



Public Assessment Report

Scientific discussion

Name of the Product

Concor AMLO 5/5, 10/5, 5/10, 10/10 mg tablets

amlodipine/bisoprolol

Procedure number:

HU/H/0237/001-004/DC

Marketing authorisation holder: Merck Ltd Budapest

Date: 23 July 2012

This module reflects the scientific discussion for the approval of Concor AMLO tablets. The procedure was finalised at 17 October 2010. For information on changes after this date please refer to the module 'Update'.

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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 Regulations 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 amlodipin/bisoprolol 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg combinations.

The Applicant and the original Marketing authorisation holder was Egis Pharmaceutical Works than the marketing authorisation had been transferred to Merck Ltd. The product brand name in the application was Opimol that has been changed to Concor AMLO (see VI. Update).

The application was submitted according to Article 10(b) of Directive 2001/83/EC (fixed combination application)

The combination product of the calcium channel blocker amlodipine and the highly β 1-selective adrenoreceptor-blocking agent bisoprolol is indicated as substitution therapy for treatment of hypertension, in patients already controlled with amlodipine and bisoprolol given concurrently at the same dose level.

The basis of the application was to submit combination products with same bioavailabilities of the active principles as those of the reference single dose products. The marketing authorisation holders of the original single dose formulations were Pfizer (Norvasc[®] tablets, amlodipine besilate) and Merck KGaA Darmstadt (Concor[®] film-coated tablets, bisoprolol fumarate). The reference products were authorized in 1992 and 1994 in Hungary, respectively.

The application therefore contained an adequate bioequivalence study but no new clinical or preclinical data, other than supporting literature where necessary.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Opimol (now Concor AMLO) 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The fixed combination of amlodipine and bisoprolol is indicated as substitution therapy for patients, whose blood pressure can be adequately controlled by simultaneously given amlodipine and bisoprolol.

The tablets are packaged in cold (OPA/Al/PVC//Al) blisters and box.

The object of development was to develop combination products with the same bioavailabilities of the active principles as in the reference single dose products. The latter were Norvasc[®] tablets containing amlodipine besilate (Pfizer) and Concor[®] film-coated tablets containing bisoprolol fumarate (Merck KGaA, Darmstadt), authorized earlier in Hungary. Taking into account that the combinations were planned to be marketed in 5 mg/5 mg, 5 mg/10mg, 10 mg/5 mg and 10 mg/10 mg strengths in dose proportional formulations, the actual reference products chosen were Norvasc 10 mg and Emconcor (Merck) 10 mg from the Danish market.

II.2 Drug Substances

Bisoprolol Fumarate

The applicant indicated to follow an Active substance Site Master File (ASMF) procedure for bisoprolol fumarate. Letter of access for ASMF has been submitted. Bisoprolol fumarate is described in the European Pharmacopoeia (Ph. Eur.).

INN name: bisoprolol fumarate.

Chemical names:

- bisoprolol hemifumarate
- (R,S)1-[4-[[2-(1-Methylethoxy)ethoxy)methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hemifumarate.
- (±)-1-(4-((2-(1-Methyl-ethoxy)ethoxy)methyl)phenoxy)-3-((1methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt.
- (±)-1-[[α-(2-Isopropoxyethoxy)-*p*-tolyl]oxy]-3-(Isopropylamino)-2-propanol fumarate (2:1) salt.

The active substance is a white or almost white, slightly hygroscopic powder, very soluble in water and methanol, freely soluble in chloroform, glacial acetic acid and alcohol, slightly soluble in acetone and ethyl acetate. It shows polymorphism.

The molecule has a chiral carbon therefore two possible enantiomers exist. The presently used drug substance is a racemic mixture. This is routinely controlled according to USP optical rotation method.

The specified manufacturing process has been adequately described; critical steps and corresponding in-process controls have been defined to ensure quality of the final substance.

In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure for Bisoprolol Fumarate has been confirmed by elementary analysis, several spectrometric spectroscopic characterization techniques. It has been demonstrated by X-ray powder diffraction analysis that the described manufacturing process consistently and exclusively yields the same polymorph form.

Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in respect of their origin and potential carry-over into the final drug substance.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has been set for identification (HPLC), specific rotation, heavy metals, fumaric acid content, melting point, clarity and colour of solution, pH of solution, absorbance, residual solvents and particle size distribution. Additional tests specific rotation, heavy metals and fumaric acid content are determined according to USP methods.

The substance complies with the requirements of the EMEA guideline on genotoxic impurities.

The Ph. Eur. specification includes the following tests for bisoprolol fumarate: appearance, identification (IR), water content, sulphated ash assay (potentiometry) and related substances (HPLC). 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.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterized.

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

During the stability studies no significant changes in any parameters were observed. The proposed retest period of 5 years is supported by the submitted stability data when stored closed and protected from light in the original containers.

GMP compliance of the Active Pharmaceutical Ingredient (API) manufacturer has been demonstrated.

Amlodipine besilate

The Applicant has submitted two Ph. Eur. Certificates of Suitability (CEP) for the drug substance amlodipine besilate. The CEP indicates that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that it is supplemented with a test for related

substances to detect any other detectable impurity by HPLC (NMT 0.10 %) and a test for the residual solvent isopropanol by GC (NMT 1000 ppm) or Ethylacetat (NMT 500 ppm).

INN name: amlodipine besilate.

Chemical name: 3-ethyl 5-methyl (4RS)-2-[(2-amino-ethoxy)-methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate

The active substance is a white or almost white powder and is freely soluble in methanol, in dimethylformamide and in dimethylsulphoxide, sparingly soluble in ethanol and slightly soluble in water, 2-propanol, 0.1 M hydrochloric acid and in acetone.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents and particle size.

The Ph. Eur. specification includes the following tests for amlodipine besilate: appearance, identification (IR), solubility, optical rotation, related substances (HPLC), water content, sulphated ash, assay (HPLC). Residual solvents (GC) and particle size 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.

Residual solvent method not described in the Pharmacopoeia is adequately drawn up and sufficiently validated.

The methods for particle size determination has been adequately described and validated methods.

Reference materials used for the control of the substance are adequately characterized and evaluated by European Directorate on Quality of Medicines (EDQM).

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

The proposed retest periods of 5 years and 36 months are supported by the submitted stability data when stored closed and protected from light up to 25° C in the original containers .

GMP compliance of the API manufacturer has been demonstrated by the Applicant.

II.3 Medicinal Product

The drug products are immediate release tablets containing fixed combination of amlodipine besilate and bisoprolol fumarate.

The formulation study was based on the composition of the two reference products; compatibility study by mixing the drug substances with the excipients in ternary mixtures and dissolution profile of the reference single dose products. The formulation development considering the optimization of percentage rate of the ingredients was discussed detailed.

Common formulation and manufacturing process was developed on amlodipine besilate and bisoprolol fumarate tablets. The four compositions of amlodipine besilate/bisoprolol fumarate tablets are dose-proportional.

A satisfactory package of data on development pharmaceuticals 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.

The excipients used in the finished product are microcrystalline cellulose, sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. regarding the risk of TSE has been demonstrated by the applicant. The functionality related characteristics of excipients have been discussed.

As regards dissolution and impurity profile the product is shown to be similar to the reference products.

Appearance in the original application:

- The amlodipine besilate/bisoprolol fumarate 5 mg/5 mg tablets appear as white or almost white, odourless, oblong, slightly convex tablets with score line on one side and with stylized E and 571 sign on the other side.
- The amlodipine besilate/bisoprolol fumarate 5 mg/10 mg tablets appear as white or almost white, odourless, oval shaped, slightly convex tablets with score line on one side and with stylized E and 572 sign on the other side.
- The amlodipine besilate/bisoprolol fumarate 10 mg/ 5 mg tablets appear as white or almost white, odourless, round, flat, bevel edged tablets with score line on one side and with stylized E and 573 sign on the other side.
- The amlodipine besilate/bisoprolol fumarate 10 mg/10 mg tablets appear as white or almost white, odourless, round, slightly convex tablets with score line on one side and with stylized E and 574 sign on the other side.

Actual appearance (see the variation in VI. Updates):

- The Concor AMLO 5 mg/5 mg tablets appear as white or almost white, odourless, oblong, slightly convex tablets with score line on one side and with stylized MS sign on the other side.
- The Concor AMLO 5 mg/10 mg tablets appear as white or almost white, odourless, round, flat, bevel edged tablets with score line on one side and with stylized MS sign on the other side.
- The Concor AMLO 10 mg/ 5 mg tablets appear as white or almost white, odourless, oval, slightly convex with score line on one side and with stylized MS sign on the other side.
- The Concor AMLO 10 mg/10 mg tablets appear as white or almost white, odourless, round, slightly convex tablets with score line on one side and with stylized MS sign on the other side.

The tablets are packed in laminated OPA/Al/PVC//Al blisters and carton box.

Description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were

also presented. Validation data on pilot scale batches are 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 prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. Certificates of analysis for the batches involved in the bioequivalence study are presented.

Standard pharmacopoeial methods are used in respect of uniformity of dosage units, resistance to crushing, friability, average mass, uniformity of mass, disintegration time, water content, hardness and microbiological purity. Validated analytical methods have been presented for assay, test for impurities and degradation products, as well as dissolution test (HPLC method). According to dissolution characteristics of the products, batch and stability data the proposed specification limit is justified and therefore acceptable.

Batch data have been provided and complied with the specification set by the manufacturer. Certificates of analysis were also provided for the working standard used.

IR spectra and certificates of analysis justifying the conformity to the Ph. Eur. monograph 3.1.11. and compliance with European Commission Regulations (78/142/EEC and 1935/2004/EC) are provided.

Finished product stability studies have been conducted in accordance with the current guidelines.

Based on the presented results, a shelf-life of 30 months for amlodipine/bisoprolol 5/5mg, 10/5 mg and 10/10 mg tablets when “stored below 30° C, in the original package in order to protect from light” is approved. Based on the presented results, a shelf-life of 24 months for amlodipine/bisoprolol 5/10 mg tablets when “stored below 30° C, in the original package in order to protect from light” is approved.

The SPC, PIL and label are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Assessing the chemical – pharmaceutical part of the submitted dossier the following conclusion has been reached.

The products have been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative contents of the active substances 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 products.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both amlodipine and bisoprolol 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.

According to the *Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products* (CHMP/EMEA/CHMP/SWP/258498/2005) amlodipin/bisoprolol combination can be considered as stated in “Scenario 1”:

“A fixed combination of compounds already approved as free combination therapy.”

In this case the Guideline CPMP/EWP/240/95 recommends the following:

“When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required.”

Both amlodipine and bisoprolol are widely used antihypertensive and antianginal medicines, their human experience are vast. As the Applicant has also presented data about significant co-administration of the two compounds the experience on the combination can also be considered sufficient.

III.2 Pharmacology

Bisoprolol

Bisoprolol is a beta-1 selective beta-blocker without intrinsic sympathomimetic or membrane-stabilizing activity. Animal and in vitro human data indicate a high selectivity of bisoprolol for the cardiac beta-1 adrenoceptor. It only shows low affinity to the β_2 -receptor of the smooth muscles of bronchi and vessels as well as to the β_2 -receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β_2 -mediated metabolic effects. The proposed mechanisms for the antianginal effect of beta-blockers (cardioprotective effects) include a decreased demand for myocardial energy and oxygen consumption, antagonism of catecholamines that are released following myocardial infarction, antiarrhythmic effects and reduction in platelet aggregation and blood viscosity. The mechanism of the antihypertensive effect of the beta-blockers is controversial. Some of the theories include a decrease in cardiac output, the suppression of renin release, the interference with central sympathetic outflow, or possibly the prevention of neurotransmitter release at presynaptic receptors. Although the mechanism of action is not clear for beta-blocker activity in hypertension, the drugs are effective for treatment of this condition and may be superior to other agents such as thiazides as initial therapy in select patient populations. Bisoprolol has a long duration of action.

Amlodipine

Amlodipine belongs to the dihydropyridine 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. Amlodipine also inhibits calcium influx through cardiac muscle but this effect is less pronounced than the relaxation of the peripheral arterioles. It mainly produces peripheral vasodilation and subsequent reduction in systemic vascular resistance, which leads to reduction in blood pressure.

In vivo pharmacodynamic studies on several animal models of hypertension, after single or repeated administration, demonstrated effective antihypertensive action following oral or intravenous administration. In addition to its antihypertensive action, amlodipine was demonstrated to have antiatherosclerotic effects, beneficial effects on renal function as well as cardioprotective effects.

Amlodipine/bisoprolol combination

The Applicant has not conducted any combination study in animals. Since there are no overlapping target organs, toxic effects or unwanted pharmacodynamic effects in the toxicology and safety pharmacology profiles of the individual compounds, moreover the preclinical safety studies indicate a wide therapeutic range compared to the recommended human dose, lack of specific preclinical safety studies on the combination of the two compounds could be considered justified.

III.3 Pharmacokinetics

Bisoprolol

The pharmacokinetic properties and the metabolism of ^{14}C bisoprolol were studied in Wistar rats, beagle dogs, and Cynomolgus monkeys. Unchanged bisoprolol was determined by high performance liquid chromatography (HPLC) or radiometrically by thin-layer chromatography.

Bisoprolol is well absorbed in rats, dogs and monkeys; independent of the route of administration (i.v. or p.o.), 70-90% of the ^{14}C -dose was recovered in urine. Faecal excretion was approximately 20% in rats and less than 10% in dogs and monkeys. Rats excreted approximately 10% of the dose in bile after i.v. as well as after oral administration. The plasma half-life of the unchanged drug was approximately 1 h in rats, 3 h in monkeys, and 5 h in dogs.

The bioavailability was 40-50% in monkeys, approximately 80% in dogs, and 10% in rats. The amount of bisoprolol excreted unchanged in the urine is 50-60% of the dose in humans, 30-40% in dogs, and approximately 10% in rats and monkeys.

Bisoprolol is absorbed almost completely from the gastrointestinal tract in human. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The drug is cleared equally by the liver and kidney. The plasma

elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. About 95% of the drug substance is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

Amlodipine

Amlodipine is almost completely absorbed after oral administration, peak plasma concentrations are achieved slowly (2-7 hours post-dose). The drug substance is widely distributed and extensively bound to plasma proteins (94 % in rats, 97 % in dogs and 97% in man).

Metabolism studies indicated extensive biotransformation of the drug in laboratory animal species and humans. The major metabolic pathways are initial oxidation of the dihydropyridine ring to the pyridine analogue, side chain oxidation and hydrolysis of one or both side chain ester groups.

Only small amounts of unchanged drug (up to 4 % dose) were determined in the urine of rats, dogs and man. Amlodipine metabolites are excreted via kidney and gastrointestinal tract. No difference between besilate and maleate salts of amlodipine was found.

III.4 Toxicology

Since both amlodipine and bisoprolol are widely used medicines and the toxicology profiles are well-known no specific studies were required. However, the Applicant has identified a new amlodipine degradation product as an impurity (named AML-2) that is not present in the monocomponent amlodipine preparations. The amount of this degradation product increases in the tablet over the time. Therefore the Applicant has performed several toxicology studies in order to identify the impurity according to the CPMP/ICH/2738/99 Guideline Q3B(R2). The performed toxicology and mutagenicity tests were adequate and sufficient to qualify impurity AML-2. The Applicant has clearly demonstrated that AML-2 neither increases the toxicity nor has genotoxic and mutagenic effects. Furthermore, as amlodipine-bisoprolol combinations without the impurity were also tested the tests have added information about the safety of this fixed dose combination and revealed no further toxicological concerns.

III.5 Ecotoxicity/environmental risk assessment

Since the amlodipine/bisoprolol tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. Therefore, no environmental risk assessment deemed necessary.

III.6 Discussion on the non-clinical aspects

The Application has been based on Article 10b of Directive 2001/83/EC, fixed dose combination. Pharmacodynamics, pharmacokinetics and toxicology of both amlodipine and bisoprolol 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 a combination of amlodipine and bisoprolol 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 adequately summarized the clinical experience with amlodipine and bisoprolol and presented the synergistic effects between the calcium-channel blockers and beta-blockers. The justification of the missing specific pharmacokinetic interaction studies between amlodipine and bisoprolol 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

Bisoprolol

Bisoprolol is absorbed almost completely (> 90%) from the gastrointestinal tract. Due to the very small first pass effect (approx. 10%), its absolute bioavailability is approximately 90% after oral administration.

Its distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites, which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with mild to moderate liver function impairment or renal insufficiency. Total clearance is approximately 15 l/h. The elimination half-life in plasma is 10-12 hours. The kinetics of bisoprolol is linear between 5 and 20 mg and independent of age.

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.

Amlodipine/bisoprolol combination

According to the literature data the two compounds do not interact in the pharmacokinetic processes.

Bioequivalence study

In order to demonstrate pharmacokinetics of the fixed dose combination and to establish bioequivalence (BE) with the free combination of the monocomponent reference preparations, one BE study (MC-0115) was conducted by Algorithme Pharma Inc. (1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1) with EGIS as sponsor between August and September 2008. The study utilised the highest dose forms (10 mg amlodipine and 10mg bisoprolol). The conduct of the study is satisfactory and the results comply with the acceptance criteria for bioequivalence as detailed in the CHMP guideline.

The originator products are Norvasc[®] tablets from Pfizer and Concor[®] tablets from Merck (both authorised for marketing in the RMS in 1990).

Design

It was a comparative, randomised, single-dose, 2-way crossover bioavailability study of amlodipine besilate/bisoprolol fumarate 10 mg/10 mg combination tablet and co-administration of amlodipine besilate 10 mg and bisoprolol hemifumarate 10 mg as separate tablets in healthy adult male volunteers under fasting conditions.

For amlodipine, blood samples (20 samples) were collected prior to and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 48, 72, 96, 120, 144 and 168 hours after drug administration.

For bisoprolol, blood samples (17 samples) were collected prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after drug administration. The wash-out period between the treatment periods was 21 days.

Bioanalytics

Amlodipine: plasma concentrations of amlodipine were determined in plasma samples of volunteers using a High Performance Liquid Chromatography / Tandem Mass Spectrometry Method (HPLC-MS/MS). The validated analytical range was 50pg/mL – 15000pg/mL for amlodipine. The internal standard was amlodipine-d₄ maleic acid.

Bisoprolol: plasma concentrations of bisoprolol were determined in plasma samples of volunteers using a High Performance Liquid Chromatography / Tandem Mass Spectrometry Method (HPLC-MS/MS). Internal standard was bisoprolol-d₅ hemifumarate. The validated analytical ranges were 0.5ng/mL – 75ng/mL for bisoprolol.

Statistics

Pharmacokinetic analysis was based on plasma concentration-time data. The following pharmacokinetic parameters were determined by applying a non-compartmental method: C_{max} , T_{max} , AUC_T , AUC_{∞} , $AUC_{T/\infty}$, K_{el} and $T_{1/2el}$ for each treatment. The primary pharmacokinetic parameters for this study were C_{max} and AUC_T and AUC_{∞} . Other parameters such as $AUC_{T/\infty}$, K_{el} , T_{max} and $T_{1/2el}$ were provided for information purposes only.

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.

Pharmacokinetic and statistical analyses were generated using Kinetic, version 8.00, an application developed at Algorithm Pharma and SAS[®] version 9.1 (Mixed procedure).

The statistical methodology is adequate. The predefined confidence interval for the test/reference ratios of the means of $AUC_{0-\infty}$, AUC_T and C_{max} parameters are between 80% and 125%.

Results

The following Tables (see on the next pages) show the results for amlodipine and bisoprolol.

The safety profiles of both the test product and the combination of the monocomponent originators were comparable. There was one unexpected adverse effect (anaemia) 21 days after administration of the test product which was assessed to be possibly related to the study drug. The Applicant has adequately answered a possible safety concern as it was due to the relatively excessive blood sampling.

There were no serious adverse events and no use of concomitant medication was required. Overall, a good tolerability was assessed for both the fixed and free combination.

Biowaiver

For the other amlodipine/bisoprolol strengths which are also applied for in this marketing authorization application (amlodipine/bisoprolol 5mg/5mg, amlodipine/bisoprolol 10mg/5mg, and amlodipine/bisoprolol 5mg/10mg fixed combination tablets) additional dissolution studies were performed to confirm the adequacy of waiver of additional bioequivalence studies. Accordingly, dissolution was investigated at different pH values (0.01M hydrochloric acid, 0.005M hydrochloric acid, acetate buffer solution pH 4.6 and phosphate buffer solution pH 6.8). Similarity of dissolution was demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength used for bioequivalence testing. As

pharmacokinetics of amlodipine and bisoprolol are linear and all the stipulated biowaiver criteria are fulfilled (CPMP/EWP/QWP/1401/98 Rev. 1), additional in vivo studies for the bioequivalence assessment of 5mg/5mg, 10mg/5mg and 5mg/10mg product series may be waived.

Table 1. Pharmacokinetic parameters of **amlodipine**:

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	5925.9	25.9	5521.1	28.3
$\ln(C_{max})$	8.6539	3.1	8.5806	3.1
T_{max} (hours) *	8.00	24.4	8.00	30.8
AUC_T (pg·h/mL)	315501.5	29.6	286138.9	34.9
$\ln(AUC_T)$	12.6217	2.3	12.5131	2.5
AUC_{∞} (pg·h/mL)	344931.2	33.4	314068.0	39.3
$\ln(AUC_{\infty})$	12.7017	2.5	12.5952	2.7
$AUC_{T/\infty}$ (%)	92.40	4.4	92.22	4.8
K_{el} (hours ⁻¹)	0.0161	16.7	0.0164	21.4
$T_{1/2el}$ (hours)	44.35	20.2	44.54	24.5

* median is presented

Comparison of Results with Standards for Bioequivalence - Amlodipine

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	8.9	5750.8	5344.0	107.61	103.24	112.17
AUC_T	10.4	303531.8	272909.2	111.22	105.98	116.72
AUC_{∞}	10.6	328865.0	296454.4	110.93	105.63	116.51

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

Table 2. Pharmacokinetic parameters of **bisoprolol**:

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C _{max} (ng/mL)	43.442	19.0	42.818	17.7
ln (C _{max})	3.7547	4.9	3.7430	4.5
T _{max} (hours) *	2.50	36.4	2.00	43.5
AUC _T (ng·h/mL)	718.962	19.2	703.572	21.1
ln (AUC _T)	6.5619	2.7	6.5369	3.0
AUC _∞ (ng·h/mL)	743.698	18.6	721.376	20.7
ln (AUC _∞)	6.5966	2.6	6.5627	2.9
AUC _{T/∞} (%)	96.61	1.6	97.46	1.1
K _{el} (hours ⁻¹)	0.0650	11.7	0.0662	13.4
T _{½el} (hours)	10.80	11.7	10.65	13.9

* median is presented

Comparison of Results with Standards for Bioequivalence - Bisoprolol

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C _{max}	6.6	42.732	42.229	101.19	98.13	104.35
AUC _T	9.3	708.229	689.576	102.70	98.35	107.25
AUC _∞	9.2	733.111	707.639	103.60	99.27	108.12

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

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. Therefore claiming essential similarity for the Applicant's product amlodipine 10mg/bisoprolol 10mg combination and the originator monocomponent tablets given concomitantly are established.

IV.3 Pharmacodynamics

Bisoprolol

Bisoprolol is a potent, highly β_1 -selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilising activity.

It only shows low affinity to the β_2 -receptor of the smooth muscles of bronchi and vessels as well as to the β_2 -receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β_2 -mediated metabolic effects. Its β_1 -selectivity extends beyond the therapeutic dose range. Bisoprolol has no explicit negative inotropic effect.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Antihypertensive effect of beta-blockers is among others due to decrease of renin activity.

Bisoprolol has its maximal effect 3-4 hours after oral administration.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

It usually exerts its maximal antihypertensive effect after 2 weeks.

Amlodipine

The pharmacodynamics of amlodipine is well established.

Amlodipine belongs to the dihydropyridine 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-a-day 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. 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

Amlodipine/bisoprolol combination

The justification for a combination of amlodipine and bisoprolol is based on their synergistic effects in their antihypertensive and antianginal mechanisms. The combination tablet may provide a better compliance of the patients than the separate pills. The Applicant provided data about co-prescription of amlodipine and bisoprolol in all CMS. Although exact data come from only Czech Republic, Hungary, Poland and Slovakia the estimation and extrapolation to the other CMSs may be acceptable. Exact data about the combined doses come only from Hungary. These data show that the most commonly co-prescribed doses are 5mg amlodipine + 5mg bisoprolol and 10 mg amlodipine + 5mg bisoprolol. The numbers compared to the other two dose combinations are approximately 10-fold higher (if the numbers of the two-two dose-combinations are added). That might raise the question whether the marketing authorization of 5mg/10mg and 10mg/10mg doses is fully justified. Indeed, since this type of data is lacking from the concerned member states it is difficult to judge the necessity of the latter doses. However, assuming similar prescribing habits of physicians in all the concerned member states, the number can be significant. Therefore the RMS does not oppose the marketing authorization of the full line.

No new specific clinical pharmacological study is needed for this dossier, in line with the requirements stated in the document 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* provided that the Applicant justifies the benefit of the combination with thorough review of the literature.

There are limited data about the co-administration of amlodipine and bisoprolol in the literature. The Applicant has amended the original Clinical Overview in order to further support this co-administration. The amendment is sufficient to support the hypertension indication. However, there are no supporting data on stable angina pectoris. Due to the lack of supporting data of the combination in stable angina pectoris the Applicant has withdrawn this originally requested indication. Now the present amlodipin/bisoprolol combination tablets are indicated for hypertension as a substitution therapy exclusively.

IV.4 Clinical efficacy

No specific clinical studies have been performed. The substitution therapy in hypertension is fully justified by the amended Clinical Overview both by the literature and the co-prescription data. The Applicant has withdrawn stable angina pectoris from the indications.

IV.5 Clinical safety

The applicant has submitted one bioequivalence study (CODE: MC-0115).

It was a single dose crossover comparative bioequivalence study of amlodipine/bisoprolol 10/10 mg combination tablets (EGIS PLC) vs. amlodipine 10 mg tablets and bisoprolol 10 mg tablets given concomitantly in healthy male volunteers

There was one adverse effect (anaemia) with the test product with the test product. The Applicant has adequately answered this safety concern as it was due to the relatively excessive blood sampling.

IV.6 Discussion on the clinical aspects

The application concerns new fixed combinations of amlodipine and bisoprolol. 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 markets of the concerned member states.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application concerns a combination of amlodipine and bisoprolol. The suggested indication is substitution therapy for patients suffering from hypertension already adequately controlled with monocomponent-containing tablets given concurrently. The active substances are widely and safely used in combinations, 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. There is nothing against granting the marketing authorisation.

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 as described by the applicant (*Version number 2.1 issued on 10 May, 2010*) 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

RMS considers that the Risk Management Plan (14 June 2010) is proper, it deals with all the safety concerns and thus there is no need for any other special pharmacological study or risk minimisation activity.

V.1.4. Periodic Safety Update Report (PSUR)

PSURs will be prepared and submitted according to the frequency written in the Article 104(6) of the 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 testing

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 patient information leaflet 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 HU/H/0237/001-004/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Product analytical methods change	IA/001	No	13.12.2010	12.01.2011	Approval	N
New alternative active substance manufacturer (bisoprolol)	002/IA/002	No	13.12.2010	12.01.2011	Approval	N
New active substance manufacturer (amlodipine) and CEP	IA/003/G	No	13.12.2010	12.01.2011	Approval	N
New CEP and product new shelf-life 3 years	IA/004	Yes	13.12.2010	12.01.2011	Approval	N
New product name Opimol 10/5 mg tablets. Product new shelf-life 30 months	IB/005	Yes	25.02.2011	27.03.2011	Approval	N
Product new shelf-life 3 years	IB/006	Yes	13.12.2010	12.01.2011	Approval	N
ATC code modification	IA/007		14.02.2011	16.03.2011	Accepted	N
New product name: Concor AMLO	IB/008		25.02.2011	29.05.2011	Approval	N
New retest period for active substance	IB/009	No	25.02.2011	27.13.2011	Approval	N
Transfer of Marketing authorisation to Merck Ltd. Budapest		Yes	30.03.2011	08.07.2011	Approval	N
Pharmacovigilance system submitted	IB/010	No	15.04.2011	04.05.2011	Approval	N
New Ph. Eur. CEP	IA/011/G	No	04.04.2011	12.01.2011	Approval	N
Change of appearance, new batch release site	IA/012/G	Yes (appearance) No (new batch release site)	21.09.2011	21.10.2011	Approval	N
Product new shelf-life 3 years	IB/013	Yes	07.03.2011	06.04.2012	Approval	N