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Public Assessment Report

Name of the Product:

Scaliant

5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets

(bisoprolol fumarate/perindopril arginine)

Procedure number: HU/H/0391/001-004/DC

Marketing authorisation holder: EGIS Pharmaceuticals Plc.

Date: 9 June 2016

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Scaliant 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets. The holder of the marketing authorisation is EGIS Pharmaceuticals Plc in the reference member state.

The active substances are bisoprolol fumarate and perindopril arginine. Each fixed combination tablet of Scaliant contains 5 mg or 10 mg bisoprolol fumarate (equivalent to 4.24 mg or 8.49 mg bisoprolol) and 5 mg or 10 mg perindopril arginine (equivalent to 3.395 mg or 6.790 mg perindopril), respectively.

The other ingredients are cellulose microcrystalline PH 102 (E460), calcium carbonate (E170), pregelatinised maize starch, sodium starch glycolate type A (E468), silica colloidal anhydrous (E551), magnesium stearate (Liga E572), croscarmellose sodium (E468), glycerol (E422), Hypromellose (E464), Macrogol 6000, titanium dioxyde (E171), Iron oxide yellow (E172), Iron oxide red (E172) and water purified.

Scaliant tablets are pink beige, oblong, bilayer scored film-coated tablets engraved with '  ' on one face and '5/5' or '5/10' or '10/5' or '10/10' on the other face. Scaliant 5 mg/5 mg and 5 mg/10 mg scored tablets can be divided into equal halves.

The tablets are packed in white polypropylene or high density polyethylene tablet containers.

Scaliant contains two active ingredients, bisoprolol fumarate and perindopril arginine in one tablet:

- bisoprolol fumarate belongs to a group of medicine called beta-blockers. Beta-blockers slow down the heart rate and make the heart more efficient at pumping blood around the body;
- perindopril arginine is an angiotensin converting enzyme (ACE) inhibitor. It works by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Scaliant fixed combination tablets are used as follows.

The 5 mg/5 mg and 10 mg/5 mg strengths are used to treat high blood pressure (hypertension) and/or stable chronic heart failure (a condition where the heart is unable to pump enough blood to meet the body's needs resulting in breathlessness and swelling) and/or to reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

The 5 mg/10 mg and 10 mg/10 mg strengths are used to treat high blood pressure (hypertension) and/or to reduce the risk of cardiac events, such as heart attack, in patients with stable coronary

artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

Instead of taking bisoprolol fumarate and perindopril arginine as separate tablets, patients will take only one tablet of Scaliant which contains both active ingredients in the same strength.

What patients need to know before taking Scaliant

Those who:
- are allergic to bisoprolol or any other beta-blocker, to perindopril or any other ACE inhibitor, or to any of the other ingredients of this medicine;
- have heart failure that suddenly becomes worse and/or that may require hospital treatment;
- have a cardiogenic shock (a serious heart condition caused by very low blood pressure);
- have a heart disease characterized by a slow or irregular heart rate (atrioventricular block second or third degree, sinoatrial block, sick sinus syndrome);
- have a slow heart rate;
- have very low blood pressure;
- have severe asthma or severe chronic lung disease;
- have severe blood circulation problems in your limbs (such as Raynaud's syndrome), which may cause your fingers and toes to tingle or turn pale or blue;
- have an untreated phaeochromocytoma, which is a rare tumour of the adrenal gland (medulla);
- have metabolic acidosis, a condition where your blood contains too much acid;
- have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if the patient or a member of the patient's family have had these symptoms in any other circumstances (a condition called angioedema);
- are more than 3 months pregnant (it is also better to avoid Scaliant in early pregnancy - see pregnancy section);
- have diabetes or impaired kidney function and are treated with a blood pressure lowering medicine containing aliskiren

must not take Scaliant.

Warnings and precautions

Those who
- have diabetes;
- have kidney problems (including kidney transplantation) or are receiving dialysis;
- have a liver problem;
- have aortic and mitral stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood);

- have heart failure or any other heart problems such as minor disturbances in heart rhythm or severe chest pain at rest (Prinzmetal's angina);
- suffer from a collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma;
- are on a salt restricted diet or use salt substitutes which contain potassium (too much potassium in the blood can cause changes in the heart rates);
- have recently suffered from diarrhea or vomiting, or are dehydrated (Scaliant may cause a fall in blood pressure);
- are to undergo LDL apheresis (which is removal of cholesterol from the blood by a machine);
- have current antiallergic treatment or are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings;
- are under strict fasting or diet;
- are to undergo anaesthesia and/or major surgery;
- have any problems with the circulation in the limbs;
- have asthma or chronic lung disease;
- have (or have had) psoriasis;
- have a tumour of the adrenal gland (phaeochromocytoma);
- have thyroid disorders (Scaliant can hide symptoms of an overactive thyroid);
- have angioedema (severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing). This may occur at any time during treatment. If the patient develops such symptoms, he/she should stop taking Scaliant and see a doctor immediately;
- are of black origin since you may have a higher risk of angioedema and this medicine may be less effective in lowering your blood pressure than in non-black patients,
- are taking any of the following medicines used to treat high blood pressure:
    - an "angiotensin II receptor blocker" (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if having diabetes-related kidney problems,
    - aliskiren

must consult their doctor before taking Scaliant.

The doctor may check the kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in the blood at regular intervals.

Taking Scaliant should not be suddenly stopped since this can cause severe worsening of heart condition. Treatment should not be discontinued abruptly, especially in patients with coronary artery disease.

The patient must tell her doctor if she thinks she is (or might become) pregnant. Scaliant is not recommended in early pregnancy, and must not be taken if the patient is more than 3 months pregnant, as it may cause serious harm to the baby if used at that stage (see pregnancy section).

Children and adolescents

Scaliant is not recommended for use in children and adolescents younger than 18.

Other medicines and Scaliant

Patients must inform their doctor if they are taking, have recently taken or might take any other medicines.

There are some medicines that may change the effect of Scaliant or their effect may be changed by Scaliant. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects.

For this reason, patients must particularly be sure to tell their doctor if taking any of the following medicines:

- medicines used to control blood pressure or medicines for heart problems (such as amiodarone, amlodipine, clonidine, digitalis glycosides, diltiazem, disopyramide, felodipine, flecainide, lidocaine, methyldopa, moxonidine, procainamide, propafenone, quinidine, rilmenidine, verapamil);
- other medicines used to treat high blood pressure, including angiotensin II receptor blocker (ARB), aliskiren or diuretics (medicines which increase the amount of urine produced by the kidneys);
- potassium-sparing drugs (e.g. triamterene, amiloride), potassium supplements or potassium-containing salt substitutes;
- potassium-sparing drugs used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5 mg to 50 mg by day;
- sympathomimetics agents to treat clinical shock (adrenaline, noradrenaline, dobutamine, isoprenaline, ephedrine) ;
- estramustine used in cancer therapy;
- lithium used to treat mania or depression;
- certain medicines used to treat depression such as imipramine, amitriptylin, monoamine oxidase (MAO) inhibitors (except MAO-B inhibitors);
- certain medicines used to treat schizophrenia (antipsychotics);
- certain medicines used to treat epilepsy (phenytoin, barbiturates such as phenobarbital);
- anaesthetic agents used for surgery;
- vasodilators including nitrates (products that make the blood vessels become wider);
- trimethoprim used to treat infections;
- heparin used to treat thin blood;
- immunosuppressants (medicines which reduce the defence mechanism of the body) such as ciclosporin, tacrolimus, used for the treatment of auto-immune disorders or following transplant surgery;
- allopurinol used to treat gout;
- parasympathomimetics medicines used to treat conditions such as Alzheimer's disease or glaucoma;
- topical beta-blockers used to treat glaucoma (increase pressure in the eye);

- mefloquine used to prevent or treat malaria;
- baclofen used to treat muscle stiffness in diseases such as multiple sclerosis;
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis);
- medicines to treat diabetes such as insulin, metformin, linagliptin, saxagliptin, sitagliptin, vildagliptin;
- non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or diclofenac or high dose of aspirin used to treat arthritis, headache, pain or inflammation.

Scaliant with food, drink and alcohol

It is preferable to takeScaliant before a meal.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Patients must tell their doctor if they think they are (or might become) pregnant. Their doctor will normally advise them to stop taking Scaliant before they become pregnant or as soon as they know they are pregnant and will advise them to take another medicine instead of Scaliant. Scaliant is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Patients who are breast-feeding or about to start breast-feeding must inform their doctor. Scaliant is not recommended for mothers who are breast-feeding, and the doctor may choose another treatment if the patient wishes to breast-feed, especially if the baby is a newborn, or was born prematurely.

Driving and using machines

Scaliant usually does not affect alertness but dizziness or weakness due to low blood pressure may occur in some patients, particularly at the start of treatment or upon change of medication as well as in conjunction with alcohol. Those who are affected in this way may have impaired ability to drive or to operate machinery.

How to take Scaliant

The recommended dose is one tablet once daily. The tablet should be swallowed with a glass of water in the morning before a meal.

Scaliant 5 mg/5 mg and 5 mg/10 mg: in some cases, the doctor may prescribe one half tablet of Scaliant once daily in the morning before a meal.

Patient with kidney disease

Scaliant is not recommended for those who are suffering from moderate and severe kidney disease. However, the doctor may prescribe one half tablet of Scaliant 5 mg/5 mg for those who suffer from moderate kidney disease. Scaliant 5 mg/5 mg is not recommended if you suffer from severe kidney disease.

Use in children and adolescent is not recommended.

What to do if more Scaliant was taken than it should have been?

If the patient takes more tablets than prescribed, he/she must contact the doctor immediately. The most likely effect in case of overdose is low blood pressure which can make feel dizzy or faint (if this happens, lying down with the legs raised can help), severe difficulty in breathing, tremors (due to decreaded blood sugar) and slow heart rate.

What to do if taking Scaliant was forgotten?

It is important to take this medicine every day as regular treatment works better. However, if a dose of Scaliant is forgotten, the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

Can taking Scaliant be stopped?

Patients are discouraged to stop taking Scaliant suddenly or changing the dose without consulting their doctor since this can cause severe worsening of heart condition. Treatment should not be discontinued abruptly, especially in patients with coronary artery disease.

Possible side effects

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

Taking this medicinal product must be stopped and a doctor must be consulted immediately, if any of the following side effects are experienced:

- severe dizziness or fainting due to low blood pressure (common – may affect up to 1 in 10 people),
- worsening of heart failure causing increased breathlessness and /or retention of fluid (common – may affect up to 1 in 10 people),
- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing (angioedema) (uncommon – may affect up to 1 in 100 people),
- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing (bronchospasm) (uncommon – may affect up to 1 in 100 people),

- unusual fast or irregular heart-beat, chest pain (angina) or heart attack (very rare – may affect up to 1 in 10,000 people),
- weakness of arms or legs, or problems speaking which could be a sign of a possible stroke (very rare – may affect up to 1 in 10,000 people),
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (very rare – may affect up to 1 in 10,000 people),
- yellowing of the skin or eyes (jaundice) which could be a sign of hepatitis (very rare – may affect up to 1 in 10,000 people),
- skin rash which often starts with red itchy patches on your face, arms or legs (erythema multiforme) (very rare – may affect up to 1 in 10,000 people).

Scaliant is usually well tolerated but, as with any medicine, people can experience different side effects, particularly when treatment is first started.

Patients who notice any of the side effects listed below or any not listed, should consult their doctor immediately.

Very common (may affect more than 1 in 10 people):
- slow heart beat.

Common (may affect up to 1 in 10 people):
- headache,
- dizziness,
- vertigo,
- taste disturbances,
- pins and needles,
- tingling or numbness of the hands of feet,
- vision disturbances,
- tinnitus (sensation of noises in the ears),
- feeling of coldness in hands or feet,
- cough,
- shortness of breath,
- gastro-intestinal disorders such as nausea, vomiting, abdominal pain, difficulty of digestion or dyspepsia, diarrhoea, constipation,
- allergic reactions such as skin rashes, itching,
- muscle cramps,
- feeling of tiredness,
- fatigue.

Uncommon (may affect up to 1 in 100 people):
- mood swings,
- sleep disturbances,
- depression,
- dry mouth,

- intense itching or severe skin rashes,
- formation of blister clusters over the skin,
- increased sensitivity of the skin to sun (photosensitivity reaction),
- sweating,
- kidney problems,
- impotence,
- an excess of eosinophils (a type of white blood cells),
- somnolence,
- fainting,
- palpitations,
- tachycardia,
- irregular heart rate (AV-conduction disturbances inflammation of blood vessels (vasculitis),
- dizziness when standing up,
- muscle weakness,
- arthralgia (joint pain),
- myalgia (muscle pain),
- chest pain,
- malaise,
- localised swelling (oedema peripheral),
- fever,
- fall,
- changes in laboratory parameters: high blood level of potassium reversible on discontinuation, low level of sodium, very low blood sugar level (hypoglycaemia) in case of diabetic patients, increased blood urea, increased blood creatinine.

Rare (may affect up to 1 in 1000 people):
- nightmares, hallucinations,
- reduced tear flow (dry eyes),
- hearing problems,
- erection problems,
- inflammation of the liver which can cause yellowing of the skin or the whites of the eyes,
- allergic runny nose, sneezing,
- allergy-like reactions such as itching, flush, rash,
- changes in laboratory parameters: increased level of liver enzymes, high level of serum bilirubin, fat levels differing from normal.

Very rare (may affect up to 1 in 10,000 people):
- confusion,
- irritation and redness of the eye (conjunctivitis),
- eosinophilic pneumonia (a rare type of pneumonia),
- inflammation of the pancreas (which causes severe pain in the abdomen and the back),
- hair loss,
- appearance or worsening of scaly skin rash (psoriasis), psoriasis-like rash,

- acute renal failure,
- changes in blood values such as a lower number of white and red blood cells, lower haemoglobin, lower number of blood platelets.

5. How to store Scaliant

This medicine does not require any special storage conditions, but it must be kept out of the sight and reach of children.

Once opened, Scaliant should be used within 20 days for tablet containers of 10 film-coated tablets, 60 days for tablet containers of 30 film-coated tablets and 100 days for tablet containers of 100 film-coated tablets.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Scaliant 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets. The procedure was finalised at 12 October 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Article 10b of 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: Belgium, France, Italy, Latvia, Luxembourg, Netherlands, Poland and Portugal) concerned the fixed combinations of bisoprolol fumarate/perindopril arginine 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg tablets (Scaliant tablets, named Asembix in Belgium, France, Latvia, Luxembourg and Portugal, Bipressil in Netherlands, Cogyr in Italy).

The combination products are indicated:

> For the 5 mg/5 mg and 10 mg/5mg strengths: the tablets are indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularisation) and/or stable chronic heart failure with reduced systolic left ventricular function in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.
>
> For the 5 mg/10 mg and 10 mg/10 mg strengths: the tablets are indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularization) in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.

The applicant has adequately demonstrated bioequivalence between the products and reference products containing the single active components. The reference products were Concor® (bisoprolol fumarate) and Coversyl® (perindopril arginine) tablets which were the original products of Merck KGAA and Les Laboratoires Servier, respectively.

Moreover, the applicant provided sufficient co-prescription data from several European countries demonstrating the use of bisoprolol and perindopril monocomponent preparations in combination.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Scaliant 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets from EGIS Pharmaceuticals Plc, Hungary (the marketing authorisation holder in the RMS).

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

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Scaliant 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets via a decentralized procedure according to Article 10b of consolidated Directive 2001/83/EC (i.e. a fixed combination application). The marketing authorisation holder is EGIS Pharmaceuticals Plc. in the RMS.

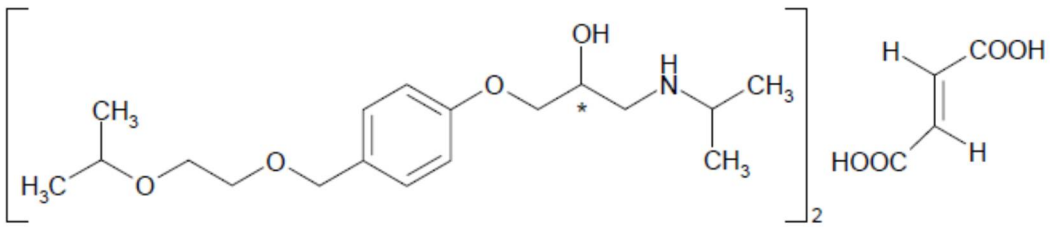
The reference products were Concor® 10 mg (bisoprolol fumarate) and Coversyl® 10 mg (perindopril arginine) tablets which were the original products of Merck KGAA and Les Laboratoires Servier, respectively.

II.2 Drug substances

II.2.1 Bisoprolol fumarate

Data on the quality and manufacture of the active substance were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: bisoprolol fumarate
Chemical name: (R,S)1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hemifumarate
or
(±)-1-(4-((2-(1-methyl-ethoxy)ethoxy)methyl)phenoxy)-3-((1methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt.
Structure:



The active substance is white or almost white powder, slightly hygroscopic; very soluble in water and freely soluble in methanol.

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

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

Testing methods are performed in accordance with the Ph. Eur. monograph and the annex of the current CEPs on bisoprolol fumarate. Reference materials used by the active substance manufacturers and the drug product manufacturer for the control of the substance are adequately characterised.

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

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

A retest period and the packaging material (LDPE bag, closed with a plastic tie in heat sealed aluminium bag and fiberboard drum) have been mentioned by the Applicant. As recommended by the Ph. Eur. monograph, bisoprolol fumarate must be protected from light.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.2.2 Perindopril arginine

The applicant provided the information on the quality and manufacture of the perindopril arginine in the part of the documentation, not in separated Active Substance Master File (ASMF). The Quality Overall Summary is adequate.

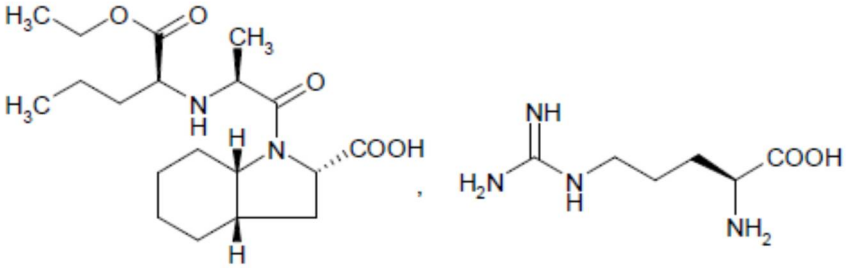
INNM (modified) name: perindopril arginine

Chemical name: L-arginine (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl) butyl]amino]propanoyl] octahydro-1*H*-indole-2-carboxylate,

or

(2S, 3aS, 7aS)-1-{(S)-N-[(S)-1-(ethoxycarbonyl) butyl]alanyl}octahydro-1H-indole-2-carboxylic acid, arginine salt.

Structure:



The active substance is white or almost white powder, hygroscopic; freely soluble in water, slightly soluble in ethanol (96 %) and practically insoluble in methylene chloride.

The active substance manufacturer presented an adequately detailed the manufacturing process.

Evidence of the structure has been confirmed by ^{1}H and ^{13}C-NMR spectra, MS, FT-IR, XRDP, DSC and TGA spectra. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Perindopril arginine is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: characters, identification (by IR, specific optical rotation and TLC), water content, sulphated ash, heavy metals, stereochemical purity, chemical purity, assay, residual solvents, residual catalysts and particle size.

Testing methods are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

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

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

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable when stored in a polyethylene double bag overwrapped in a heat sealed aluminium complex bag placed in a cardboard drum, without any special storage conditions.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of development was to develop combination products with the same bioavailability as those of the single dose reference products administered simultaneously.

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

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

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

5 mg/5 mg film-coated tablet: pink beige, oblong, bilayer scored film-coated tablet of 8.3 mm length and 4.5 mm width, engraved with ' ' on one face and '5/5' on the other face. The tablet can be divided into equal doses.
5 mg/10 mg film-coated tablet: pink beige, oblong, bilayer scored film-coated tablet of 9.8 mm length and 5.4 mm width, engraved with ' ' on one face and '5/10' on the other face. The tablet can be divided into equal doses.
10 mg/5 mg film-coated tablet: pink beige, round, bilayer film-coated tablet with a diameter of 7 mm and a curvature radius of 12.7 mm, engraved with ' ' on one face and '10/5' on the other face.
10 mg/10 mg film-coated tablet: pink beige, oblong, bilayer film-coated tablet of 10 mm length and 5.7 mm width, engraved with ' ' on one face and '10/10' on the other face.

The excipients used in the finished product are cellulose microcrystalline PH 102, calcium carbonate, pregelatinized maize starch, sodium starch glycolate type A, silica colloidal anhydrous, magnesium stearate, croscarmellose sodium. The film-coating contains the following excipients: glycerol, hypromellose, macrogol 6000, magnesium stearate, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172).

All excipients used, with the exception of the colorants, comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

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

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The film-coated tablets are packaged in white polypropylene tablet container equipped with a low-density polyethylene flow reducer and a white opaque stopper containing a desiccant gel or high density polyethylene tablet container equipped with a polypropylene stopper containing desiccant. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months (in PP container of 10 tablets) and 30 months (in PP container of 30 tablets and in HDPE container of 100 tablets) with no special storage conditions is approved.

The SmPC, Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

Both bisoprolol and perindopril are widely used antihypertensive and antianginal medicines as well as applied in stable congestive heart failure; 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

Bisoprolol is a highly selective β1-adrenoceptor blocking agent without intrinsic sympathomimetic activity and low to moderate local anaesthetic activity. As demonstrated in binding experiments, and in classical pharmacological studies using rats, guinea pigs, cats, and dogs, bisoprolol markedly differentiated between β_1-adrenoceptors of the heart, or the renal juxtaglomerular apparatus, and the beta 2-subtype in arterial blood vessels, bronchi, liver, or skeletal muscle. Up to concentrations nearly 100-fold higher than the therapeutic plasma levels in humans, bisoprolol did not affect the functional refractory period of the heart, and was devoid of a direct suppressive effect on myocardial contractility and of calcium antagonistic properties in heart and vascular muscle. The pattern of haemodynamic effects of bisoprolol is typical of β-blockers and included decreases in blood pressure (BP), heart rate (HR), and cardiac output (CO), concomitant with an increase in calculated total peripheral resistance. In contrast to other β-blockers, bisoprolol increased renal blood flow in anaesthetized dogs. Bisoprolol lowered BP in hypertensive dogs and rats, attenuated the development of spontaneous HT in rats, decreased plasma renin activity and protected the heart from the sequelae of transient ischemia. It did not block presynaptic β-adrenoceptors in blood vessels. Serum lipids and the serum lipoprotein profile remained unaltered after bisoprolol. Bisoprolol was devoid of affinity for autonomic receptors other than β-adrenoceptors or for autacoid receptors.

Bisoprolol was also shown to have cardioprotective effect in dogs and anaesthetised pigs and improve survival in rats with severe cardiac failure induced by autoimmune myocarditis with observations suggesting that bisoprolol may improve survival independently of its effect on left ventricular function by reducing sudden death in patients with severe cardiac failure.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Upon incubation of the bronchial tissue with therapeutically effective concentrations of 5 different β_1-blockers, the results show that amongst the β-blockers tested, atenolol and bisoprolol showed the least activity on bronchi. When present in concentration equivalent to therapeutic plasma levels, the doses of isoprenaline required for relaxation must be multiplied by 2.82 for atenolol and 1.95 for bisoprolol compared to 32.6 for propranolol. Bisoprolol therefore was 16.7 times less active than propranolol on human bronchi.

High doses of bisoprolol (30 and 100 mg/kg, single oral administration (PO)) did not influence the behaviour of rats with the exception of a slight sedative action, i.e. reduced motor activity and partly closed eyes.

Doses of 0.5, 1, 2, 4 and 8 mg/kg bisoprolol administered PO to rhesus monkeys did not alter the motor activity and the threatening behaviour of rhesus monkeys. The width of the pupils and the body temperature were also not influenced.

Bisoprolol at 10, 30 or 100 mg/kg did not influence the lipid metabolism of adult normolipemic rats after repeated PO administration for 11 days, nor was there any quantitative change in the serum lipid and lipoprotein pattern in young hyperlipemic rats treated at the same dose levels for 5 days.

Bisoprolol at oral doses of 1, 3 or 10 mg/kg did neither alter the rate of the gastrointestinal transit in mice nor the volume of gastric secretion and total acidity of pylorus-ligated rats. The highest dose tested increased the free acidity significantly in rats.

Oral doses of 30 and 100 mg/kg bisoprolol administered PO to rats, had no diuretic or saluretic effect. At 300 mg/kg, bisoprolol did not influence diuresis but caused a slight and brief increase in the elimination of Cl^-, Na^+ and K^+.

Neither single nor multiple treatments (once daily during 4 days) with 1, 3 and 10 mg/kg bisoprolol orally had any influence on the spontaneous activity of mice.

Perindopril

Perindopril is an angiotensin converting enzyme (ACE) inhibitor acting through its metabolite, perindoprilat. ACE is an exopeptidase which converts angiotensin I to angiotensin II (which has vasoconstricting properties) and also degrades bradykinin (which has vasodilating properties) to an inactive heptapeptide. Pharmacological studies demonstrated the antihypertensive efficacy of perindopril in animal models of genetic HT (spontaneously hypertensive rat) or renovascular (Goldblatt model) HT.

The inhibition of ACE after acute administration of perindopril is associated with an increase of renal bradykinin in rat and a potentiation of the bradykinin effects on BP.

In a rabbit model of atherosclerosis, perindopril has shown beneficial effects in various severities of atherosclerotic lesions. These effects were also reported in mini pigs in which perindopril prevented the atherosclerosis-induced deleterious effects on the vascular wall function and structure, especially by reducing fragmentation of aortic elastic laminae.

The safety pharmacology of perindopril was tested on the central nervous system (CNS), immune system, respiratory system and gastro-intestinal tract and was shown to have no effect.

The effects of perindopril on the CNS were studied in the rat and mouse. Electroencephalographic studies in the rat showed that perindopril induced a reduction in the total sleep time and an increase in the latency of slow wave sleep from 10 mg/kg intraperitoneally (IP). In the mouse, doses up to 100 mg/kg (IP or subcutaneous (SC)), 50 mg/kg (PO) and 100 µg per animal administered by the intracisternal route demonstrated that perindopril and perindoprilat did not antagonise the response to a heat stimulus.

The immunological tolerance of perindopril was tested in vitro and in vivo, in the mouse, rat and guinea pig. In vitro, the response of the T and B lymphocytes was not modified.

The O_2 consumption and CO_2 production, as well as the arterial or venous blood gases were unchanged after administration of 1 mg/kg perindopril in the anaesthetised dog. In the anaesthetised guinea pig, perindopril (30 or 100 µg/kg, intravenous (IV)) had no effect on the reactivity of tracheobronchial muscles to histamine, acetylcholine and serotonin.

The gastro-intestinal tolerance of perindopril was studied in the rat. No effects have been detected except a slight slowing of intestinal passage at subcutaneous doses of 10 and 30 µg/kg, which was not observed at 100 µg/kg. An examination of the gastric and intestinal mucosa after PO administration of perindopril (1 to 30 mg/kg) for 4 days failed to reveal any increase in the number of mucosal ulcerations, although there was an increased frequency of melena.

Bisoprolol/perindopril combination

Bisoprolol and perindopril have distinct pharmacodynamic targets and patients treated with the fixed dose combinations will be exposed to the same levels of the active ingredients and their metabolites as those which were fully tested in clinical trials with the individual agents, which are already widely co-prescribed, as demonstrated by the IMS co-prescription data and for which the non-clinical safety assessments of both monotherapies have been extensively documented.

Both beta-blockers and ACE are considered to be cardioprotective drug therapies. Their mechanisms of action are different and complementary.

In the treatment of hypertension, beta-blockers block some of the effects of the sympathetic nervous system, which increases the heart rate and raises blood pressure with stress and/or activity. Beta-blockers lower blood pressure in part by decreasing the rate and force at which the heart pumps blood. Angiotensin-converting enzyme (ACE) inhibitors block production of angiotensin II, this causes narrowing of blood vessels and increases blood pressure. By reducing production of angiotensin II, ACE inhibitors allow blood vessels to widen, which lowers blood pressure and improves heart output. Beta-blockers are known to reduce the increase in renin that can be observed after ACE inhibition, and therefore add to the reduction in angiotensin II formation via the renin-angiotensin cascade. The combination of an ACE inhibitor and a β-blocker has been shown to reduce BP by decreasing both the peripheral vascular resistance and cardiac output.

In the treatment of stable coronary artery disease, beta-blockers and ACE-inhibitors allow to fulfil the 2 aims of the treatment being to obtain relief of symptoms and to prevent CV events. Beta-blockers act directly on the heart to reduce heart rate, contractility, atrioventricular conduction and ectopic activity. Additionally, they may increase perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas. Beta-blockers are clearly effective in controlling exercise-induced angina, improving exercise capacity and limiting both symptomatic as well as asymptomatic ischaemic episodes. ACE inhibitors should be used to prevent cardiovascular events in with CAD, especially with co-existing hypertension, LVEF ≤40%, diabetes or CKD, unless contra-indicated.

In the treatment of chronic heart failure, there is consensus that these treatments are complementary and that a beta-blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of heart failure with reduced ejection fraction. The concomitant use of β-blocker and ACE inhibitors is recommended in the respective product information of each mono-component for the treatment of HF.

All the above information supports the safety and efficacy of the concomitant use of bisoprolol and perindopril and argues against the possibility of any negative pharmacodynamic interactions.

In addition, the bisoprolol/perindopril arginine fixed dose combination is intended as a substitution therapy for patients already being treated with bisoprolol and perindopril mono-therapies given concomitantly and therefore the safety profile for the patients remains unchanged.

In line with the European guideline on the *non-clinical development of fixed combinations of medicinal products* (EMEA/CHMP/SWP/258498/2005, 2008), no pharmacodynamics interaction studies or additional safety pharmacology studies have therefore been performed with the combination.

III.3 Pharmacokinetics

Bisoprolol

The pharmacokinetic properties of [^{14}C]-bisoprolol were studied in Wistar rats, beagle dogs, and Cynomolgus monkeys. Bisoprolol was well absorbed in these species; 70-90% of the ^{14}C-dose was recovered in urine, with faecal excretion approximately 20% in rats and less than 10% in dogs and monkeys. Rats excreted approximately 10% of the dose in bile after IV as well as PO administration. The plasma half-life of the unchanged drug was approximately 1h in rats, 3h in monkeys, and 5h in dogs. The bioavailability was 40-50% in monkeys, approximately 80% in dogs, and 10% in rats. After IV administration, high levels of radioactivity were found in lung, kidneys, liver, adrenals, spleen, pancreas, and salivary glands. After PO administration, the highest concentration occurred in the liver and kidneys. Both the blood-brain and placental barriers were penetrated, but only to a small degree. No accumulation of radioactivity in tissues was observed after repeated dosing (1 mg/kg/day). The metabolism of bisoprolol was studied in the same three animal species and in humans. The major metabolites are the products of O-dealkylation and subsequent oxidation to the corresponding carboxylic acids. 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. Serum protein binding was low in all species tested in vitro (13-16% rat; 23-26% dog; 25-26% monkey; 26-33% human)

Perindopril

The pharmacokinetics and metabolism studies performed in animals by administration of [^{14}C]-perindopril tert-butylamine and [^{14}C]-perindoprilat provided complete information about the in vivo pharmacokinetics of perindopril and its metabolites in three species studied (rat, dog and monkey). The in vivo pharmacokinetics of perindopril in dogs and monkeys is qualitatively similar to its pharmacokinetics in humans and, quantitatively, the dog is the species closest to man. In rodents (especially in rats), perindopril is immediately hydrolysed into perindoprilat. Therefore these animals are not exposed to perindopril. No differences were observed in the PK parameters of perindopril, perindoprilat and their respective glucuronides after repeated PO administrations of perindopril tert-butylamine or perindopril arginine in dogs, indicating they are bioequivalent, as seen in man.

Bisoprolol/perindopril combination

No non-clinical pharmacokinetic interactions study was performed with bisoprolol fumarate/perindopril arginine fixed dose combination. Human data are available from the results of the pharmacokinetic interaction study.

III.4 Toxicology

Bisoprolol

Toxicology studies in animals have established that bisoprolol has a wide margin of safety. In multiple-dose studies in the rat and dog, findings were related to pharmacologic effects and/or were class effects known to occur with other β-blocker and thus were not specific to bisoprolol. In the rat, at high multiples of human therapeutic doses, increased serum triglycerides, focal myocardial necrosis, increased heart weight/size, and pulmonary phospholipidosis were observed. In the dog, the tolerance threshold for bisoprolol was determined by its pharmacologic actions (i.e., hypotension) which resulted in lethality as reported below. Increases in serum triglycerides and hepatocyte inclusion bodies were also seen in dogs.

Non-clinical data on bisoprolol reveal no special hazard for humans based on conventional genotoxicity testing. The mutagenic potential of bisoprolol was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, the unscheduled deoxyribonucleic acid synthesis test, the micronucleus test in mice, and the cytogenetics assay in rats. There was no evidence of mutagenic potential in these in vitro and in vivo assays.

Long-term studies were conducted with oral bisoprolol administered via the diet to mice (20 and 26 months) and rats (24 months). No evidence of carcinogenic potential was seen in mice dosed up to 250 mg/kg/day or rats dosed up to 125 mg/kg/day. These doses were associated with plasma drug concentrations which are 38 times (mice) or 15-18 times (rats) greater than those expected in humans following 10 mg/day of bisoprolol.

Reproduction studies with bisoprolol in rats did not show any impairment of fertility at doses up to 150 mg/kg/day of bisoprolol, or 375 and 77 times the maximum recommended human dose (MRHD) (20 mg) on the basis of body weight and body surface area, respectively.

In rats, bisoprolol was not teratogenic at doses up to 150 mg/kg/day, which is 375 and 77 times the MRHD on the basis of body weight and body surface area, respectively. Bisoprolol was foetotoxic (increased late resorptions) at 50 mg/kg/day and maternotoxic (decreased food intake and body weight gain) at 150 mg/kg/day. The foetotoxicity in rats occurred at 125 times the MRHD on a body weight basis and 26 times the MRHD on the basis of body surface area. The maternotoxicity occurred at 375 times the MRHD on a body weight basis and 77 times the MRHD on the basis of body surface area.

In rabbits, bisoprolol was not teratogenic at doses up to 12.5 mg/kg/day, which is 31 and 12 times the MRHD based on body weight and body surface area, respectively, but was embryolethal (increased early resorptions) at 12.5 mg/kg/day.

Perindopril

Single dose toxicity studies were performed with perindopril *tert*-butylamine in two rodent species: the mouse and rat, of both sexes, after IV and PO administrations. An additional evaluation was carried out in the beagle dog, by administering cumulative oral doses of perindopril *tert*-butylamine. In addition, the IV toxicity of perindoprilat was evaluated in the mouse and rat (safety tests to determine the maximum dose for administration). No mortality was observed by gavage in rodents at doses up to 3000 mg/kg. By IV route, the LD50 was 704 mg/kg and 679 mg/kg in M and F, respectively in the mice and 323 mg/kg and 423 mg/kg in M and F, respectively in the rat. In the dog, there was no mortality up to 1600 mg/kg after oral administration of perindopril. Salient clinical signs were emesis, decreased motor activity. Acute toxicity of perindopril arginine (2000 mg/kg) was studied in Wistar rats and Swiss mice. No mortality, no changes in body weight and food consumption, and no lesions at the necropsy were observed. The only finding was sialism (hypersalivation) in all of the treated rats. Perindopril arginine was devoid of acute toxicity after single-dose PO administration at 200 mg/kg.

Repeated oral dose toxicity studies were carried out with perindopril *tert*-butylamine in rat (Fischer and Wistar – up to 18 months), beagle dog (6 months) and Cynomolgus monkey (12 months). In general, perindopril was well tolerated after repeated oral administrations. The target organ was the kidney, with reversible damage. Based on the available exposure in animals and when compared to that in human after single oral administration of 10 mg of perindopril, the safety margin for perindoprilat ranges approximately from 2 to 4. For perindopril, the safety margin is at least 57.

No relevant mutagenic nor clastogenic potential was detected for perindopril in a comprehensive battery of tests including Ames test, mouse lymphoma assay, *in vivo* and in vitro clastogenicity tests and micronucleus test . The genotoxic potential of perindoprilat and several metabolites and/or potential impurities were also evaluated (including the Ames test) and no genotoxicity was detected.

Two studies were carried out for at least 104 weeks in the Fischer 344 rat and in the B6C3F1 mouse, given an oral treatment (drinking water) of 0.75, 2.0 and 7.5 mg/kg/day. Under the conditions of these studies, perindopril *tert*-butylamine had no carcinogenic effect.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no signs of embryotoxicity or teratogenicity. However, ACE inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

Bisoprolol/perindopril combination

No special hazard for humans is anticipated from the combination based on the studies on the individual components and their impurities. Exposure to each active substance of the fixed dose combination is no greater and no less than for the mono-components used as single agents.

III.5 Ecotoxicology/environmental risk assessment (ERA)

This application submitted in accordance with article 10b of Directive 2001/83/EC consists in a fixed dose combination of bisoprolol fumarate and perindopril arginine. The two components are already individually marketed since at least 25 years worldwide and this fixed combination is proposed for substitution in patients adequately controlled with the individual component of bisoprolol fumarate and perindopril arginine given concomitantly at the same dose.

Therefore the use of bisoprolol fumarate/perindopril arginine combinations 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 perindopril 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 perindopril is based on their complementary or synergistic effects on several pathophysiologic mechanisms. The combination is intended for use as a substitution in patients suffering from hypertension, chronic stable coronary artery disease and chronic stable congestive heart failure. 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 perindopril and presented the beneficial effects of the combination with beta-blockers and ACE-inhibitors.

To support the application the applicant has submitted one bioequivalence study and one pharmacokinetic interaction study.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Bisoprolol

Bisoprolol has an absolute biological availability of 88%.

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 impaired liver function or renal insufficiency. However, a daily dose of 10 mg should not be exceeded in patients with severely impaired hepatic or renal function.

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

The kinetics of bisoprolol are linear and independent of age. Bisoprolol can be administered in fasting or fed condition without any change of the absorption process

Perindopril

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites. The plasma half-life of perindopril is 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required.

A linear relationship has been demonstrated between the dose of perindopril and its plasma exposure.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Bisoprolol and perindopril

The applicant has conducted a pharmacokinetic interaction study. The study has proven that there is no pharmacokinetic interaction between bisoprolol and perindopril.

IV.2.2 Bioequivalence study

An open label, single centre, randomized, single dose, laboratory blinded, 2-period, 2-sequence, crossover bioequivalence study of bisoprolol fumarate/perindopril arginine 10/10 mg combination tablets (Les Laboratoires Servier) vs. bisoprolol fumarate 10 mg

tablets and perindopril arginine 10 mg tablets given concomitantly in healthy male volunteers under fasting conditions was performed in order to compare the rate and the extent of absorption of the combination product and the originator products Concor® 10 mg film coated tablets, manufactured by Merck Serono GmbH, Germany and Coversyl® 10 mg tablets, manufactured by Les Laboratoires Servier.

The bioequivalence study has been performed as required by the EMA *guideline on the investigation of the bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr, 2010).

All treatments were administered after an overnight fast of at least 10 hours. In each of the 2 study periods, either the test product (the fixed dose combination tablet containing 10 mg of bisoprolol and 10 mg of perindopril) or the reference treatment (one Concor® 10 mg tablet and one Coversyl® 10 mg tablet given concomitantly) were administered orally as a single dose under fasting conditions. The 2 periods were separated by an adequate wash-out period.

The study was conducted according to GCP and GLP.

Plasma concentrations of bisoprolol were identified and quantified using a protein precipitation extraction from human samples and a reversed-phase high-performance liquid chromatography (HPLC) with MS/MS detection.

Plasma concentrations of perindopril were measured using validated methods involving protein precipitation extraction from human samples and reversed-phase HPLC with MS/MS detection.

Plasma concentration of perindoprilat were also identified and quantified using validated methods involving protein precipitation extraction from human samples and reversed-phase HPLC with MS/MS detection.

For bisoprolol and perindopril, all acceptance criteria, as defined in the validation protocols, were fulfilled. Bioanalytical methods were found to be specific, sensitive, linear, precise, reproducible and with an adequate recovery.

Therefore, the results obtained on human plasma samples with both methods must be considered as reliable allowing a correct evaluation of the pharmacokinetic profiles of the products administered and a correct assessment of their bioequivalence.

The analytes were stable during the whole analytical procedure and when stored under the tested conditions. In particular, the potential interaction between the two active ingredients in the biological matrix was studied. The results showed the stability of all samples. All provided stability results fulfil the criteria laid in the *Guideline on bioanalytical method validation* (21 July 2011, EMEA/CHMP/EWP/192217/2009).

The following pharmacokinetic parameters were calculated:

- Area Under the Curve (AUC_T) from T_0 to the last measurable point,
- Maximum observed drug concentration C_{max},
- Other parameters such as AUC_∞, T_{max}, $AUC_{T/\infty}$, K_{el} and $T_{½el}$ were also calculated for information purposes only.

The C_{max} and AUC_T for bisoprolol and perindopril were the primary variables. They were compared statistically between treatments in order to assess bioequivalence. Two-sided 90% confidence interval of the ratio of geometric LSmeans obtained from the ln-transformed pharmacokinetic parameters was calculated.

An analysis of variance (ANOVA) using general linear models was performed with the following factors: sequence, subject within sequence, period, and treatment. Ratios of test versus reference treatment were derived together with the corresponding 90% confidence intervals. The confidence intervals (CIs) were calculated by re-transformation of the shortest CI for the difference of the Ln-transformed least squares mean values.

The statistical analyses were conducted in accordance with the EMA *Guideline on the investigation of the bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr, 2010) and *Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party* (EMA/618604/2008 Rev.8, 2013), 10 October 2013, in particular Chapter 10: Clarification on the recommended statistical method for the analysis of a bioequivalence study.

Bioequivalence in the primary parameters AUC_T and Cmax of bisoprolol and perindopril was concluded if the 90% confidence interval (CI) for the treatment FDC/ individual drugs ratio of the least-squares means was fully contained within the 80.00-125.00% acceptance range.

The pharmacokinetic variables are adequate. The predefined confidence intervals are according to the Guideline on the Investigation of Bioequivalence, AUC_T is acceptable. The mentioned guideline states that "AUC truncated at 72 h ($AUC_{(0-72h)}$) may be used as an alternative to $AUC_{(0-t)}$ for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half-life of the drug". The statistical software is acceptable. The statistics are described adequately, the methods are acceptable.

The 90% confidence intervals of the geometric mean ratios for bisoprolol and perindopril are presented in the tables below.

Bioequivalence evaluation of bisoprolol

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	Within-subject CV%
AUC_T	100.12	97.89 – 102.40	7.0
C_{max}	99.39	96.66 – 102.20	8.7

Bioequivalence evaluation of perindopril

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	Within-subject CV%
AUC_T	104.22	(100.57 – 108.01)	11.1
C_{max}	106.55	(100.48 – 112.99)	18.3

The geometric mean ratios of the AUC_T and C_{max} of the test and reference products fall within the predefined range of 80%-125% therefore fulfil the criteria of bioequivalence.

Biowaiver

The applicant has requested for a biowaiver to the 5 mg/5 mg, 5 mg/10 mg and 10 mg/5 mg bisoprolol/perindopril combinations. The product consists of two layers. The bio-waiver criteria have been laid down in the mentioned bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr, 2010 and the different strengths fulfil these criteria, since

- all strengths are manufactured by the same manufacturer and process,
- the qualitative composition of different strengths is the same,
- the composition of the strengths are quantitatively proportional by the respective layer,
- dissolution profiles for the 5 mg/5 mg, 5 mg/10 mg and 10 mg/5 mg strengths and the highest strength (10 mg/10 mg) of the batch used in the bioequivalence study are similar under identical conditions for both bisoprolol and perindopril,
- both bisoprolol and perindopril have linear pharmacokinetics in the applied dose range.

Based on the above fulfilled criteria further bioequivalence studies with these strengths can be waived.

IV.3 Pharmacodynamics

The applicant has not conducted clinical trials with the combinations but their use with mono-component preparations has been demonstrated. The literature overview is adequate.

Bisoprolol

Bisoprolol is a potent highly β1-selective-adrenoreceptor blocking agent, without intrinsic stimulating and relevant membrane stabilising activity. Its β1-selectivity extends beyond the therapeutic dose range. It only shows low affinity to the β2-receptor of the smooth muscles of bronchi and vessels as well as to the β2-receptors concerned with metabolic regulation.

Bisoprolol presents a cardioprotective activity. The most prominent effect of bisoprolol is its negative chronotropic effect, resulting in a reduction in resting and exercise heart

rate and stroke volume, leading to a reduction of the cardiac output and oxygen consumption.

For a similar reduction in brachial blood pressure, bisoprolol was shown to decrease more significantly central systolic blood pressure and aortic pulse pressure as compared to atenolol.

Bisoprolol was shown to improve endothelial function and left ventricular function.

Perindopril

Perindopril is an inhibitor of the angiotensin converting enzyme that converts angiotensin I into angiotensin II, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release), reduced secretion of aldosterone, as well as increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system).

Perindopril reduces peripheral vascular resistance, leading to BP reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate (HR). Perindopril improves the endothelial function in a number of ways, by increasing the bioavailability of nitric oxide and the activity of superoxide dismutase and through inhibition of active oxygen producing enzymes, relieving oxidative stress. It also inhibits the metabolism of bradykinin, increases intracellular Ca2+ levels, enhances expression of growth factors leading to constriction of peripheral arterioles and cardiac hypertrophy, as well as activates atherogenic signalling pathways and promotes the expression of pro-inflammatory cytokines.

Bisoprolol and perindopril combination

In the treatment of hypertension, beta-blockers block some of the effects of the sympathetic nervous system, which increases the heart rate and raises blood pressure with stress and/or activity. Beta blockers lower blood pressure in part by decreasing the rate and force at which the heart pumps blood. ACE inhibitors block production of angiotensin II that causes narrowing of blood vessels and increases blood pressure. By reducing production of angiotensin II, ACE inhibitors allow blood vessels to widen, which lowers blood pressure and improves heart output. Beta-blockers are known to reduce the increase in renin that can be observed after ACE inhibition, and therefore add to the reduction in angiotensin II formation via the renin-angiotensin cascade. The combination of an ACE inhibitor and a β-blocker has been shown to reduce BP by decreasing both the peripheral vascular resistance and cardiac output.

In the treatment of stable coronary artery disease, beta-blockers and ACE inhibitors allow to fulfil the two aims of the treatment being to obtain relief of symptoms and to prevent CV events. Beta-blockers act directly on the heart to reduce heart rate, contractility, atrioventricular conduction and ectopic activity. Additionally, they may increase

perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas. Beta-Blockers are clearly effective in controlling exercise-induced angina, improving exercise capacity and limiting both symptomatic as well as asymptomatic ischaemic episodes. ACE inhibitors should be used to prevent cardiovascular events in with CAD, especially with co-existing hypertension, left ventricular ejection fraction (LVEF) ≤40%, diabetes or chronic kidney disease, unless contra-indicated.

In the treatment of chronic heart failure, there is consensus that these treatments are complementary and that a beta-blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of heart failure with reduced ejection fraction.

Therefore, it is established that bisoprolol and perindopril have complementary mode of action, reinforced by their specific pharmacodynamics properties, and represent useful combination in patients with hypertension and/or stable coronary artery disease and/or chronic heart failure.

The combination tablet may provide a better compliance of the patients than the separate pills. The Applicant provided details of the co-prescription of bisoprolol and perindopril from various countries. The provided data are sufficient to support the need of the applied fix dose combinations of bisoprolol and perindopril.

IV.4 Clinical efficacy

No specific clinical efficacy studies have been performed and none 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*. Nevertheless, the applicant has summarized the results of several open label combination studies conducted with bisoprolol and perindopril in all three claimed indications. Furthermore, the Applicant has submitted the post-hoc analyses of the studies EUROPA, CONFIDENCE II, PROTECT I and PROTECT III (Shake the Habit). All the results support the beneficial effect of bisoprolol/perindopril combination in all three claimed indications.

Co-prescription data

The applicant has provided co-prescription data as a study report to justify the dose selection from several European countries.
The results show that among prescriptions of perindopril with beta-blockers collected within the frame of the proposed indications**,** bisoprolol was the most frequently co-prescribed beta-blocker with perindopril.

The provided co-prescription data are sufficient to support the need of the applied fixed dose combinations of bisoprolol and perindopril.

When a combination product is intended for substitution indication only, its prescription merely complies with a widely used medical approach. Therapeutic considerations are mainly based on therapeutic and not regulatory guidelines. The applicant has referred to those guidelines as well. The co-prescription and efficacy data support the need for such a combination product.

The data provided are sufficient to prove the efficacy of the combination in all three claimed indications.

IV.5 Clinical safety

Further safety assessment of bisoprolol/perindopril combinations was based on the post-hoc analysis of the studies CONFIDENCE II, PROTECT I and PROTECT III (Shake the Habit) for hypertension, the post-hoc analysis of EUROPA study for coronary artery disease, the CIBIS II study for heart failure as well as on the applicant's own pharmacovigilance database. The analyses show that the safety profile of the combination is not different from the well-established safety profiles of bisoprolol and perindopril. The most expected common safety concern is hypotension. Since bisoprolol/perindopril fixed dose combination is developed as a substitution therapy in patients already treated with bisoprolol and perindopril given concomitantly in the same dose as in the combination it is unlikely that new risks would emerge after switching to the combination. Therefore the safety of the bisoprolol/perindopril fixed dose combination is acceptable.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• Hypotension. • Hyperkalaemia. • Neutropenia / agranulocytosis / thrombocytopenia. • Angioedema. • Foetotoxicity / use during 2nd and 3rd trimesters of pregnancy. • Bradycardia. • Hypoglycaemia. • Second or third degree atrioventricular blocks.

Summary of safety concerns	
Important potential risks	Use during 1st trimester of pregnancy
Missing information	Lactating women

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the bisoprolol fumarate/perindopril arginine 5 mg/5 mg, 5 mg/10 mg, 10mg /5 mg and 10 mg/10 mg film-coated tablets of EGIS Pharmaceuticals Plc. No additional activities are proposed.

Risk Minimisation Measures: routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to the bisoprolol fumarate/perindopril arginine 5 mg/5 mg, 5 mg/10 mg, 10mg /5 mg and 10 mg/10 mg film-coated tablets of EGIS Pharmaceuticals Plc. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

With regard to PSUR submission, the marketing authorisation holder should take the following into account:

- Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lock Points (DLP) and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

According to the latest published EURD list (3 June 2016, EMA/630645/2012 Rev. 44) the bisoprolol-perindopril combination has a PSUR submission frequency of 5 years. Since the authorisation of this product based on Article 10b of Directive 2001/83/EC there is no waive for this product and MAH should submit PSURs routinely. The submission deadline for the first PSUR is 01. 20. 2021, the DLP is 10. 22. 2020.

IV.7 Discussion on the clinical aspects

The application concerns a fixed dose combination of bisoprolol fumarate and perindopril arginine. The suggested indication is substitution therapy for patients suffering from hypertension or chronic stable coronary artery disease or chronic stable congestive heart failure 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 several 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

V.1 Summary

The present applications concern Scaliant 5 mg/ 5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets, fixed-dose combinations of bisoprolol fumarate and perindopril arginine. The applicant and the holder of marketing authorisation is EGIS Pharmaceuticals Plc. (Hungary) in the RMS.

The indication of the fixed-dose combinations are as follows.

> For the 5 mg/5 mg and 10 mg/5mg strengths: the tablets are indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularisation) and/or stable chronic heart failure with reduced systolic left ventricular function in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.
>
> For the 5 mg/10 mg and 10 mg/10 mg strengths: the tablets are indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularization) in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.

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

The applicant has adequately demonstrated bioequivalence between the products and reference products containing the single active components. The reference products were Concor® (bisoprolol fumarate) and Coversyl® (perindopril arginine) tablets which were the original products of Merck KGAA and Les Laboratoires Servier, respectively.

Moreover, the applicant provided sufficient co-prescription data from several European countries demonstrating the use of bisoprolol and perindopril monocomponent preparations in combination.

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 Scaliant 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

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. 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