Public Assessment Report

Scientific discussion

Name of the Product:
Egiramlon 2.5/2.5, 5/5, 10/5, 5/10 and 10/10 mg hard capsules

ramipril / amlodipine

Procedure number:
HU/H/0303/001-005/DC

Applicant:
EGIS Pharmaceuticals PLC

Date: 03 September 2012

This module reflects the scientific discussion for the approval of Egiramlon capsules.
The procedure was finalised at 06 November 2011.
For information on changes after this date please refer to the module 'Update'.

Content

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Czech Republic, Latvia, Lithuania, Poland, Romania, Slovakia) concerned the fixed combinations of 2.5/2.5 mg, 5/5 mg, 5/10 mg, 10/5 mg and 10/10 mg amlodipine/ramipril (amlodipine in its besilate form) in hard capsules.

The Applicant was EGIS Pharmaceuticals PLC (Hungary). The product name in the CMSs Bulgaria, Lithuania and Poland was Ramlon while in the other CMSs and in the RMS Egiramlon. (This latter name is used throughout this Public Assessment Report.)

The application was submitted according to Article 10b of Directive 2001/83/EC (fixed combination)
The combination is intended for use as a substitution in patients suffering from hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets.
The justification for a combination of the ACE-inhibitor ramipril and calcium-channel blocker amlodipine is based on their synergistic effects. The Applicant has adequately summarized the clinical experience with ramipril and amlodipine and presents the synergistic effects between the ACE inhibitors and calcium-channel blockers.

To support the application the Applicant has submitted one bioequivalence study with the 10 mg/10 mg capsules as test product. Norvasc® 10 mg tablets (Amlodipine, Pfizer, Hungary) and Tritace® 10 mg tablets (Ramipril, Sanofi-aventis, Hungary) were selected as reference formulations.

For this type of application no new further clinical or preclinical data, other than supporting literature where necessary.

II. QUALITY ASPECTS

II.1 Introduction

The Marketing Authorization Application of Egiramlon 2,5mg/2,5mg, 5mg/5mg, 10mg/10mg, 5mg/10mg, 10mg /5mg capsules are in compliance with the Article 10b of the Directive 2001/83/EC (i.e. a fixed combination application).
There are two drug substances in the drug product: amlodipine and ramipril. The maximum daily dose is 10 mg for both active substances as specified in the submitted Summary of Product Characteristics.

Egiramlon is indicated for treatment of hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets.

For the comparative bioavailability study only Amlodipine/Ramipril 10/10 mg hard capsules were selected as test, and Norvasc® 10 mg tablets (Amlodipine, Pfizer, Hungary) and Tritace® 10 mg tablets (Ramipril, Sanofi-aventis, Hungary) were selected as reference formulations.

II.2 Drug Substances

II.2.1 Amlodipine besilate

The substance is described in the European Pharmacopoeia (Ph. Eur.) and CEP (Certificate of Ph. Eur.) procedures are followed for this substance. The CEPs indicate that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with a test for residual solvents by GC.

INN name: amlodipine besilate
Chemical name: 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene-sulphonate.

The active substance is a white or almost white powder slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents, particle size distribution and microbial impurities. The Ph. Eur. specification includes the following tests for amlodipine besilate: appearance, solubility, identification (IR), optical rotation, related substances (HPLC), water content, sulphated ash, assay (HPLC). The specification is in accordance also with the Ph. Eur. general monograph *on Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly

justified. The in-house analytical methods and the validation of these additional tests have been presented. This is considered to be acceptable.

The substance complies with the requirements of the EMA guideline on *Genotoxic impurities*.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period of 5 years or 3 years and the packaging material (double polyethylene bag in multiple coated paper-bag or fibre drum) have been mentioned on the CEPs.

GMP compliance of the active pharmaceutical ingredient (API) manufacture is demonstrated by the applicant.

II.2.2 Ramipril

Ramipril is described in the Ph. Eur. and CEP procedures are followed for this substance as well. The CEPs indicate that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with a test for residual solvents by GC.

INN name: ramipril
Chemical name: (2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propa- noyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid

The active substance is a white or almost white crystalline powder sparingly soluble in water, freely soluble in methanol.

The substance is specified in line with the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents.

The Ph. Eur. specification includes the following tests: appearance, identification (IR), optical rotation, related substances (HPLC), loss on drying, sulphated ash, assay (HPLC). Residual solvents (GC) are also controlled. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified. The in-house analytical methods and the validation of these additional tests have been presented. This is considered to be acceptable.

The substance complies with the requirements of the EMA guideline on *Genotoxic impurities*.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period of 2 years - if stored at a temperature not exceeding 30°C in double transparent PE bags placed into a blue HDPE container - have been mentioned on one of the CEPs.

The other CEP has no re-test period but stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 36 months is acceptable if stored below 25°C in a double polyethylene bags in HDPE drum.

GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the development was to enlarge the product range with combination products containing amlodipine in the form of besilate salt and ramipril in 2.5/2.5, 5/5, 5/10, 10/5 and 10 mg/10 mg strengths. The objective of development was to develop products the bioavailability of which is the same as those of the single reference products. The marketing authorisation holders of the original formulations are Pfizer (of Norvasc® tablets containing amlodipine besilate) and Sanofi-aventis (of Tritace® tablets containing Ramipril).

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies product with the following composition, appearance and packaging was obtained. Excipients: crospovidone, hypromellose, cellulose, microcrystalline, glycerol dibehenate, red iron oxide (E172), titanium dioxide (E171), gelatine, brilliant blue (E133), allura red AC (E129), azorubine (E122), indigotine (E132). All excipients used comply with their respective Ph. Eur. monographs (with exception of colouring materials, which comply with the Directive 2008/128/EC.). Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

The appearance of the capsules is as follows.

Amlodipine/ramipril 2.5 mg/2.5 mg hard capsules: unmarked self-closing Coni Snap type, size 3, hard gelatine capsule with opaque, flesh coloured body and opaque, flesh coloured cap filled with white or almost white granular powder.

Amlodipine/Ramipril 5 mg/5 mg hard capsules: unmarked self-closing Coni Snap type, size 3, hard gelatine capsule with opaque, amethyst coloured body and opaque, amethyst coloured cap filled with white or almost white granular powder.

Amlodipine/Ramipril 5 mg/10 mg hard capsules: unmarked self-closing Coni Snap type, size 0, hard gelatine capsule with opaque, flesh coloured body and opaque, amethyst coloured cap filled with white or almost white granular powder.

Amlodipine/Ramipril 10 mg/5 mg hard capsules: unmarked self-closing Coni Snap type, size 0, hard gelatine capsule with opaque, flesh coloured body and opaque, maroon coloured cap filled with white or almost white granular powder.

Amlodipine/Ramipril 10 mg/10 mg hard capsules: unmarked self-closing Coni Snap type, size 0, hard gelatine capsule with opaque, maroon coloured body and opaque, maroon coloured cap filled with white or almost white granular powder.

The capsules are packed in OPA/Al/PVC//Al blisters and cardboard box.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as required by the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented. Certificates of analysis were also provided for the working standard used.

Specification and analytical test methods are described. IR spectra and certificates of analysis justifying the conformity to the Ph. Eur. monograph 3.1.11. is provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 30 months with storage condition of
"Do not store above 30 °C. Store in the original package in order to protect from moisture"
is approved.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The RMS has reached the conclusion that the product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both amlodipine and ramipril are well known.

Claiming that both drugs are widely used well-known active substances the Applicant has not performed further studies. The overview is based on literature review.

As amlodipine/ramipril combinations are indicated for hypertension substitution therapy exclusively and the scientific knowledge and clinical experience relating this combination is vast, no further non-clinical studies are required. The overview based mostly on literature review is, thus, appropriate.

III.2 Pharmacology

No new data but a literature overview has been submitted.

III.3 Pharmacokinetics

No new data but a literature overview has been submitted.

III.4 Toxicology

No new data but a literature overview has been submitted.

III.5 Ecotoxicity/environmental risk assessment

The combination product is indicated for a substitution indication and as such will replace the use of the co-administered single products. Thus the exposure of the environment to amlodipine and ramipril will not increase by use of this product and an environmental risk assessment was not required. A suitable justification for the absence of an environmental risk assessment was provided by the applicant.

III.6 Discussion on the non-clinical aspects

The Application is based on Article 10b of Directive 2001/83/EC, fixed dose combination. Pharmacodynamics, pharmacokinetics and toxicology of both ramipril and amlodipine are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The justification for the combinations of amlodipine and ramipril is based on their synergistic effects on several physiopathologic mechanisms. The combination is intended for use as a substitution in patients suffering from hypertension. In this case no specific clinical pharmacological study is needed in agreement with the requirements stated in the documents CHMP/EWP/240/95 Rev. 1 *Guideline on Clinical Development of Fixed Combination Medicinal Products* and CHMP/EWP/191583/2005 *Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention*.

The Applicant has adequately summarized the clinical experience with ramipril and amlodipine and presented the synergistic effects between the ACE inhibitors and calcium-channel blockers. The justification of the missing specific pharmacokinetic interaction studies between ramipril and amlodipine is acceptable. To support the application the Applicant has submitted one bioequivalence study conducted in accordance with the *Guideline on Bioequivalence* (CHMP/EWP/QWP/1401/98/Rev.1).

IV.2 Pharmacokinetics

IV.2.1 Literature data

Amlodipine

Amlodipine is slowly but almost completely absorbed from the human gastrointestinal tract. Oral bioavailability of amlodipine ranges from 52 to 88%, with the mean of 64%. After oral doses of 2.5, 5, and 10 mg, linear and age-independent relationships were observed between the dose and both AUC and C_{max}. Time to C_{max} (t_{max}) after oral administration was ranging from 6 to 12 h. Absorption of amlodipine is unaffected by food, peak concentration, time to peak concentration, plasma half life and area under the plasma concentration curve (AUC) were not significantly different between fed and fasting state.

The mean volume of distribution (V_d) after a single dose intravenous application of amlodipine was 21 l/kg indicating that a large proportion of the body load of drug is in the tissues rather than in the blood. Amlodipine is highly protein bound with more than 95 %.

Amlodipine is slowly but extensively (about 90%) metabolised in the liver with possible involvement of CYP3A activity, therefore caution is advised when amlodipine is administered concomitantly with CYP3A inducers or inhibitors. Only 4-5% of unchanged drug recovered in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels

of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Amlodipine has no active metabolites.

Ramipril

Absorption: following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution: the serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Metabolism: ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination: excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

The AUC is dose-proportional over the range of 2.5 to 20 mg daily.

Amlodipine/ramipril combination

Regarding the possible pharmacokinetic interactions the Applicant has provided some comparative data about the pharmacokinetic parameters of a single drug and co-administered drugs. Furthermore, the Applicant logically argues that in case of substitution indication the patient is already taking both compounds. As a conclusion the Applicant has sufficiently justified the lack of the pharmacokinetic interaction study.

IV.2.2 Bioequivalence study

In order to demonstrate pharmacokinetics of the fixed dose combination and to establish bioequivalence with the free combination of the monocomponents, one bioequivalence (BE) study was conducted by Algorithme Pharma Inc. (1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1) with EGIS Pharmaceuticals PLC as sponsor between September and November 2009.

The study utilised the highest dose forms (10mg amlodipine besilate and 10 mg ramipril). The conduct of the study was satisfactory and the results complied with the acceptance criteria for bioequivalence as detailed in the relevant CHMP guideline.

Design: this was a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study. The treatment phases were separated by a washout period of at least 35 days.

For amlodipine, blood samples were collected prior to and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 48 and 72 hours post drug administration.

For ramipril (including ramiprilat metabolite) blood samples were collected prior to and 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 48 and 72 hours post drug administration.

Bioanalytics: plasma concentrations of ramipril, ramiprilat and amlodipine were determined by a validated LC-MS-MS method.

Statistics: for C_{max}, AUC_T, AUC_∞: ANOVA after logarithmic transformation, classic (shortest) 90% confidence intervals for the intra-individual ratios. Bioequivalence was concluded if the corresponding 90% confidence intervals for the ratio of the means of AUC_∞, AUC_T and C_{max} parameters of both active ingredients were included between 80% and 125%. A non-parametric test was used for the untransformed t_{max} parameter.

The results are shown in the following Tables.

Pharmacokinetic parameters of ramipril

PARAMETER	TEST		REFERENCE		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{max} (ng/mL)	22.922	51.4	22.552	48.4	0.06	N.S.
ln (C_{max})	2.9955	18.7	3.0070	16.1	0.05	N.S.
T_{max} (hours) §	0.50	66.4	0.50	47.7	261.5	<0.05
AUC_T (ng·h/mL)	15.953	51.1	15.590	56.2	0.64	N.S.
ln (AUC_T)	2.6633	17.3	2.6397	16.9	0.90	N.S.
AUC_∞ (ng·h/mL)	18.785	55.5	18.221	65.4	0.83	N.S.
ln (AUC_∞)	2.7994	19.2	2.7513	19.8	2.60	N.S.
$AUC_{T/\infty}$ (%)	97.81	1.3	98.08	1.4	0.08	N.S.
K_{el} ($hours^{-1}$)	0.5350	65.1	0.6117	75.1	0.43	N.S.
$T_{½el}$ (hours)	1.83	52.5	1.68	57.1	0.10	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a non-parametric approach.

Comparison of Results with Standards for Bioequivalence - Ramipril

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	25.4	19.941	20.206	98.69	89.44	108.90
AUC_T	11.2	14.328	13.979	102.49	98.09	107.10

* units are ng/mL for C_{max} and ng·h/mL for and for AUC_T

Pharmacokinetic parameters of amlodipine

PARAMETER	TEST		REFERENCE		F (treatment)	p *
	MEAN	C.V. (%)	MEAN	C.V. (%)		
C_{max} (pg/mL)	5821.2	22.6	5870.5	22.4	0.15	N.S.
ln (C_{max})	8.6426	2.8	8.6536	2.6	0.25	N.S.
T_{max} (hours) §	7.00	27.5	7.00	26.2	312.5	N.S.
AUC_T (pg·h/mL)	221896.1	27.0	220692.7	26.3	0.15	N.S.
ln (AUC_T)	12.2701	2.4	12.2677	2.3	0.04	N.S.
AUC_∞ (pg·h/mL)	331848.5	37.9	325942.7	33.7	0.42	N.S.
ln (AUC_∞)	12.6410	3.1	12.6360	2.8	0.05	N.S.
$AUC_{T/\infty}$ (%)	69.51	11.9	69.66	11.5	0.03	N.S.
K_{el} ($hours^{-1}$)	0.0175	22.9	0.0175	22.9	0.01	N.S.
$T_{½el}$ (hours)	41.83	24.5	41.75	24.7	0.01	N.S.

* N.S.= Not Significant. Significant whenever p-value < 0.05.
§ For T_{max}, the median is presented and the statistical analysis is based on a non-parametric approach.

Comparison of Results with Standards for Bioequivalence - Amlodipine

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	9.3	5663.3	5725.5	98.91	95.35	102.61
AUC_T	6.6	213088.0	212449.2	100.30	97.72	102.95

* units are pg/mL for C_{max} and pg·h/mL for AUC_T

Safety Results: thirteen (13) of the forty (40) subjects experienced a total of twenty-one (21) adverse events during the study. Fifteen (15) adverse events (11 different types) were reported after the single dose administration of the Test product and eight (8) adverse events (7 different types) were reported after the single dose administration of the Reference products. Two (2) adverse events associated with post-study laboratory test results (haemoglobin decreased and lymphocyte count decreased) were imputed to both formulations. None of these events possibly related to the investigational products were unexpected. No serious adverse events (SAEs) were recorded in this study.

Conclusion: the results of the bioequivalence study comply with the requirements of the CPMP/EWP/QWP/1401/98 Rev. 1. *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* except that according to the Guideline measurement of the pharmacokinetic parameters of the active metabolite is not

necessary. It was not assessed. Therefore claiming essential similarity for the Marketing authorisation holder's product ramipril 10mg / amlodipine 10mg combination and the originator monocomponent tablets given concomitantly are established.

IV.2.3 Biowaiver

The Applicant requested a biowaiver to the 2.5mg/2.5mg, 5mg/5mg, 10mg/5mg and 5mg/10mg amlodipine/ramipril combinations.

The following conditions have been fulfilled:

- All strengths are manufactured by the same manufacturer and process.
- Both amlodipine and ramipril have linear pharmacokinetics in the applied dose range.
- The qualitative composition of the different strengths is the same.
- The ratio between amounts of each active substance and excipients is the same regarding the 2.5/2.5mg, 5/5mg and the 10/10mg strengths. The ratio of the excipients is similar regarding the 5/10 mg and 10/5 mg strengths when comparing to the 10/10 mg and the concentration of each active substance is less than 5% (the other active substance is to be considered as filler in this regard)
- Dissolution profiles for the 2.5/2.5, 5/5, 10/5 and 5/10 strengths and the highest strength (10/10) of the batch used in the BE study were demonstrated to be similar under identical conditions for both amlodipine and ramipril.

As all the stipulated biowaiver criteria have been fulfilled (see the Guideline CPMP/EWP/QWP/1401/98 Rev. 1), additional *in vivo* studies for the bioequivalence assessment of 2.5mg/2.5mg, 5mg/5mg, 10mg/5mg and 5mg/10mg product series may be waived.

IV.3 Pharmacodynamics

Amlodipine

The pharmacodynamics of amlodipine is well established.

Amlodipine belongs to the dihydropiridine Ca^{++}-channel blockers. It inhibits the calcium influx through the L-type (slow) Ca^{++}-channels. As calcium is an essential mediator of smooth muscle contraction amlodipine relaxes smooth muscles especially the blood vessels. By this vasodilating effect amlodipine reduces the peripheral vascular resistance this way it reduces blood pressure and the afterload for the heart as well. By decreasing afterload it reduces the oxygen demand of the heart. Furthermore, dilation of coronary arteries improves the cardiac oxygen supply. These two latter mechanisms may result in preventing angina attacks in chronic stable angina as well as in Prinzmetal's angina (coronary spasm). Despite its marked vasodilatory effect it does not cause strong reflex tachycardia. The negative inotropic effect of amlodipine on the heart is weak provided by its good vasoselectivity over the cardiac L-type channels.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of its administration.

In patients with angina, by once daily administration it increases total exercise time, time to angina onset, and time to significant ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.
It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma

Ramipril

The pharmacodynamics of ramipril is well-established.

Ramipril belongs to the group of the inhibitors of the angiotensin converting enzyme (ACE, also known as kininase II). Ramipril is a prodrug the ACE inhibitory effect is provided by its active metabolite, ramiprilat. ACE catalyses the conversion of angiotensin I to the potent vasoconstrictor angiotensin II as well as the degradation of the vasodilator bradykinin. Reduced angiotensin II formation and the inhibition of the metabolism of bradykinin lead to vasodilation.

As angiotensin II is also responsible for the secretion of aldosterone the hormone responsible for sodium and water retention by stimulating sodium and water reabsorption in the collecting tubules in the kidney as well as for excreting potassium ACE inhibitors may cause hyperkalemia while marked diuretic effect cannot be observed. The higher level of bradykinin may be responsible for the most common adverse effect dry cough.

Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.
In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Amlodipine/ramipril combination

The justification for a combination of amlodipine and ramipril is based on their synergistic effects in their antihypertensive mechanisms. The combination tablet may provide a better compliance of the patients than the separate pills. The Applicant provided details of the co-prescription of amlodipine and ramipril from the Concerned Member States and Hungary.

IV.4 Clinical efficacy

The efficacy of amlodipine and ramipril has already been demonstrated during the clinical development of both substances.

As for the amlodipine/ramipril combinations, the Applicant has not performed clinical trials. As the combination is solely for substitution therapy according to the relevant CHMP/EWP/191583/2005 *Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention* pharmacodynamic studies are not required.

IV.5 Clinical safety

The clinical safety of the individual components has been well established. The bioequivalence study did not raise any safety concerns.

IV.6 Discussion on the clinical aspects

The application concerns new fixed combinations of amlodipine and ramipril. The suggested indication is substitution therapy for patients suffering from hypertension already adequately controlled with monocomponent containing tablets given concurrently.

To support the application the Applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time. For further justification the Applicant has provided co-prescription data from the Concerned Member States and Hungary. The discussion of the lack of pharmacokinetic interactions between ramipril and amlodipine is sufficient in the Clinical Overview and therefore acceptable.

There is no objection against granting the marketing authorization from a clinical point of view. The application is approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application concerns fixed combinations of amlodipine and ramipril. These active substances are widely and safely used, the application of the present product does not pose any new risk.

The submitted documentation is formally adequate and scientifically sound. The benefit/risk assessment is positive.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for amlodipine/ramipril 2.5/2.5 mg, 5/5 mg, 5/10 mg, 10/5 mg and 10/10 mg hard capsules**,** in the treatment of hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets is approvable.

V.1. Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The RMS considers that the Pharmacovigilance system of EGIS Pharmaceuticals Ltd. (May 2010) as described by the Applicant 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 notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V.1.3 Risk Management Plan

The RMS considers that all of the important identified and potential risks discussed during the assessment period above are adequately reflected in the SmPC.

The RMS also welcomes the aggregate analysis that will be made in the Periodic Safety Update Reports on all identified and important potential risks (including off-label use and products used in patient co-morbidity).

Besides of this aggregate analysis the Applicant expressed its intention to collect follow up information targeted to of off-label use in children and on the use during breast feeding and a targeted follow up using questionnaire in the case of the use in pregnancy.

V.1.4 Periodic Safety Update Report (PSUR)

The Applicant has taken a commitment to prepare and submit Periodic Safety Update Reports according to the requirements of the Directive 2001/83/EC.

V.1.5 Legal status

Prescription-only medicine.

V.2 Summary of Product Characteristics (SmPC)

The SmPC is acceptable.

V.3 Package Leaflet and 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 Hungarian.

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.

VI. UPDATE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Increase of the product shelf-life to 36 months	HU/H/0303/001-005/IB/001	Yes	20. 02. 2012	21. 03. 2012	Approval	N
New product manufacturing site added	HU/H/0303/001-005/IB/002	No	20. 02. 2012	21. 03. 2012	Approval	N
Product name change in Lithuania	HU/H/0303/001-005/IB/004	Yes	02. 05. 2012	01. 06. 2012	Approval	N
New alternative ramipril manufacturer	HU/H/0303/001-005/IA/005	No	16. 07. 2012	05. 08. 2012	Approval	N
Following the Article 30 Referral for products including amlodipine as active substance, updated SmPC and PIL are submitted. Additionally, the applicant proposes to update the SmPC in accordance with CMDh QRD template dated October 2011.	HU/H/0303/001-005/IB/006	Yes	16. 07. 2012	15. 08. 2012	Approval	N