COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Perindopril tert-butylamine/Amlodipine Denk 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets

(perindopril tert-butylamine/amlodipine besilate)

NL/H/4881/001-004/DC

Date: 30 June 2020

This module reflects the scientific discussion for the approval of Perindopril tert-butylamine/Amlodipine Denk 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets. The procedure was finalised at 24 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Perindopril tert-butylamine/Amlodipine Denk 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets, from Denk Pharma GmbH & Co. KG.

The product is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Coveram arg 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets which has been registered in The Netherlands by Les Laboratoires Servier since 14 May 2008 through mutual recognition procedure FR/H/0325/001.

The concerned member states (CMS) involved in this procedure were Germany and Malta.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Perindopril tert-butylamine/Amlodipine Denk are all white to off-white, biconvex tablets.

- 4 mg/5 mg strength – oval tablets marked with '4/5' on one side. Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).
- 4 mg/10 mg strength – rectangular tablets marked with '4/10' on one side. Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 10 mg amlodipine (as besilate).
- 8 mg/5 mg strength – triangular tablets marked with '8/5' on one side. Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
- 8 mg/10 mg strength – round tablets marked with '8/10' on one side. Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate).

The tablets are packed in Aluminium/Aluminium blisters.

The excipients are: sodium starch glycolate (type A), glycerol dibehenate, anhydrous calcium hydrogen phosphate, trehalose dihydrate, microcrystalline cellulose, light magnesium oxide, crospovidone and magnesium stearate.

II.2 Drug Substances

The active substances are Perindopril tert-butylamine and amlodipine besilate, both established active substances described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for both active substances. 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.

Perindopril tert-butylamine
Perindopril tert-butylamine is white or almost white crystalline powder and is freely soluble in water and in ethanol (90%), soluble or sparingly soluble in methylene chloride. Perindopril tert-butylamine exists in various polymorphic forms. Only the (α)-form is manufactured.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional requirements from both CEPs. Batch analytical data demonstrating compliance with this specification have been provided for one batch from each supplier.

Stability of drug substance
The active substance is stable for 3 or 4 years (depending on the manufacturer) when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Amlodipine besilate
Amlodipine besilate is a white or almost white powder and slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional requirements from both CEPs. Batch analytical data demonstrating compliance with this specification have been provided for one batch from each supplier.

Stability of drug substance
The active substance is stable for 2 or 5 years (depending on the manufacturer) when stored under the stated conditions. Assessment thereof was part of granting the CEP 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. The choice of excipients is justified, and their functions explained. From the comparative dissolution studies complementary to the *in vivo* bioequivalence studies, similarity in dissolution was confirmed between the test and reference batch in pH 2, 4.5 and 6.8 media. The general biowaiver criteria are met. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. As the process is a standard process for the 8 mg/10 mg, 8 mg/5 mg and 4 mg/5 mg strength, the process has been adequately validated. As the total amount of active substance present in the formulation of the 4/10 tablets is less than 2% this manufacturing process is considered as a non-standard process. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their corresponding Ph.Eur. monographs. 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 description, identification, uniformity of dosage units, average weight, disintegration, dissolution, assay, related substances and microbiological purity. 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 four pilot scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for batches of each strength stored at 25°C/60% RH (36 months) at 30°C/75% (36 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. The batches were stored in the proposed packaging. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'Store in original package in order to protect from light and moisture'.

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 Perindopril tert-butylamine/Amlodipine Denk 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 Ecotoxicity/environmental risk assessment (ERA)

Since Perindopril tert-butylamine/Amlodipine Denk is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Coveram which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies 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

Perindopril tert-butylamine and amlodipine besilate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Perindopril tert-butylamine/Amlodipine Denk 8 mg/10 mg tablets (DENK PHARMA GmbH & Co., Germany) is compared with the pharmacokinetic profile of the reference product Coveram arg 10 mg/10 mg tablets (Les Laboratoires Servier, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the additional strengths (8 mg/5 mg, 4 mg/10 mg, and 4 mg/5 mg) has been requested. The strength selected for the bioequivalence study, 8 mg/10 mg represents the highest strength and the lower strengths are, according to the MAH, quantitatively proportional. The data on bioequivalence can therefore be a waiver to the additional strengths 4 mg/5 mg, 4 mg/10 mg and 8 mg/5 mg.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 20-37 years. The study was conducted in two groups (6 subjects in group-I and 30 in group-II). Based on the safety analysis of the subjects dosed in group-I (period one), group II was dosed. Each subject received a single dose (8 mg perindopril and 10 mg amlodipine) of one of the 2 formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 21 days.

For perindopril blood samples were collected at pre-dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.3, 1.7, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours after administration of the products.

For amlodipine blood samples were collected at pre-dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.3, 1.7, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The wash-out long enough, the sampling period (72 hours) long enough, and sampling scheme adequate to estimate pharmacokinetic parameters. Sufficient samples are planned around the expected t_{max} (1 hour and 6-12 hours for perindopril and amlodipine, respectively). Amlodipine and perindopril can be taken with or without food.

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
One subject was withdrawn due to an adverse event (allergic conjunctivitis), one subject was withdrawn because of emesis and one subject was considered dropped out. Therefore, 33 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=33	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	144 ± 29	145 ± 28	124 ± 27	0.8 (0.5-1.0)
Reference	148 ± 28	148 ± 28	128 ± 26	0.5 (0.5-1.7)
***Ratio (90% CI)**	0.97 (0.94 – 1.01)	--	0.96 (0.90 – 1.03)	--
CV (%)	7.7	--	15.7	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions.

Treatment N=33	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	296 ± 56	--	7.0 ± 1.2	9

				(4-12)
Reference	287 ± 56	--	6.9 ± 1.4	9 (3-12)
***Ratio** **(90% CI)**	1.04 (1.00 – 1.07)	--	1.02 (0.98 – 1.05)	--
CV (%)	8.2	--	8.8	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Perindopril tert-butylamine/Amlodipine Denk is considered bioequivalent with Coveram.

The MEB 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.3 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 tert-butylamine/Amlodipine Denk.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Coveram. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management

is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Perindopril tert-butylamine/Amlodipine Denk 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Coveram arg 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. Coveram 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 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 essential similarity has been demonstrated for Perindopril tert-butylamine/Amlodipine Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 March 2020.

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