National Institute of Pharmacy
Directorate
of the National Institute for Quality- and Organizational Development in Healthcare and Medicines
Budapest, Hungary

Public Assessment Report

Name of the Product:

Opimol
5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg tablets

(bisoprolol fumarate/amlodipine)

Procedure number: HU/H/0341/001-004/DC

Marketing authorisation holder: EGIS Pharmaceuticals Plc.

Date: 10 January 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Opimol (in Bulgaria, Latvia, Lithuania, Poland and Romania Alotendin, in the Czech Republic and in the Slovak Republic Bigital) 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. The holder of the marketing authorisation is EGIS Pharmaceuticals Plc.

The active substances are: bisoprolol fumarate/amlodipine (as besilate).

The other ingredients are: silica, colloidal anhydrous, magnesium stearate, sodium starch glycolate (type A) and microcrystalline cellulose.

The tablets are white or almost white, odourless,
- the 5 mg/5 mg tablets oblong, slightly convex,
- the 5 mg/10 mg tablets round, flat, bevel edged,
- the 10 mg/5 mg tablets oval shaped, slightly convex,
- the 10 mg/10 mg tablets round, slightly convex

with score line on one side and with embossed MS on the other side.

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

Opimol is indicated for the treatment of high blood pressure as substitution therapy in patients who are adequately controlled with the individual products given concurrently at the same doses level as in the combination, but as separate tablets.

What should be known before taking

Should not take Opimol or ask their doctor before taking it those who
- are allergic to amlodipine, bisoprolol (active substances), dihydropyridinederivates or any of the other ingredients of this medicine;
- have serious narrowing of the outflow tract of the left ventricle(e.g. high grade aortic stenosis);
- suffer from acute heart failure, unstable heart failure after acute myocardial infarction or heart failure requiring intravenous drugs to increase strength of myocardial contraction;
- suffer from shock due to abnormal function of heart (in such cases blood pressure is extremly low and circulation is close to collapse);
- suffer from heart disease characterized by very slow heart beat or irregular heart contraction (2^{nd} or 3^{rd} degree atrioventricular block, sinoatrial block, sick sinus syndrome);
- have extremly low blood pressure (first value is permanently less than 100 mmHg);
- have severe bronchial asthma or chronic obstructive pulmonary disease;
- have serious peripheral arterial disease;

- have Raynaud syndrome, which is characterized by numbness, buzz and decoloration of fingers on hands and feet exposed to cold;
- have untreated pheocromocytoma, which is a rare tumour of adrenal glands' marrow;
- have such metabolic conditions where pH of blood becomes acidic.

Warnings and precautions

Opimol can be administered with special care in the following conditions, therefore patients to whom any of the following conditions applies should consult their doctor, for the doctor may feel it necessary to take special measures (e.g. additional treatment), if any of the above conditions exists:

- elderly age;
- heart failure;
- diabetes with highly variable blood sugar levels;
- strict diet;
- concomittant antiallergic (desensitizing) treatment (e.g. in order to prevent allergic rhinitis);
- mild disorder of electronic regulatory system of heart rhythm (first degree AV-block);
- coronary perfusion disorder (Prinzmetal's angina)
- vascular disease of extremities characterized by decreased perfusion;
- psoriasis;
- hyperthyreosis;
- hepatic or renal disease;
- treated pheocromocytoma, which is a rare tumour of adrenal glands' marrow;
- bronchial asthma or other chronic obstructive lung disease.

Moreover, those who are going to have an operation inform the anaesthetist on Opimol taking.

Children and adolescents

This medicine should not be given to children or adolescents (below the age of 18), because its benefits and risks have not been tested in these age groups.

Other medicines and Opimol

Therapeutic and side effects of this medicine may be biased by other medicines being concomitantly taken. Interactions can arise, even if other medicine has been taken within just a short time. The doctor (or a pharmacist) should be informed abouton taken, having recently taken or pssoibly to be taken other medicines.

Coadministration of the following medicines with Opimol is not recommended:

- verapamil- and diltiazem type calcium channel blockers for these drugs are used for the treatment of high blood pressure and chronic stable angina pectoris;
- centrally acting antihypertensives (e.g.: clonidine, methyldopa, moxonodine, rilmenidine), but taking these medicines should not be stopped without consulting the doctor.

The following medicines may only be co-administered with Opimol in certain circumstances with special caution under medical supervision:

- certain heart rhythm regulator preparations (quinidine, disopyramide, lidocaine, phenytoin, flecainide, propaphenon, amiodarone). These drugs are used for the treatment of irregular or abnormal heart rhythm;
- topically applied beta-blocker preparations (e.g. eye-drops used to treat glaucoma);
- parasympathomimetics, these drugs are used to potentiate function of smooth muscle in diseases of stomach, intestinum, bladder and in glaucoma;
- insulin and oral antidiabetics;
- hypnotics, anaesthetic agents;
- heart glycosides (digitalis), drugs used to treat heart failure;
- non-steroidal antiinflammatory drugs (NSAIDs, these drugs may be given for the treatment of joint inflammation, pain or arthritis);
- sympathomimetics (e.g. isoprenalin, dobutamine, norepinephrine, epinephrin). These drugs are used for the treatment of serious circulation disorders in case of emergence;
- any drugs lowering blood pressure, due to their therapeutic or adverse effect (e.g. antihypertensive medicines, tricyclic antidepressants, barbiturates, phenothiazines).

In addition, possible effects of a coadministration of the following medicines with Opimol need to be considered by the prescribing doctor:

- mefloquine, used to prevent or treat malaria;
- monoamino-oxidase (MAO) inhibitors (except MAO-B inhibitors) used to treat depression;
- drugs affecting metabolism of amlodipine or bisoprolol (e.g. rifampicine, ketoconazole, itraconazole, erythromycin, ritonavir, and St. John's wort);
- ergotamine derivates (drugs used to treat bleedings of gynaecological origin).

Opimol tablets and alcohol

The alcohol may potentiate blood pressure lowering effect of the preparation.

Pregnancy and breast-feeding

As no appropriate amount of clinical experience is available concerning pregnant women, it can be administered only after careful individual consideration of risk/benefit ratio by a doctor, therefore it is necessary to inform the prescribing doctor if the patient may be pregnant or plans to have a baby. In case of its administration in pregnancy, careful monitoring of the foetus' and the new-born's condition may be necessary.

Opimol is not recommended during breast-feeding.

Driving and using machines

Opimol may impair driving or using machines by causing dizziness, headache, fatigue or nausea – especially when the treatment is startwd or changed, and when alcohol is consumed – therefore the doctor decides individually at what kind of dosage the patient can drive or use machines.

How to take Opimol tablets

The recommended dose is one tablet of the strength prescribed. Usually there is no need of dose adjustment in mild to moderate liver or kidney disease, but in serious liver or kidney disease the doses may be modified.

There is no need of dose adjustment in elderly patients, however, caution is advised when the dose is increased.

Opimol should be taken in the morning, with or without food, with a little fluid without chewing it. The score line is only there to help to break the tablet if there are difficulties in swallowing it whole.

What to do if more Opimol tablets were taken than prescribed

n this case the doctor should be consulted immediately.

What to do if taking Opimol tablets was forgotten

The patient should try to make up the missed dose as soon as possible. If it is already time to take the next dose, no double dose should be taken to make up for a forgotten dose, because missed amounts cannot be compensated but the risk of overdose occurs.

May patients stop taking Opimol?

Patients should not stop taking this medicine abruptly, or change recommended dose before consulting the doctor, for in such cases the heart failure may temporarily worsen. The treatment must not been discontinued abruptly especially in patients with coronary disease. If cessation of treatment is necessary, dose must be reduced gradually.

Possible side effects

Like all medicines, opimol tablets can cause side effects, although not everybody experiences them.

Common side effects (that may affect up to 1 in 10 people): headache, dizziness, somnolence (especially at the beginning of the treatment), palpitation, flush, abdominal pain, ankle swelling, oedema, fatigue, feeling of coldness and numbness in the extremities, gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

Uncommon side effects (that may affect up to 1 in 100 people): insomnia, mood changes (including anxiety), depression, temporary loss of consciousness (syncope), hypaesthesia, paraesthesia, abnormal sense of taste (dysgeusia), tremor, visual disturbances (including diplopia),

tinnitus, hypotension, dyspnoe, rhinitis, altered bowel habits (including diarrhoea and constipation), dyspepsia, dry mouth, alopecia, small bleedings in the skin and mucosa (purpura), skin discolouration, increased sweating, itching, rash, exanthema, arthralgia, myalgia, muscle cramps, back pain, frequent micturition, micturition disorder, nycturia, impotence, breast enlargement in men, chest pain, asthenia, pain, malaise, weight increase, weight decrease, sleep disorders, heart conduction disorders, deterioration of pre-existing heart failure, slow heart rate (less than 50 beat per minute), low blood pressure, bronchospasm in patients with bronchial asthma or a history of obstructive pulmonary disease, muscle weakness and cramps, exhaustion*.

*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1-2 weeks.

Rare side effects (that may affect up to 1 in 1,000 people): confusion, elevated level of triglyceride, nightmares, sense illusion, which is an abnormal sensation without detectable stimulus, similar to real sensation and seems real (hallucination), decreased tear secretion (it must be taken into consideration if you wear contact lenses), hearing impairments, allergic rhinitis, hepatitis, hypersensitivity reactions such as itching, flush, rash, elevated liver enzymes.

Very rare side effects (that may affect up to 1 in 10,000 people): decrease of number or white blood cells and platelets, allergic reactions, elevated level of blood sugar, hypertonia, peripheral neuropathy, heart attack, cardiac arrhythmia, patchy inflammation of small blood vessels (vasculitis), cough, gastritis, gingival hyperplasia, pancreatitis, jaundice, acute swelling of skin or mucosa involving most frequently eyelids, lips, joints, genitals, glottis, pharynx and tongue (angio-oedema), serious inflammation of skin or mucosa with red vesicles (erythema multiforme), urticaria, widespread erythema and scaling of the skin (exfoliative dermatitis), serious blistering lesions of the skin and mucous membranes of the mouth, genital and anal regions, with fever, sore throat and fatigue (Stevens-Johnson syndrome), sensitivity to the sunlight, conjunctivitis, drugs with similar mechanism of action than bisoprolol (active ingredient of the preparation) may evoke or worsen psoriasis (chronic skin disease with itchy scaly red patches) or may cause psoriasis-like skin disorder.

How to store Opimol tablets

Do not store above 30°C. Store in the original container in order to protect from light.

Do not use this medicine if the visible signs (discoloration) of deterioration appear.

Keep this medicine out of the sight and reach of children.

Scientific discussion during the initial procedure

This module reflects the scientific discussion for the approval of Opimol 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. The procedure was finalised at 02 June 2014. For information on changes after this date please refer to the module 'Update'.

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*, 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 and Slovak Republic) concerned fixed combinations of bisoprolol and amlodipine concerning a second brand products of already authorized fix dose combinations of bisoprolol and amlodipine.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Opimol (in Bulgaria, Latvia, Lithuania, Poland and Romania Alotendin, in the Czech Republic and in the Slovak Republic Bigital) 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets from EGIS Pharmaceuticals Plc.

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

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

II. QUALITY ASPECTS

II.1 Introduction

The fixed combination of the calcium ion antagonist amlodipine and the highly β1-selective adrenoreceptor-blocking agent bisoprolol is indicated as substitution therapy for patients, whose blood pressure and/or chronic stable angina pectoris can be adequately controlled by simultaneously given amlodipine and bisoprolol.

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

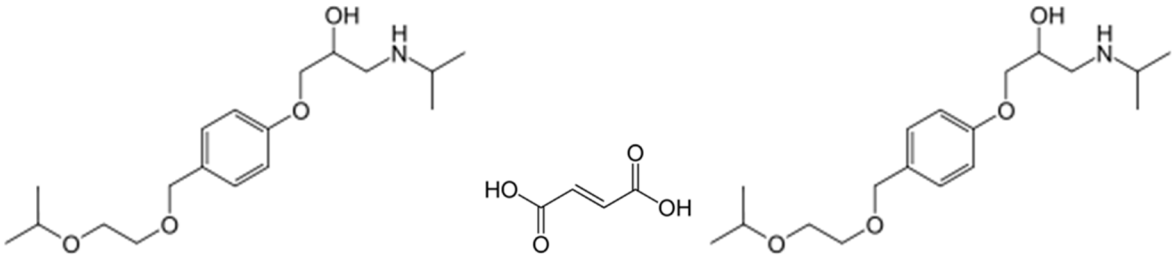
The object of the development was to develop combination products with the same bioavailabilities of the active principles as in the reference monocomponent products. The latter were Norvasc® tablets containing amlodipine besilate (Pfizer) and Concor® film-coated tablets containing bisoprolol fumarate (Merck KGaA, Darmstadt), authorised 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

II.2.1 Bisoprolol fumarate

The Applicant has submitted two European Pharmacopoeia (Ph. Eur.) Certificates of Suitability (CEP) for this drug substance. The CEPs indicate that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that they are supplemented with a test for the residual solvent acetone (NMT 500 ppm) by GC (in the first case) and with a test for impurity (Imp. R of the monograph: NMT 0.15 %) and with a test for the residual solvent acetone (NMT 1000 ppm) by GC, in the second case.

INN name: bisoprolol fumarate
Chemical names: (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-(Isopropyla mino)-2-propanol fumarate (2:1) salt.
Structure:



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.

It has been demonstrated by X-ray powder diffraction analysis that the described manufacturing process consistently and exclusively yields the same polymorph form.

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

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

The Ph. Eur. specification includes the following tests for bisoprolol fumarate: appearance, identification (IR), related substances (HPLC), water content, sulphated ash, assay (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 the P. Eur. are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterized and evaluated by EDQM.

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

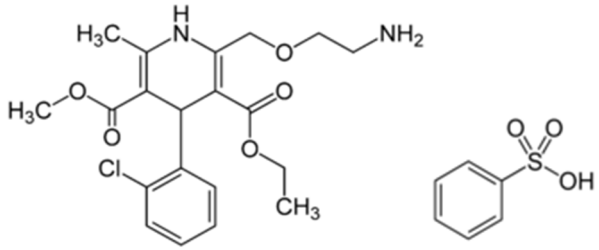
During the stability studies no significant changes in any parameters were observed. The proposed retest period of 5 years is supported by the submitted stability data when stored closed and protected from light in the original containers.

GMP compliance of the drug substance manufacturer has been demonstrated by the Applicant.

II.2.2 Amlodipine besilate

The Applicant has submitted two Ph. Eur. CEPs for this drug 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 the residual solvent isopropanol by GC (NMT 1000 ppm) or with a test for the residual solvent ethyl acetate (NMT 500 ppm) by GC, respectively.

INN name: amlodipine besilate
Chemical name: 3-ethyl- 5-methyl- (4RS)-2-[(2-amino-ethoxy)-methyl]-4-(2-chloro-phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Structure:



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: 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 Ph. Eur. is adequately drawn up and sufficiently validated. The laser diffraction method for particle size determination has been adequately described and validated.

Reference materials used for the control of the substance are adequately characterized and evaluated by EDQM.

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

One of the CEPs has been supplemented with the retest period, which is five years with no special storage condition. In case of the other manufacturer, the proposed retest periods of 4 years are supported by the submitted stability data when stored well-closed and protected from light up to a temperature of 25 °C.

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 bisoprolol fumarate and amlodipine besilate.

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 in detail. A common formulation and manufacturing process was developed bisoprolole fumarate and amlodipine besilate tablets. The four compositions of are dose-proportional.

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.

The excipients used in the finished product were 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 function related characteristics of the excipients have been discussed.

The tablets are white or almost white, odourless,

- the 5 mg/5 mg tablets oblong, slightly convex,
- the 5 mg/10 mg tablets round, flat, bevel edged,
- the 10 mg/5 mg tablets oval shaped, slightly convex,
- the 10 mg/10 mg tablets round, slightly convex

with score line on one side and with embossed MS on the other side. The score line is only to facilitate breaking for ease of swallowing.

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

The tablets are packed in OPA/Al/PVC//Al blisters and 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, their batch and stability data the proposed specification limits are 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.

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

Based on the presented results, a shelf-life of 36 months is approved with the following storage condition: “Do not store above 30 ºC. Store in the original container in order to protect from light.”

The SmPC, the Package Leaflet (PIL) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have 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 products.

The products are, from chemical-pharmaceutical points of views, acceptable.

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 non-clinical 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) bisoprolol/amlodipine 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 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 (CPMP/EWP/240/95)."

Both amlodipine and bisoprolol are widely used antihypertensive and antianginal medicines the human experience is 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 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. Some degree of blockade of the bronchial beta-2 receptors may occur with bisoprolol; however, this is clinically not significant and only evident with high doses (30 to 40 mg orally). 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 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. 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 in 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

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 (TLC).

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 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 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 justify the impurity according to the CPMP/ICH/2738/99 Guideline Q3B(R2).

The performed toxicology and mutagenicity tests were adequate and sufficient to qualify the impurity. The applicant has clearly demonstrated that it neither increases the toxicity compared to the previously reported findings of amlodipin/bisoprolol without the impurity, nor has genotoxic and mutagenic effects. Furthermore, as bisoporolol/amlodipine combinations without the impurity were also tested, the study has provided further information on the safety of this fixed dose combination and revealed no further toxicological concerns.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Opimol tablets are intended for substitution of monocomponent preparations used in the same doses and strengths, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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 bisoprolol 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 a combination of bisoprolol and amlodipine 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 bisoprolol and amlodipine and presented the synergistic effects between the calcium-channel blockers and beta-blockers. The justification of the missing specific pharmacokinetic interaction studies between bisoprolol 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

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 are linear between 5 and 20 mg and independent of age.

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.

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 study was conducted. The study utilised the highest strengths (10 mg bisoprolol and 10 mg amlodipine). The reference products were Norvasc 10 mg tablets (Pfizer) and Emconcor 10 mg film-coated tablets (Merck). The conduct of the study was satisfactory and the results comply with the acceptance criteria for bioequivalence as detailed in the relevant CHMP guideline.

It was a comparative, randomised, single-dose, 2-way crossover bioavailability study of the 10 mg/10 mg strength of the test (T), the new combination tablet *versus* co-administration of amlodipine besilate 10 mg and bisoprolol hemifumarate 10 mg as separate tablets (Reference preparations R) in healthy adult male volunteers under fasting conditions.

Plasma concentrations of bisoprolol and amlodipine were determined in plasma samples of volunteers using a High Performance Liquid Chromatography / Tandem Mass Spectrometry Method (HPLC-MS/MS).

Pharmacokinetic statistical 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 $T_{½el}$ for each treatment. The primary pharmacokinetic parameters for this study were C_{max}, AUC_T and AUC_∞. Other parameters such as $AUC_{T/\infty}$, K_{el}, T_{max} and $T_{½el}$ were provided for information purposes only.

For C_{max}, AUC_T and AUC_∞ ANOVA was used 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 statistical methodology is adequate. The predefined confidence interval for the test/reference ratios of the means of AUC0-∞, AUC_T and C_{max} parameters are between 80% and 125%.

The results are shown on the following Tables.

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_∞

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_∞

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 the bioequivalence of the claimed combination 10 mg bisoprolol'10 mg amlodipine product and the originator monocomponent tablets given concomitantly is established.

Biowaiver

For the other bisoprolol/amlodipine strengths also applied for in this marketing authorization application additional dissolution studies were performed that confirmed the adequacy of the biowaiver from additional bioequivalence studies.

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 bio-waiver criteria are fulfilled (CPMP/EWP/QWP/1401/98 Rev. 1), additional in vivo studies for the bioequivalence assessment with the lower strengths series may be waived.

IV.3 Pharmacodynamics

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.

The pharmacodynamics of amlodipine is well established. It belongs to the dihydropiridine Ca^{++}-channel blockers. Amlodipine 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. 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

The justification for a combination of bisoprolol and amlodipine 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 5 mg bisoprolol/5 mg amlodipine and 5 mg bisoprolol/10mg amlodipine. 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 may raise the question whether the marketing authorization of 10mg/5mg and 10mg/10mg doses is fully justified. Since this type of data lack from the concerned member states it is difficult to judge the necessity of the latter doses. However, assuming similar prescribing habit of physicians in all the concerned member states altogether 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 agreement 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 can justify the benefit of the combination with thorough review of the literature.

There are limited data about the co-administration of bisoprolol and amlodipine in the literature. The applicant has amended the original Clinical Overview in order to further support the co-administration of amlodipine and bisoprolol. The amendment is sufficient to support the hypertension indication. The bisoprolol/amlodipine combination tablet is indicated for hypertension as a substitution therapy.

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. The safety profiles of both the test product and the combination of the monocomponent originators were comparable.

There were no serious adverse events and no use of concomitant medication was required.

In conclusion, a good tolerability was assessed for both the fixed and the free combinations.

IV.6 Risk Management Plan

The Risk Management Plan submitted by the applicant was accepted during the procedure.

Safety concern	
Important identified risks	Bradycardia Atrioventricular conduction disturbances Aggravation of chronic heart failure Myocardial infarction Bronchospasm (with Bronchial Asthma or Chronic Obstructive Disease) Pancreatitis Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis Syncope Hepatobiliary disorders
Important potential risks	Renal failure Fibrosis conditions (including Peyronie's disease, Retroperitoneal fibrosis, Pulmonary Fibrosis) Interstitial Lung Disease Attempted/completed Suicide and Suicidal Ideation Off-label Use
Missing information	Use during pregnancy and lactation Paediatric use Use in patients with hepatic impairment

On-going and Planned Additional safety Studies/Activities in the Pharmacovigilance Plan

Not applicable.

Summary of Post Authorization Efficacy Development Plan

Not applicable.

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bradycardia	Listed in the SmPCs: • Contraindications: symptomatic bradycardia • Adverse reactions: bradycardia Other routine risk minimisation measures: Prescription only medicine	Not applicable
Atrioventricular conduction disturbances	Listed in the SmPCs: • Contraindications: second or third degree AV block (without a pacemaker); sinoatrial block • Adverse reactions: atrioventricular conduction disturbances Other routine risk minimisation measures: Prescription only medicine	Not applicable
Aggravation of chronic heart failure	Listed in the SmPCs: • Warnings and precautions: Patients with heart failure should be treated with caution. An increased risk of a further deterioration of the ventricular pump function cannot be excluded. • Adverse reactions: worsening of pre-existing heart failure Other routine risk minimisation measures: Prescription only medicine	Not applicable
Myocardial infarction	Listed in the SmPCs: myocardial infarction Other routine risk minimisation measures: Prescription only medicine	Not applicable
Bronchospasm	Listed in the SmPCs: • Contraindications: severe bronchial asthma or severe chronic obstructive pulmonary disease • Adverse reactions: bronchospasm in patients with bronchial asthma or a history of obstructive pulmonary disease Other routine risk minimisation measures: Prescription only medicine	Not applicable
Pancreatitis	Listed in the SmPCs: adverse reactions: pancreatitis Other routine risk minimisation measures: Prescription only medicine	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Stevens Johnson Syndrome, erythema multiforme, exfoliative dermatitis	Listed in the SmPCs: adverse reactions: Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis Other routine risk minimisation measures: Prescription only medicine	Not applicable
Syncope	Listed in the SmPCs: adverse reactions: syncope Other routine risk minimisation measures: Prescription only medicine	Not applicable
Hepatobiliary disorders	Listed in the SmPCs: adverse reactions: hepatitis, jaundice Other routine risk minimisation measures: Prescription only medicine	Not applicable
Drug-drug interactions with class I antiarrhythmic drugs, calcium antagonists of the verapamil type and to a lesser extent of diltiazem type, CYP 3A4 inhibitors and simvastatin	Drug interactions listed in the SmPC section 7, Interactions	Not applicable
Renal failure	Not applicable (potential risk)	Not applicable
Fibrosis conditions	Not applicable (potential risk)	Not applicable
Attempted/completed Suicide and Suicidal Ideation	Not applicable (potential risk)	Not applicable
Off-label Use	Not applicable (potential risk)	Not applicable
Use in pregnancy / lactation (missing information)	SmPC warning: bisoprolol may cause harmful effects on pregnancy and/or the foetus/newborn.	Not applicable
Use in paediatric patients (missing information)	SmPC non-recommendation: bisoprolol + amlodipine cannot be recommended in the paediatric population.	Not applicable
Use in patients with hepatic impairment (missing information)	SmPC warning: caution advised when used in patients with hepatic impairment.	Not applicable

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.
For these application the bioequivalence studies described in section IV.2 are pivotal.

The application concerns a second brand product of already authorised fixed combinations of bisoprolol and amlodipine. The proposed 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 present application concerns Opimol 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets. The applicant and the future holder of authorisation is EGIS Pharmaceuticals Plc.

The active substances are: bisoprolol fumarate/ amlodipine (as besilate).

Opimol tablets are indicated for the treatment of high blood pressure as substitution therapy in patients who are adequately controlled with the individual products given concurrently at the same doses level as in the combination, but as separate tablets.

Bioequivalence between Opimol 10 mg/10 mg tablets was successfully demonstrated with two marketed monocomponent preparations, Norvasc 10 mg (Pfizer) tablets and Emconcor (Merck) 10 mg film-coated tablets. The results could be extrapolated to other strengths.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

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

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 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*.

National Institute of Pharmacy
Directorate of GYEMSZI
Budapest, Hungary

Public Assessment Report Number:
HU/H/0150/003/DC

VI. Upgrade: 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