IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Perindopril Krka 8 mg tablets
Perindopril tert-butylamine
PA1347/041/003

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

This module reflects the scientific discussion for the approval of Mariper. The procedure was finalised on 17 December 2009. For information on changes after this date please refer to the module 'Updates'.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mariper 2 mg, 4 mg and 8 mg tablets, from Miklich Laboratorios, S.L. The product is indicated for treatment of hypertension and symptomatic heart failure and reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

Perindopril is an ACE inhibitor that inhibits the conversion of angiotensin I into angiotensin II. Inhibition of ACE leads to reduced plasma level of angiotensin II which consequentially increases plasma rennin activity (by inhibition of the negative feedback of rennin release). Perindopril acts through its active metabolite perindoprilat. Other metabolites are inactive.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Coversyl 2 mg, 4 mg and 8 mg tablets, which has been registered in France since 1988 by Les Laboratoires Servier. In Denmark Coversyl 2 mg, 4 mg and 8 mg tablets have been registered by les Laboratoires Servier since 1989 (8 mg since 2004).

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each 2 mg tablet contains 2 mg of perindopril tert-butylamine, equivalent to 1.669 mg of perindopril. Each 4 mg tablet contains 4 mg of perindopril tert-butylamine, equivalent to 3.338 mg of perindopril. Each 8 mg tablet contains 8 mg of perindopril tert-butylamine, equivalent to 6.676 mg of perindopril.

The 2 mg tablets are white to almost white, round, slightly biconvex tablets with bevelled edges.
The 4 mg tablets are white to almost white, oval, slightly biconvex, one side scored tablets with bevelled edges. The tablets can be divided into equal halves.
The 8 mg tablets are white to almost white, round, slightly biconvex, one side scored tablets with bevelled edges. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Mariper is packed in blisters (OPA/Al/PVC film, Al foil) in pack sizes of 10, 14, 28, 30, 50, 56, 60, 90 and 100 tablets in a box. However, not all pack sizes may be marketed.

The excipients are: Calcium chloride hexahydrate; lactose monohydrate; crospovidone; cellulose, microcrystalline; silica, colloidal anhydrous and magnesium stearate.

CompliancewithGoodManufacturingPractice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance is perindopril tert-butylamine, which is described in Ph. Eur.
The Active Substance Master File (ASMF) procedure is used for the active substance.
Starting materials are relatively complex but in general adequate information has been provided to substantiate the proposed starting materials. The synthesis has been adequately described.

The control tests and specifications for drug substance have been adequately drawn up.

Stability studies have been performed in accordance with EU/ICH guidelines. The presented stability data justifies the proposed re-test period and storage conditions.

II.3 Medicinal Product

The development of the product has been outlined, the choice of excipients justified and their functions explained. The manufacturing process has been adequately described. The process has been validated on pilot scale batches. A commitment has been made that process validation in accordance with the protocol in 3.2.P.3.5 will be performed on the first three production scale batches of each tablet strength manufactured at the proposed manufacturing site.

The product specifications cover appropriate parameters for this dosage form. Satisfactory validations of the analytical methods have been conducted. Batch analysis has been performed on three pilot scale batches of each tablet strength. The batch analysis results show that the finished products meet the specifications proposed.

Stability studies have (overall) been conducted in accordance with EU/ICH guidelines. Three pilot scale batches of each tablet strength in the OPA/Al/PVC/Al blister have been included in the studies. A shelf-life period of 24 months (= period covered by long term data + 6 months) with the storage condition "Do not store above 30°C. Store in the original package in order to protect from moisture and light" is approved for the finished product in Al/Al blister.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of perindopril tert-butylamine are well known. As perindopril tert-butylamine is a widely used, well-known active substance and this product is a generic formulation of Coversyl tablets, which is available on the European market , the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Environmentalriskassessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of perindopril tert-butylamin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction
Perindopril tert-butylamine is a well-known active substance with established efficacy and tolerability. For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Mariper 8 mg tablets is compared with the pharmacokinetic profile of the reference product Prexanil 8 mg tablets from the Slovenian market.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 56 days between the two administrations. 8 mg was administered in each period.

Blood samples were collected pre-dosing and at 0.167, 0.333, 0.50, 0.75, 1.0, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 12, 24, 36, 48, 72, 96, 120 and 144 hours post administration of a single-dose 8 mg tablet for the analyses of perindopril (up to 12 hours) and perindoprilat.

44 healthy male subjects (19-45 years/ 39 Caucasian, 2 Asian and 3 Black) participated in the study. All 44 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Bioequivalence were to be concluded if the 90% geometric confidence interval of the ratio (A/B) of LSM for ln-transformed AUC0-t, AUC0-∞ and Cmax were within the acceptance range of 80-125%.

Table 1. Pharmacokinetic parameters of perindopril under fasted conditions.

Treatment N=44	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	99.27 (29.5%)	100.56 (29.0%)	83.18 (48.0%)	0.75 (57.6%)	0.94 (50.2%)
Reference	100.79 (24.5%)	101.73 (24.4%)	81.51 (34.4%)	0.78 (51.7%)	0.91 (28.8%)
*Ratio (90% CI)	98.50% (93.84-103.38%)	98.85% (94.45-103.46%)	102.05% (88.99-117.03%)		
CV (%)	13.6%	12.8%	39.6%		

$AUC_{0-\infty}$ 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

Table 2. Pharmacokinetic parameters of perindoprilat under fasted conditions.

Treatment N=44	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	239.52 (30.2%)	290.55 (29.20%)	15.15 (53.2%)	4.24 (35.5%)	72.99 (53.4%)
Reference	234.86 (28.6%)	283.17 (27.5%)	14.81 (48.7%)	3.99 (25.7%)	71.09 (42.8%)
*Ratio (90% CI)	101.98% (98.37-105.73%)	99.92% (94.97-105.12%)	102.26% (95.35-109.67%)		
CV (%)	10.1%	11.3%	19.7%		

$AUC_{0-\infty}$ 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

The 90% CI for the ln-transformed primary variables AUC0-t, AUC0-inf and Cmax for perindopril and perindoprilat are within the acceptance range of 80-125%.

Based on the submitted bioequivalence study Mariper 8 mg tablets is considered bioequivalent with Prexanil 8 mg tablets, Les Laboratories Servier.

The 2 mg and 4 mg tablets are dose proportional with the 8 mg tablets. The pharmacokinetics of the active substance are linear in the therapeutic dose range. The results of the bioequivalence study performed with the 8 mg strength therefore apply to the other strengths.

The RMS has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.2 Risk management plan & Pharmacovigilance system

Perindopril tert-butylamine was first approved in 1988, and there is now more than 10 years post- authorisation experience with the active substance. The safety profile of perindopril tert-butylamine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. OVERALL CONCLUSIONS

PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Coversyl tablets marketed by Les Laboratoires Servier.
Furthermore, the SmPC and package leaflet have been updated according to final SPC wording for "Angiotensin Converting Enzyme (ACE) inhibitors & Angiotensin II Receptor Antagonists (AIIRAs): Use during pregnancy & lactation (for Perindopril) agreed by PhVWP October 2008.

Readability test

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Prenessa 2 mg, 4 mg and 8 mg tablets. The bridging report submitted by the applicant has been found acceptable.

OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The product Mariper 2 mg, 4 mg and 8 mg tablets form has a proven chemical-pharmaceutical quality and is a generic form of Coversyl tablets. Coversyl tablets is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with what has been approved for the reference product Coversyl. In addition, the SmPC and package leaflet have been updated according to final SPC wording for "Angiotensin Converting Enzyme (ACE) inhibitors & Angiotensin II Receptor Antagonists (AIIRAs): Use during pregnancy & lactation (for Perindopril) agreed by PhVWP October 2008.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Mariper with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 December 2009.

The PSUR submission cyclus is 3 years. The first PSUR will be submitted with the DLP of 2010-01.

The date for the first renewal will be: 17 December 2014.

The following post-approval commitments have been made during the procedure:

• On-going stability studies with pilot scale batches will be continued as long as results comply with specification limits otherwise to the scheduled endpoints
• Process validation in accordance with the protocol in 3.2.P.3.5 will be performed on the first three production scale batches of each tablet strength manufactured at the proposed manufacturing site.
• Certificates of analysis for the first three consecutive production scale batches of each tablet strength will be forwarded when available.
• Stability studies per one batch of each tablet strength manufactured using perindopril erbumine anhydrate α-form will be performed when available.
• A commitment has been made to place the first three production batches of each tablet strength on long term stability studies through the proposed shelf-life and on accelerated studies for 6 months using the stability protocol as presented in P.8.1.

• Pharmacovigilance system. The EudraVigilance registration is pending. The applicant hereby commits to conclude the EMEA eudravigilance registration before the product is on the market.

VI. REVISION DATE

12/12/2025

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From DK/H/1649/001-003 to IE/H/1450/001-003		12/12/2025	12/12/2025