LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

SE/H/1346/01-05/DC
Ramipril/Amlodipine Proton Pharma

(ramipril/amlodipine)

Applicant:
Proton Pharma S.A.

This module reflects the scientific discussion for the approval of Ramipril/Amlodipine Proton Pharma. The procedure was finalised on 2014-05-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

PROTON PHARMA S.A. has applied for a marketing authorisation for Ramipril/Amlodipine Proton Pharma, capsule, hard; 2, 5 mg/5 mg, 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg according to Article 10 b (fixed combination) of Directive 2001/83/EC, through the Decentralised Procedure with Sweden acting as reference member state (RMS).

The active substances are ramipril and amlodipine. Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, thus relaxing the smooth muscles in the arterial wall, decreasing total peripheral resistance and hence, reducing blood pressure (BP). Ramipril by inhibition of ACE reduces angiotensin II formation and decreases bradykinin breakdown what leads to vasodilatation. This fixed dose combination is classified to the pharmaceutical group: an angiotensinconverting enzyme inhibitor and calcium channel blocker, with ATC code: C09 BB07. The proposed indication for ramipril/amlodipine 2,5 mg/5 mg, 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg, hard capsules, comprise the treatment of hypertension as substitution therapy in patients receiving ramipril and amlodipine from separate tablets. The product cannot be used for initiating treatment of hypertension.

The active substances are not considered as new active substances.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Ramipril/Amlodipine Proton Pharma is presented in the form of capsules, hard containing 2.5 mg, 5 mg or 10 mg ramipril in combination with 5 mg or 10 mg amlodipine corresponding to 6.93 mg and 13.87 mg amlodipine besilate, respectively. The excipients are cellulose microcrystalline, calcium hydrogen phosphate, anhydrous, sodium starch glycolate (type A), maize starch pregelatinised, sodium stearyl fumarate, iron oxide red, iron oxide yellow and black (only the 10mg/10mg), titanium dioxide and gelatine. The capsules are packed in aluminium blisters.

II.2 Drug Substance

Ramipril and amlodipine besilate have a monograph in the Ph Eur.

Ramipril is a white or almost white crystalline powder which is sparingly soluble in water and freely soluble in methanol.
Amlodipine besilate is a white or almost white powder which is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol. The structures of ramipril and amlodipine besilate have been adequately proven and their physico-chemical properties sufficiently described. The routes of synthesis have been adequately described.

The active substances specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest periods.

II.3 Medicinal Product

Ramipril/Amlodipine Proton Pharma capsules, hard are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin except the gelatine for which compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been demonstrated.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30° C in the original package, protected from light.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A non-clinical overview dated February 13, 2013 covering 89 references up to year 2013 has been provided. This is considered to be sufficient. The ingredients of Ramipril/Amlodipine Proton Pharma, hard capsules are well known and established excipients that does not raise any concern.

III.2 Ecotoxicity/environmental risk assessment

Ramipril/Amlodipine Proton Pharma is limited to patients already receiving ramipril and amlodipine from separate tablets/capsules. It is therefore assumed that the overall consumption of the active substances will not increase significantly. The absence of a complete ERA is considered acceptable based on the absence of any significant increase of the environmental exposure of ramipril and amlodipin.

III.3 Discussion on the non-clinical aspects

No new non-clinical studies have been performed with the combination ramipril/amlodipin. Since there is adequate clinical experience with co-administration of ramipril/amlodipin and since there is no significant toxicological concern with the combination, this is considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The proposed indications for Ramipril-Amlodipine comprise the treatment of hypertension as substitution therapy in patients receiving ramipril and amlodipine from separate tablets and the product cannot be used for initiating treatment of hypertension.

IV.2 Pharmacokinetics

The indication applied for is a substitution indication. As there is a wide therapeutic experience available and a pharmacological rationale for the use of both drugs in combination, showing bioequivalence of the components in free combination with the FDC (fixed dose combination) was the pivotal aspect in the clinical part of this application.

Bioequivalence studies were submitted for the amlodipine-ramipril strengths 10 mg/10 mg and 5 mg/10 mg and a biowaiver for the additional strength is acceptable.

The studies were randomised, two-treatment, two-period, two-sequence single-dose crossover trials conducted in 60 healthy volunteers under fasting conditions where the free combination was compared with the FDC.

Subjects were divided into two equal subgroups, i.e. subgroup A (subjects No. 1 - 30) and the subgroup B (subjects No. 31 - 60). Due to high variability of ramipril all 60 subjects were planned for evaluation of bioequivalence of ramipril (subgroup A + B), but only 30 subjects were planned for evaluation of amlodipine bioequivalence (subgroup A).

The pharmacokinetic results for amlodipine-ramipril are presented below:

Summary table of the comparative bioequivalence data: a pivotal bioequivalence study on Amlodipine/Ramipril 10 mg / 10 mg hard capsules

Summary Table of the Comparative Bioequivalence Data

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
R-amlodipine						
$AUC_{(0\text{-}72h)}$ (ng·h/mL)	30	106.64	101.03	105.56	102.00	109.24
C_{max} (ng/mL)	30	2.70	2.60	103.82	99.18	108.69
S-amlodipine						
$AUC_{(0\text{-}72h)}$ (ng·h/mL)	30	110.10	104.76	105.10	101.72	108.60
C_{max} (ng/mL)	30	2.64	2.51	105.05	100.35	109.96
Ramipril						
$AUC_{(0\text{-}t)}$ (ng·h/mL)	60	23.74	21.30	111.44	104.69	118.61
C_{max} (ng/mL)	60	33.80	34.03	99.34	89.25	110.57

Summary table of the comparative bioequivalence data: a pivotal bioequivalence study on Amlodipine/Ramipril 5 mg / 10 mg hard capsules

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
R-amlodipine						
$AUC_{(0\text{-}72h)}$ (ng·h/mL)	30	44.82	43.26	103.62	99.68	107.71
C_{max} (ng/mL)	30	1.21	1.20	100.20	95.55	105.06
S-amlodipine						
$AUC_{(0\text{-}72h)}$ (ng·h/mL)	30	50.19	47.62	105.41	102.13	108.80
C_{max} (ng/mL)	30	1.22	1.19	102.65	97.81	107.72
Ramipril						
$AUC_{0\text{-}t}$ (ng·h/mL)	60	20.20	17.46	115.73	109.30	122.55
C_{max} (ng/mL)	60	30.59	27.70	110.45	99.30	122.85

Bioequivalence, in terms of rate (Cmax) and extent (AUC) of exposure, was demonstrated for amlodipine and ramipril in both studies.

Based on the submitted bioequivalence studies, the new combination is considered bioequivalent with administration of the free combination.

IV.3 Pharmacodynamics, Clinical efficacy and Clinical safety

The both substances are well known and the joint application of two components of the two components is already in widespread use in the proposed dosage strengths. The two components have proven to have acceptable efficacy and safety. The primary aim of the combination is to reduce the number of tablets the patient has to take, which may potentially enhance adherence to therapy.

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. The clinical studies reviewed by the applicant include doses of amlodipine 2.5 mg to 10 mg and ramipril 1.25 mg to 20 mg. Sales data shows that two strengths of amlodipine, 5 mg and 10 mg as well as that the three strengths of ramipril, 2.5 mg, 5 mg and 10 mg are used in clinical practice. Fixed-dose combinations with strengths 5mg and 10 mg in different combinations have been marketed in some European countries as presented by the Applicant. Sales data show that these strengths are used in clinical practice, even if the strength ramipril/amlodipine 5mg/10mg is quite uncommon compared to 5mg/5mg and 10mg/5mg strengths.

The potential risk of medication errors was discussed during the procedure. In the updated version of Product Information for Ramipril/Amlodpine, the following prescribing convention has been established: the first strength indicates the strength of ACE inhibitor, which is followed by the strength of calcium channel blocker (amlodipine). Only product invented names that include the generic names of the active substances (i.e. Ramipril/Amlodipine Proton Pharma) were accepted by the RMS.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet 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 language used for the purpose of user testing the PIL was Polish. The results show that the package leaflet 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.

The risk/benefit ratio is considered positive and Ramipril/Amlodipine Proton Pharma, capsule, hard; 2,5 mg/5 mg, 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Ramipril/Amlodipine Proton Pharma, capsule, hard; 2,5 mg/5 mg, 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg was successfully finalised on 2014-05-14.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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