Pharmaceutical form and strength(s)	Tablet; 7 mg/5 mg/2.5 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1347/117/001
Marketing Authorisation Holder	KRKA, dd.
MRP/DCP No.	IE/H/1263/001/DC
Reference Member State	IE
Concerned Member State	CY, DE, ES, LT, LV, PL, SI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dalnecombi 7 mg/5 mg/2.5 mg tablets.

II.2 Drug substance

The active substances is perindopril arginine, amlodipine besilate and indapamide, established active substances. Amlodipine besilate and indapamide are described in the European Pharmacopoeia. All active substances are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

Each active substance specification is considered adequate to control the quality and where applicable meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur..

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 have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 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.8 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 Dalnecombi.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Tricorlix on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Dalnecombi 7 mg/5 mg/2.5 mg tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. Further 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

Perindopril arginine, amlodipine besilate and indapamide are well known active substances with established safety, efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Tricorlix marketed by Les Laboratoires Servier.

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

IV.2 Pharmacokinetics

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Dalnecombi 7 mg/5 mg/2.5 mg tablets is compared with the pharmacokinetic profile of the reference product Viacorind 7 mg/5 mg/2.5 mg tablets.

Study 22-735 was a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study comparing the test product (Dalnecombi 7 mg/5 mg/2.5 mg tablets) to the reference product (Viacorind 7 mg/5 mg/2.5 mg tablets) in healthy adult human subjects under fasting conditions.

A summary of the pharmacokinetic parameters is presented in the tables below:

Perindopril

Treatment	**AUC_{0-t}** xg/ml/h	**C_{max}** xg/ml
Test	63.61 (21.54)	54.26 (16.76)
Reference	62.99 (20.76)	54.18 (17.50)
***Ratio (90% CI)**	100.66 (97.41 - 104.03)	100.59 (94.72 – 106.83)

Amlodipine

Treatment	**AUC_{0-72}** xg/ml/h	**C_{max}** xg/ml
Test	113.85 (22.78)	2.89 (0.54)
Reference	114.15 (21.52)	2.94 (0.57)
***Ratio (90% CI)**	99.58 (97.26-101.94)	98.29 (95.39 – 101.29)

Indapamide

Treatment	**AUC_{0-t}** xg/ml/h	**C_{max}** xg/ml

Test	2342.80 (24.32)	118.72 (19.30)
Reference	2279.14 (22.12)	125.14 (19.72)
***Ratio (90% CI)**	102.39 (100.75 – 104.05)	94.79 (90.75 – 99.00)

In accordance with the regulatory requirements, the test/reference ratios and their 90 % confidence intervals calculated for AUC_{0-t} (or AUC_{0-72h}) and C_{max} were inside the normal range of acceptability (80.00 – 125.00 %) to show bioequivalence between the test and reference product. Based on the pharmacokinetic parameters of each of the active substances, the reference product, Viacorind 7 mg/5 mg/2.5 mg tablets, marketed by Les Laboratoires Servier and test product, Dalnecombi 7 mg/5 mg/2.5 mg tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none are required for an application of this type.

IV.5 Clinical Safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from this study.

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 Perindopril arginine/Amlodipine/Indapamide Krka 7mg/5mg/2.5mg."

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 6.2 signed 14/05/2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- 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.

For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Dalnecombi 7 mg/5 mg/2.5 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of a suitable approved reference product (Tricorlix). Tricorlix 7 mg/5 mg/2.5 mg tablets is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown between Dalnecombi and the reference product.

V. OVERALL CONCLUSIONS

Dalnecombi 7 mg/5 mg/2.5 mg tablets is a generic form of Tricorlix 7 mg/5 mg/2.5 mg tablets. Tricorlix is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considers that Dalnecombi 7 mg/5 mg/2.5 mg tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

17.01.2030