COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Perindopril tert-butylamine/Amlodipine CF 4/5 mg, 4/10 mg, 8/5 mg and 8/10 mg, tablets (perindopril tert-butylamine and amlodipine)

NL/H/4640/001-004/DC

Date: 25 November 2022

This module reflects the scientific discussion for the approval of Perindopril tert-butylamine/Amlodipine CF 4/5 mg, 4/10 mg, 8/5 mg and 8/10 mg, tablets. The procedure was finalised on 27 April 2016 in Sweden (SE/H/1500/01-04/DC). After a transfer on 27 November 2018, the current RMS is the Netherlands. 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 CF, from Centrafarm B.V.

The active substances are perindopril and amlodipine. Perindopril belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme inhibitors). Amlodipine belongs to a group of medicines called calcium antagonists. Both substances are used in the treatment of high blood pressure (hypertension) and/or treatment of stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).

For current indications, see the Summary of Product Characteristics.

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

The applicant have obtained a product specific PIP waiver from the PDCO/EMA for all subsets/indication of the paediatric population for Perindopril/Amlodipin in the treatment of hypertension and treatment of stable coronary artery disease.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its chemical properties are sufficiently described.

The manufacturing process of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests, and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage described in the Summary of Product Characteristics sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Perindopril/amlodipine is a combination of two established antihypertensive agents, both of which have been in use for more than 15 years. The proposed new fixed combination is proposed to be 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.

III.2 Pharmacology

Perindopril is a long-acting ACE inhibitor, acting through its only active metabolite perindoprilat. It inhibits the renin-angiotensin system by preventing both the conversion of angiotensin I to angiotensin II and the degradation of bradykinin, thereby reducing the vasoconstriction and left ventricular remodelling characteristic of heart failure. The inhibition of angiotensin II formation, particularly in the vasculature, is the primary pharmacological action of perindopril, leading to a reduction in peripheral vascular resistance with no significant change in heart rate. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It has been suggested that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors.

Amlodipine belongs to the dihydropyridine class of calcium channel blockers. Amlodipine inhibits calcium influx into cardiac and vascular smooth muscle via L-type calcium channels. The main site of action is the peripheral vasculature, although it produces vasodilation in coronary vascular beds. Amlodipine preserves circadian patterns of blood pressure changes and has favourable effects on cardiac output, systemic vascular resistance and left ventricular function, but has little effect on heart rate or cardiac conduction. Preclinical studies indicate that amlodipine is a potent antihypertensive agent with natriuretic and diuretic properties that may enhance its ability to reduce blood pressure without attendant fluid retention. In animal studies amlodipine has also demonstrated cardioprotective effects.

Reductions in atheroma formation and regression of myocardial hypertrophy have also been associated with amlodipine in animal models.

III.3 Pharmacokinetics

No new studies on pharmacokinetics have been performed. An overview based on published literature has been provided. Toxicokinetics of the combination has been studied as part of a toxicological study on the combination.

Perindopril is a prodrug that is converted hepatically to the diacid product, perindoprilat; the major drug-related material excreted in urine. Though perindopril, as a result of exaggerated pharmacological action on tissue-associated ACE, can cause renal function impairment, this is less likely to have an effect on amlodipine pharmacokinetics as amlodipine is extensively metabolised in the liver by CYP3A. There is no information regarding interactions of perindopril with CYP450 enzymes. Theoretically, these two drugs are not expected to have any significant pharmacokinetic interactions with other drugs according to the applicant.

III.4 Toxicology

The toxicological properties of perindopril and amlodipine are established and well known. The applicant has provided an overview based on published literature which is considered to be sufficient. In addition, a 3-month repeat dose toxicity study in rats, including toxicokinetic data, performed in accordance with GLP has been performed by the applicant. In general, data obtained showed a similar exposure with the combination perindopril/amlodipine as compared to that obtained after administration of single compounds. No pharmacokinetic/toxicokinetic interaction is thus indicated by the results obtained. Comparison of the toxicological findings seen after administration of perindopril and amlodipine as single compounds as compared to the combination suggests a slight potentiation of the known perindopril induced kidney toxicity by amlodipine. The SmPC has been updated to include this information in section 5.3 of the SmPC. The slight potentiation of perindopril renal toxicity observed in the non-clinical toxicological study does not raise any new concerns over the clinical safety of perindopril/amlodipine and does not have any influence on the risk/benefit ratio of the combination product.

III.5 Ecotoxicity/environmental risk assessment

The proposed new fixed combination is indicated as a substitution therapy and is therefore not expected to increase the use of perindopril or amlodipine. No increased environmental risk is therefore anticipated.

III.6 Discussion on the non-clinical aspects

The review of non-clinical data available for perindopril and amlodipine overall indicates no major issues for concern for the combination of these two substances. No increased

environmental risk due to perindopril or amlodipine is anticipated due to the use of the fixed combination.

IV. CLINICAL ASPECTS

IV.1 Introduction

The proposed indications for Perindopril tert-butylamine/Amlodipine CF 4/5 mg, 4/10 mg, 8/5 mg and 8/10 mg, tablets, comprise the treatment of essential hypertension and/or stable coronary artery disease as substitution therapy in patients who are adequately controlled on perindopril and amlodipine given as separate tablets. The product cannot be used for initiating treatment.

IV.2 Pharmacokinetics

For a new FDC indicated for substitution therapy, bioequivalence with the mono-components given concomitantly should be demonstrated. In addition, the interaction potential between the active substances should be properly addressed.

Two pharmacokinetic studies were performed by the MAH. One bioequivalence study was conducted to show therapeutic equivalence to the innovator products and one interaction study was conducted to demonstrate the lack of pharmacokinetic interaction between amlodipine and perindopril.

Study 1 – Bioequivalence: single dose, 8 mg/10 mg, fasted
Bioequivalence was evaluated in a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 36 healthy volunteers under fasting conditions, comparing Perindopril erbumine 8 mg/Amlodipine 10 mg FDC tablets with Coversyl (perindopril arginine) 10 mg tablet + Norvasc (amlodipine) 10 mg tablet. The study design was satisfactory. Plasma concentrations of perindopril and amlodipine were analysed by a sufficiently validated HPLC/MS/MS method.

Bioequivalence was demonstrated; for AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both perindopril and amlodipine.

The results from the bioequivalence study with the 8 mg/10 mg strength may be extrapolated to the other strengths of 4 mg/5 mg, 4 mg/10 mg and 8 mg/5 mg, since all conditions listed in section 4.1.6 of the Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/ 1401/98 Rev. 1 are fulfilled.

Study 2 – Interaction: single dose, 10 mg/10 mg, fasted

This was a randomized, open label, three treatment, two period, two sequence, crossover study in parallel cohorts to assess the single-dose pharmacokinetics of Coversyl (Perindopril arginine 10 mg) tablets & Norvasc (Amlodipine 10 mg) tablets when administered together or alone, in 44 healthy adult subjects, under fasting conditions.

No interaction was observed after single-dose administration of amlodipine and perindopril. Although the interaction study was not designed to evaluate a worst-case scenario under therapeutic conditions, no pharmacokinetic interaction is expected given the known pharmacokinetic characteristics of the active substances.

Pharmacokinetic conclusion

Bioequivalence was demonstrated and no pharmacokinetic interaction is anticipated.

IV.3 Pharmacodynamics / Clinical efficacy / Clinical safety

The primary aim of this fixed dose combination product is to reduce the number of tablets the patient has to take, which may potentially enhance adherence to therapy.

Recent treatment guidelines, e.g. 2013 ESH/ESC Guidelines for the management of arterial hypertension, address the fact that certain, more severely ill hypertensive patients, could be treated with more than one drug from the start of therapy. The therapy should however be initiated with the individual monocomponents to allow for proper dose titration.

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary. The main consideration, as the applicant was seeking for substitution indication, was therefore evidence of the well-established use of the free combination in both suggested indications, which was provided by the applicant.

The proposed dose strength for Perindopril (4 mg, 8 mg) is lower than the approved dose for the originator Coversyl Novum. (4 mg vs 5 mg). This is due to different salts; Coversyl Novum contains perindopril arginine whereas this fixed dose combination contains perindopril tert-butylamine. In both cases, the amount of perindopril is almost the same; 4 mg of perindopril-tert-butylamin corresponds to 3.3 mg perindopril and 5 mg perindoprilarginin corresponds to 3.4 mg perindopril. RMS was of the position that the salt form should be clearly specified in the trade name, as the RMS believes that there is a risk for medication error. Moreover this would be the only perindopril product in SE with a different salt form to other approved perindopril products.

IV.4 Risk Management Plan

As perindopril tert-butylamin/amlodipine is a fixed dose combination of the mono-components, substances from the originators, the safety concerns should essentially be the

same as for the originators. Because the originators have been on the market for some years, there are no Risk Management Plans available for Norvasc or Coversyl.

The three MAHs involved in the procedure have provided three different Risk Management Plans. The RMPs provided by the applicants have been prepared as per Guideline on good Pharmacovigilance practice (GVP) module V. One common list of safety concerns for all products involved in the procedure has been recommended by RMS, which was accepted by the applicant.
The summary of safety concerns for Pernidopril tert-butylamin/Amlodipine is presented below.

Table 1. Summary of safety concerns as approved in RMP

Important identified risks	• Teratogenicity following exposure during the second and third trimester of pregnancy • Angioedema • Hepatic impairment • Renal impairment • Decreased blood cell count • Serious skin disorders (e.g. Stevens-Johnson Syndrome) • Hyperkalaemia • Hypotension • Co-administration with lithium, and NSAIDs
Important potential risks	• Teratogenicity following exposure during the first trimester of pregnancy • Co-administration with CYP3A4 inhibitors • Pulmonary oedema in patients with heart failure
Missing information	• Use in children and adolescents • Exposure during breast feeding

As the two active substances in the suggested fixed dose combinations are used clinically as combinations of separate tablets and as these FDCs are intended for substitution therapy only, routine pharmacovigilance with an adequate pharmacovigilance system is considered sufficient to adequately follow up the safety profile of the FDCs with perindopril and amlodipine.

The RMPs for perindopril tert-butyamine / amlodipine for the MAH (DLP 7 March 2016) are approved.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and a market authorisation was granted to Perindopril tert-butylamine/Amlodipine CF 4/5 mg, 4/10 mg, 8/5 mg and 8/10 mg, tablets.

The decentralised procedure for Perindopril tert-butylamine/Amlodipine CF, 4mg/5mg, 4mg/10mg, 8mg/5mg, 8mg/10mg, tablet was positively finalised on 2016-04-27 in Sweden.

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
NL/H/4640/IB/005/G	Update of product information in line with PRAC recommendation C.I.3.z) Update of product information following PSUSA outcome	Yes	11-10-2019	Approved	N/A
NL/H/4640/1-4/IB/006	Change in test procedure for the finished product	No	6-3-2020	Approved	N/A
NL/H/4640/1-4/IA/007	Name change of the secondary packager	No	23-3-2020	Approved	N/A
NL/H/4640/1-4/R/001	Renewal	Yes	26-5-2021	Approved	N/A
NL/H/4640/1-4/IA/008	Deletion of manufacturing site/ packaging site B.III.1.a)4 Deletion of Ph.Eur. certificates	No	18-11-2020	Approved	N/A
NL/H/4640/1-4/IA/009	Minor change in the manufacturing process of the finished product	No	5-1-2021	Approved	N/A
NL/H/4640/IB/010/G	Addition of a new specification parameter to the specification with its corresponding test method of the finished product; Change in calculation of the related substances	No	17-11-2021	Approved	N/A
NL/H/4640/1-4/IB/011	Amendments in SmPC/ PL in accordance with CMDh PSUSA outcome	Yes	15-12-2021	Approved	N/A
NL/H/4640/1-4/IB/012	Amendments in SmPC/ PL in accordance with CMDh PSUSA outcome	Yes	25-8-2022	Approved	N/A