

**PHARMACEUTICAL COMPOSITION COMPRISING A BETA BLOCKER,
A CONVERTING ENZYME INHIBITOR AND
AN ANTIHYPERTENSIVE OR A NSAID**

Technical field

- 5 The present invention relates to a fixed pharmaceutical composition comprising a beta blocker, an angiotensin converting enzyme inhibitor (CEI) and a 3rd therapeutic agent, and to the use of said composition in the treatment and prevention of cardiovascular diseases and more especially arterial hypertension and/or stable coronary artery disease.
- 10 More especially, the present invention relates to a fixed pharmaceutical composition comprising a beta blocker, an angiotensin converting enzyme inhibitor (CEI) and a 3rd therapeutic agent, wherein:
- the beta blocker is bisoprolol or an addition salt thereof with a pharmaceutically acceptable acid, their hydrates and crystalline forms,
 - 15 - the converting enzyme inhibitor is perindopril or an addition salt thereof with a pharmaceutically acceptable acid or base, their hydrates and crystalline forms, and
 - the 3rd therapeutic agent is selected from another antihypertensive or a non-steroidal anti-inflammatory drug.

Prior art/context of the invention

- 20 Cardiovascular diseases are the leading cause of death both in developed countries and in developing countries, they are responsible for one third of deaths. Deaths associated with cardiovascular diseases are expected to increase to 23.3 million in 2030.

- 25 In Europe, cardiovascular diseases are the leading cause of premature mortality and of disability-adjusted life years in men and women, causing almost 4.1 million deaths per year, that is to say 46% of all deaths. Almost 1.8 million of these deaths (20% of all deaths) are due to a coronary heart disease (CHD). One in six men and one in seven women in Europe will die of a myocardial infarction (MI).

Hypertension and coronary artery disease are major steps of the cardiovascular disease continuum, which culminates in the development of advanced-stage cardiac diseases. Hypertension is the leading cause of death in the world, causing approximately 7.5 million deaths (which represents approximately 13% of deaths). Coronary artery disease is the most frequent consequence of hypertension and is the leading cause of death in Europe. Heart failure is the terminal pathology, the consequence of numerous cardiac diseases. The mortality rate currently still remains high with 50% survival at 5 years.

Consequently, it is necessary to optimise the care and treatment strategy for patients.

Chronic diseases such as cardiovascular diseases generally require long-term multi-therapy, which increases the risk of non-compliance with the treatment and also the associated safety concerns. Patients are classed as non-compliant if the proportion of days on which treatment is covered is less than 0.80.

Fixed associations allow treatment to be simplified by reducing the daily number of tablets, and consequently they have the potential to improve patients' adherence to treatment.

A meta-analysis of nine studies has been carried out, comparing the administration of a fixed combination and of the individual components. The effectiveness of the compliance with a combined therapy in comparison with a therapy of administration of the individual components was examined. This meta-analysis evaluated the use of fixed combined therapies in different clinical contexts, including hypertension, heart failure, myocardial infarction, hypercholesterolaemia, diabetes, tuberculosis, and infection with the human immunodeficiency virus. The results of this meta-analysis showed far better compliance with the fixed combinations as compared with the administration of the separate components. The rate of compliance was improved by 26% in the patients receiving fixed combinations.

The use of polypills for the treatment of secondary cardiovascular diseases has received increasing attention as well as the support of the World Health Organisation (WHO) and the World Heart Federation (WHF).

The European Society of Cardiology (ESC), in its guidelines, especially those of 2012 and 2013, specifically recommends the association of beta blockers and CEIs for the treatment and/or prevention of arterial hypertension in heart failure patients post infarction or suffering from atrial fibrillation. More generally, beta blockers and CEIs can also be used on their own

or in association as initial treatment or maintenance treatment for arterial hypertension.

Two objectives have been expressed for the treatment of stable coronary artery disease, namely:

- a) Improvement of symptoms and control of the cardiac rhythm: beta blockers are indicated
5 as first line treatment (direct action on the heart, improvement of perfusion in the ischaemic zone), and
 - b) Prevention of the occurrence of cardiovascular events, especially in the case of a concomitant pathology such as hypertension, heart failure or diabetes.
- 10 Bisoprolol and perindopril are both approved active ingredients for medicaments which have been marketed throughout the world for several years. Their efficacy and tolerance profiles are consequently well established. Medicaments comprising these two active ingredients are widely used in medical practice and are very often co-prescribed. In fact, the medicaments in question have common indications, namely hypertension and coronary artery disease.
- 15 Moreover, their mechanisms of action are complementary and their beneficial effects on morbimortality in cardiovascular diseases have been demonstrated in large-scale clinical trials (the CIBIS study for bisoprolol and the EUROPA study for perindopril).

The beta blockers which are co-prescribed with perindopril include acebutolol, atenolol, bisoprolol, metoprolol and nebivolol. Bisoprolol is the beta blocker that is most co-prescribed
20 with perindopril, followed by atenolol.

The doses of perindopril and bisoprolol that are most co-prescribed in the two target indications of the association, namely hypertension and stable coronary artery disease, are indicated in the table below:

Table 1: Number of co-prescriptions of perindopril and bisoprolol
– IMS Health 2011-2013; 5 countries*

		Prescriptions	Total %
Total perindopril + bisoprolol		1 894 791	
Perindopril 10 & 8 mg	Total bisoprolol		
	10 mg	161 675	8.5%
	7.5 mg	21 550	1.1%
	5 mg	167 391	8.8%
	3.75 mg	13 616	0.7%
	2.5 mg	63 349	3.3%
	1.25 mg	44 623	2.4%
Perindopril 5 & 4 mg	Total bisoprolol		
	10 mg	234 362	12.4%
	7.5 mg	13 819	0.7%
	5 mg	502 932	26.5%
	3.75 mg	13 406	0.7%
	2.5 mg	221 926	11.7%
	1.25 mg	145 617	7.7%
Perindopril 2.5 & 2 mg	Total bisoprolol	0	
	10 mg	66 830	3.5%
	7.5 mg	7 233	0.4%
	5 mg	44 976	2.4%
	3.75 mg	19 126	1.0%
	2.5 mg	69 637	3.7%
	1.25 mg	82 723	4.4%

*IMS – Dec 2011 – Dec 2013; 5 countries, France, Hungary, Belgium, Italy, Romania
Diag: I10, I11, I20.9, I25 & I50

The doses of perindopril are expressed in terms of arginine salt (2.5 mg, 5 mg or 10 mg) or in terms of *tert*-butylamine salt (2 mg, 4 mg or 8 mg), and the doses of bisoprolol are expressed in terms of base.

The 5 mg dose of perindopril arginine salt followed by 10 mg is the dose that is most co-prescribed with bisoprolol 2.5 mg, 5 mg and 10 mg.

There is therefore a real need for a fixed pharmaceutical composition comprising a beta blocker and a CEI for use in the treatment and prevention of cardiovascular diseases and more especially the treatment of arterial hypertension and stable coronary artery disease.

It is within this context that the present invention proposes to develop a new fixed combination comprising a beta blocker such as bisoprolol, an antihypertensive selected from a

CEI such as perindopril, and at least a 3rd therapeutic agent selected from another antihypertensive or a non-steroidal anti-inflammatory drug (NSAID).

Summary of the invention

5 The present invention relates to a fixed pharmaceutical composition comprising a beta blocker, an angiotensin converting enzyme inhibitor (CEI) and at least a 3rd therapeutic agent, and to the use of said composition in the treatment and prevention of cardiovascular diseases and more especially arterial hypertension or stable coronary artery disease.

10 More especially, the present invention relates to a fixed pharmaceutical composition comprising a beta blocker, an angiotensin converting enzyme inhibitor (CEI) and at least a 3rd therapeutic agent, wherein:

- the beta blocker is bisoprolol or an addition salt thereof with a pharmaceutically acceptable acid, and more especially the fumarate salt thereof, their hydrates and crystalline forms,
- the converting enzyme inhibitor is perindopril or an addition salt thereof with a 15 pharmaceutically acceptable acid or base, and more especially the *tert*-butylamine, tosylate or arginine salts thereof, their hydrates and crystalline forms, and
- the 3rd therapeutic agent is selected from:
 - o another antihypertensive which is a calcium channel inhibitor or a diuretic, or
 - o a non-steroidal anti-inflammatory drug (NSAID).

20 The calcium channel inhibitor that is preferably used belongs to the class of the dihydropyridines and is amlodipine or an addition salt thereof with a pharmaceutically acceptable acid or base, and more especially the besylate or maleate salts thereof, their hydrates and crystalline forms.

25 The diuretic that is preferably used is indapamide or an addition salt thereof with a pharmaceutically acceptable acid or base, their hydrates and crystalline forms.

The NSAID that is preferably used is acetylsalicylic acid, or aspirin, or an addition salt thereof with a pharmaceutically acceptable acid or base, their hydrates and crystalline forms.

Detailed description of the invention

The present invention relates to a fixed pharmaceutical composition comprising bisoprolol or its pharmaceutically acceptable salts, their hydrates and crystalline forms, perindopril or its pharmaceutically acceptable salts, their hydrates and crystalline forms, and a 3rd therapeutic agent, and to the use of said composition in the treatment or prevention of cardiovascular diseases.

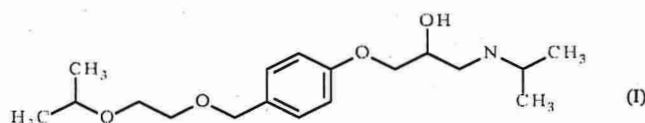
The present invention relates also to a fixed pharmaceutical composition comprising bisoprolol, perindopril and, as the 3rd therapeutic agent, a calcium channel inhibitor which is amlodipine or its pharmaceutically acceptable salts, their hydrates and crystalline forms, and to the use of said composition in the treatment or prevention of cardiovascular diseases.

The present invention relates also to a fixed pharmaceutical composition comprising bisoprolol, perindopril and, as the 3rd therapeutic agent, a diuretic which is indapamide or its pharmaceutically acceptable salts, their hydrates and crystalline forms, and to the use of said composition in the treatment or prevention of cardiovascular diseases.

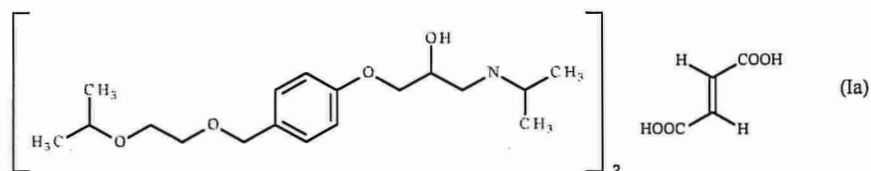
The present invention relates also to a fixed pharmaceutical composition comprising bisoprolol, perindopril and, as the 3rd therapeutic agent, a non-steroidal anti-inflammatory drug (NSAID) which is acetylsalicylic acid, also called aspirin, or its pharmaceutically acceptable salts, their hydrates and crystalline forms, and to the use of said composition in the treatment or prevention of diseases.

Cardiovascular diseases are understood more precisely as being the treatment or prevention of arterial hypertension or stable coronary artery disease.

Bisoprolol, or (R,S)1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[1-methylethyl]-amino]-2-propanol, of formula (I):



is a beta blocker. Bisoprolol has previously been described in French patent FR 2 367 053 or US 4 258 062. Bisoprolol fumarate is a white powder of formula (Ia):



Bisoprolol fumarate, which is marketed under the name Cardensiel®, is indicated in the treatment of stable chronic heart failure with reduced left systolic ventricular function, as a supplement to converting enzyme inhibitors (CEIs) and diuretics and, optionally, cardiac glycosides. Cardensiel® is a divisible or non-divisible film-coated tablet obtained by conventional direct compression. The various dosages of Cardensiel® available are 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, expressed in terms of bisoprolol fumarate, with an initial dosage of 1.25 mg once per day, which is then increased gradually up to 10 mg, which is the maintenance dose. Whatever the dose, the dosage is always one administration per day.

Two fixed associations comprising bisoprolol are currently marketed: Lodoz® and Asabis®:

(a) The association of bisoprolol fumarate and hydrochlorothiazide which is marketed under the name Lodoz® is indicated for slight to moderate arterial hypertension. Lodoz® is a monolayer film-coated tablet obtained by conventional direct compression. The various dosages of Lodoz® available are:

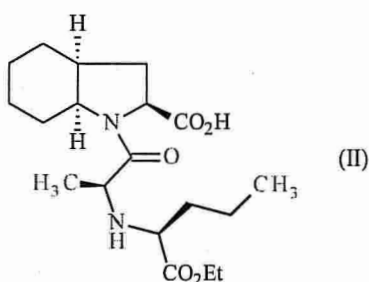
Lodoz®	Per tablet (in mg)		
Bisoprolol fumarate	2.5	5	10
Hydrochlorothiazide	6.25	6.25	6.25

(b) The association of bisoprolol fumarate and acetylsalicylic acid which is marketed under the name Asabis® is indicated for the treatment of hypertension in patients who have previously been stabilised with the individual components, and for the treatment of angina pectoris in patients who have previously been stabilised with the individual components. Asabis® is a capsule containing bisoprolol fumarate, which is either in the form of a simple mixture of bisoprolol/excipients or in the form of granules, and acetylsalicylic acid in the form of a film-coated tablet. The various dosages of Asabis® available are:

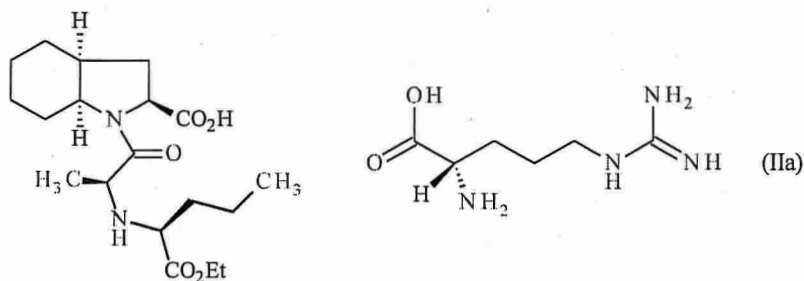
Asabis®	Per tablet (in mg)	
Bisoprolol fumarate	5	10
Acetylsalicylic acid	75	75

Patent application EP 2 359 815 describes the association of bisoprolol fumarate and amlodipine besylate and the use thereof in the treatment of hypertension and angina pectoris. The pharmaceutical composition comprising bisoprolol and amlodipine is either a monolayer tablet obtained by conventional direct compression, or a capsule in which bisoprolol and
5 amlodipine are in powder form.

Perindopril, or (2S)-2-[(1S)-carbethoxybutylamino]-1-oxopropyl-(23,3aS,7aS)perhydroindole-carboxylic acid, of formula (II):



10 is an angiotensin I converting enzyme inhibitor (CEI). Perindopril has previously been described in patent EP 0 049 658. In that European patent, in conventional manner, it is mentioned that the compounds of the invention can be in the form of addition salts with a pharmaceutically acceptable base or mineral or organic acid. Patents EP 0 308 341, EP 1 256 590, EP 1 268 424, EP 1 279 665, EP 1 321 471, EP 1 333 026, EP 1 362 864,
15 EP 1 367 061, EP 1 367 062, EP 1 367 063, EP 1 371 659, EP 1 380 590, EP 1 380 591, EP 1 403 275, EP 1 420 028, EP 1 420 029, EP 1 422 236, EP 1 603 558 and EP 1 7533 720 describe a method for obtaining perindopril salts, more specifically the *tert*-butylamine salt. The L-arginine salt of perindopril of formula (IIa) was described for the first time in European patent EP 1 354 873:



20 The alpha and beta crystalline forms of the L-arginine salt of perindopril have been described in European patents EP 1 989 182 and EP 2 016 051, respectively, the delta crystalline form has been described in European patent EP 2 612 850, and the gamma crystalline form has been described in international application WO 2009/157018.

Perindopril, which is marketed under the name Coversyl®, is indicated in the treatment of arterial hypertension, of stable coronary artery disease, especially for the risk of cardiac events in patients with a past history of myocardial infarction and/or revascularisation, and of heart failure, especially for the treatment of symptomatic heart failure. Coversyl® is a divisible or non-divisible monolayer film-coated tablet. The various dosages of Coversyl® available are: 2.5 mg, 5 mg and 10 mg, expressed in terms of perindopril arginine, or 1.6975 mg/2.5 mg tab.; 3.395 mg/5 mg tab.; 6.790 mg/10 mg tab., expressed in terms of perindopril. The dosage must be adapted to the patient. However, the recommended initial dose is 5 mg per day, given in the morning.

Two fixed associations comprising perindopril are currently marketed: Coveram® and Bipreterax®:

- (a) The association of perindopril arginine and amlodipine besylate which is marketed under the name Coveram® is indicated for the treatment of essential arterial hypertension and/or of stable coronary artery disease, as a substitution, in patients who are already controlled with perindopril and amlodipine taken simultaneously at the same dosage. Coveram® is a monolayer tablet. The various dosages of Coveram® available are:

Coveram®	Per tablet (in mg)			
Perindopril arginine	5	5	10	10
(that is to say, in terms of perindopril: 3.395 mg/tab. containing 5 mg perindopril arginine or 6.790 mg/tab. containing 10 mg perindopril arginine)				
Amlodipine	5	10	5	10
(in the form of amlodipine besylate: 6.935 mg/tab. containing 5 mg amlodipine or 13.870 mg/tab. containing 10 mg amlodipine)				

- (b) The association of perindopril arginine and indapamide which is marketed under the name Bipreterax® is indicated for the treatment of essential arterial hypertension and is also indicated in patients for whom the arterial pressure is insufficiently controlled by perindopril on its own. Bipreterax® is a monolayer film-coated tablet. The various dosages of Bipreterax® available are:

Bipreterax®	Per tablet (in mg)	
Perindopril arginine	5	10
(that is to say, in terms of perindopril: 3.395 mg/tab. containing 5 mg perindopril arginine or 6.790 mg/tab. containing 10 mg perindopril arginine)		
Indapamide	1.25	5

Patent EP 1 800 678 describes the association of ivabradine and perindopril and the use thereof in the treatment of arterial hypertension. Patent application EP 2 404 600 describes the use of the same association in the treatment of heart failure.

Two other fixed associations with perindopril which have obtained marketing authorisation (MA) in Europe are Triplixam® and Cosyrel®.

The association of perindopril arginine, indapamide and amlodipine besylate which is marketed under the name Triplixam® is indicated for the treatment of essential arterial hypertension, as a substitution, in patients already controlled with the fixed-dose association perindopril/indapamide and amlodipine, taken simultaneously at the same dosages.

Triplixam® is a monolayer tablet. The various dosages of Triplixam® available are:

Triplixam®	Per tablet (in mg)				
Perindopril arginine	2.5	5	5	10	10
(that is to say, in terms of perindopril: 1.6975 mg/tab. containing 2.5 mg perindopril arginine or 3.395 mg/tab. containing 5 mg perindopril arginine or 6.790 mg/tab. containing 10 mg perindopril arginine)					
Indapamide	0.6258	1.25	1.25	2.5	2.5
Amlodipine	5	5	10	5	10
(in the form of amlodipine besylate: 6.935 mg/tab. containing 5 mg amlodipine or 13.870 mg/tab. containing 10 mg amlodipine)					

The association of perindopril arginine and bisoprolol fumarate which has obtained MA under the name Cosyrel® is indicated for the treatment of hypertension, stable coronary artery diseases or chronic heart failure, as a substitution, in patients already controlled with perindopril and bisoprolol, taken simultaneously at the same dosages. Cosyrel® is a bilayer

tablet. The various dosages of Cosyrel® available are:

Cosyrel®	Per tablet (in mg)			
Perindopril arginine	5	5	10	10
(that is to say, in terms of perindopril: 3.395 mg/tab. containing 5 mg perindopril arginine or 6.790 mg/tab. containing 10 mg perindopril arginine)				
Bisoprolol fumarate	5	10	5	10

To date and to our knowledge, there is no fixed pharmaceutical composition which combines a beta blocker, a CEI and:

- a calcium channel inhibitor, or
- a diuretic, or
- 5 - a NSAID.

There is therefore a real need for patients suffering from cardiovascular diseases such as arterial hypertension or stable coronary artery disease to have the benefit of such a fixed pharmaceutical composition.

- 10 A fixed pharmaceutical composition has the advantage that it allows the manufacturing costs to be reduced but, above all, it permits better compliance with the treatment on the part of the patients and, consequently, better control of their pathology.

In the present invention, the fixed therapeutic combination of at least three active ingredients belonging to different therapeutic classes having complementary effects, which are

- 15 1) bisoprolol, 2) perindopril as well as:

- a) amlodipine, or
- b) indapamide, or
- c) acetylsalicylic acid,

therefore has the advantage of simultaneously targeting several risk factors which are
20 responsible for cardiovascular diseases.

The use of these fixed therapeutic combinations:

- bisoprolol + perindopril + amlodipine,
- bisoprolol + perindopril + indapamide, and
- 25 - bisoprolol + perindopril + acetylsalicylic acid

is the treatment or prevention of arterial hypertension or stable coronary artery disease as substitution therapy in adult patients who are controlled jointly in monotherapy with

bisoprolol, perindopril and/or the active ingredients a) to c) at the same doses as those present in the fixed pharmaceutical composition.

5 The fixed pharmaceutical composition according to the invention is to be taken once per day in the morning.

It is therefore possible to simplify the taking of a treatment in patients receiving medicaments separately and thus improve compliance by limiting the number of tablets.

10 All the active ingredients mentioned hereinbefore are medicaments which have obtained marketing authorisation and which have been marketed throughout the world for many years. All these components are well known active substances with well established efficacy and tolerance.

15 Bisoprolol is a beta blocker with a high affinity for the beta-1 receptors, without intrinsic sympathomimetic activity or a membrane stabilising effect. Bisoprolol in the form of the fumarate salt is marketed under the name Cardensiel® and is indicated for the treatment of stable chronic heart failure with reduced left systolic ventricular function, in addition to converting enzyme inhibitors and diuretics and, optionally, cardiac glycosides.

20 Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (angiotensin converting enzyme ACE). This converting enzyme, or kinase, is an exopeptidase which permits the conversion of angiotensin I into vasoconstrictive angiotensin II, causing degradation of vasodilatory bradykinin to an inactive heptapeptide. Perindopril in the form of
25 the arginine salt is marketed under the name Coversyl® and is indicated for:

- the treatment of arterial hypertension,
- reducing the risk of cardiac events in patients with a past history of myocardial infarction and/or revascularisation, and
- the treatment of symptomatic heart failure.

30 Amlodipine is a calcium ion flux inhibitor belonging to the dihydropyridine family (slow calcium channel blocker or calcium channel inhibitor) and inhibits the transmembrane entry

of calcium ions into the cardiac muscle and the vascular smooth muscle. Amlodipine in the form of the besylate salt is marketed under name Amlor® and is indicated for:

- hypertension,
- chronic stable angina, and
- 5 - vasospastic angina.

Indapamide is a sulfamide diuretic, pharmacologically related to the thiazide diuretics. Indapamide hemihydrate is marketed under the name Fludex® and is indicated for the treatment of arterial hypertension.

○ 10 Acetylsalicylic acid is a platelet activation inhibitor: by blocking platelet cyclo-oxygenase by acetylation, it inhibits the synthesis of thromboxane A₂, a physiological activator substance released by the platelets, and which would play a role in the complications of atheromatous lesions. Acetylsalicylic acid 100 mg is marketed, for example, under the name Aspirin Protect® and is indicated for:

- the prevention of secondary cardiovascular and cerebrovascular complications in
- 15 patients having an ischaemic atheromatous disease (for example: myocardial infarction, stable and unstable angina, complete or transient cerebrovascular accident of ischaemic origin),
- the prevention of thromboembolic events after surgery or vascular intervention, and
- reduction of the occlusion of grafts following coronary artery bypass.

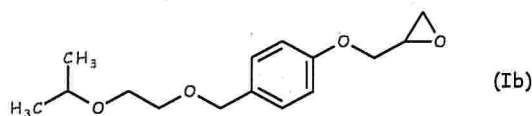
○ 20 One of the major risks of fixed pharmaceutical combinations results from a possible interaction between the different active ingredients present in the combination. In addition, the active ingredients may prove to be incompatible with some excipients which are nonetheless necessary for the formulation of one or other of the active ingredients.

25 However, one of the major risks of fixed pharmaceutical combinations results from a possible interaction between the different active ingredients present in the combination.

Apart from excipients, when the active ingredients are formulated alone, bisoprolol alone, perindopril alone, or the 3rd therapeutic agent alone, they may contain impurities and/or

30 degradation products in the starting materials, but also potential impurities in the end product.

For example, one of the organic impurities that results from the synthesis route of bisoprolol is epoxibiso or 1-[4-[(2-isopropoxyethoxy)methyl]phenoxy]-2,3-epoxypropane of formula (Ib):



- 5 This impurity epoxibiso is always present in the starting material.

When three active ingredients are present in a fixed pharmaceutical composition, in addition to the constraints associated with the active ingredients alone, there may be problems of underdosage in the final composition, but also problems of stability of the active ingredients as well as the appearance of new impurities in addition to the already known impurities of the active ingredients taken in isolation.

- 10 All the fixed associations of perindopril currently on the market and Triplixam®, which has just obtained its MA, are monolayer tablets. No problem of underdosage of the active ingredients or of stability or of formation of new impurities has been reported with the fixed pharmaceutical compositions.

- 15 The fixed association Cosyrel®, which contains perindopril and bisoprolol and has just obtained its MA, is the only fixed association of perindopril which is in the form of a bilayer tablet. In fact, whether it is the monolayer tablet obtained by direct compression or the monolayer tablet obtained by wet granulation, the formulations did not give satisfactory results from the point of view of dosage and/or stability. A tablet in bilayer form made it possible to propose a solution to the disadvantages mentioned hereinbefore.

- 20 Compatibility analyses performed by the Applicant for the different active ingredients of the present invention have shown that there is incompatibility when the 3 active ingredients, each in powder form, are mixed. Table A below shows the degradation of the active ingredients in the case of the association of bisoprolol, perindopril and amlodipine.

- 25 According to the results of Table A, in the fixed pharmaceutical composition according to the invention which comprises bisoprolol, perindopril and amlodipine, it is necessary to separate

on the one hand the bisoprolol from the perindopril and on the other hand the bisoprolol from the amlodipine and the perindopril from the amlodipine.

Table A : Compatibility study of the active ingredients

Active ingredients	Known impurities of bisoprolol	Known impurities of perindopril	Known impurities of amlodipine
Bisoprolol	0.01	-	-
Perindopril	-	0.88	-
Amlodipine	-	-	0.00
Bisoprolol + perindopril	0.32	3.85	-
Bisoprolol + amlodipine	1.76	-	2.28
Perindopril + amlodipine	-	1.03	0.09
Bisoprolol + perindopril + amlodipine	0.34	5.74	2.22

- 5 In order to obtain a stable fixed pharmaceutical composition comprising at least three active ingredients, it is therefore found to be necessary to physically separate the active ingredients.

The present invention solves this problem because the Applicant has developed a fixed pharmaceutical composition in capsule form comprising mini-granules of the different active ingredients or else mini-granules of the different active ingredients and gastro-resistant aspirin tablets. When the 3 active ingredients are in the form of granules, there cannot be any interaction between the 3 active ingredients simultaneously inasmuch as they cannot be in contact simultaneously. In the case of the present invention, contact between the active ingredients is only possible 2 by 2, thus avoiding simultaneous contact between all the active ingredients present in the capsule.

The present invention solves the problem by developing a fixed pharmaceutical composition comprising bisoprolol, perindopril and amlodipine, in which composition interactions between the different active ingredients and interactions with the excipients are non-existent. Moreover, in this composition, the active ingredients are bioequivalent to the individual compounds which are the marketed individual tablets.

More especially, the present invention proposes a fixed pharmaceutical composition in capsule form comprising bisoprolol, perindopril and amlodipine and in which:

- the bisoprolol is in the form of mini-granules,
- the perindopril is in the form of mini-granules, and
- the amlodipine is in the form of mini-granules.

5 Likewise and for the same reasons as mentioned hereinbefore, the present invention also comprises a fixed pharmaceutical composition comprising:

- A) bisoprolol mini-granules, perindopril mini-granules and amlodipine mini-granules,
- B) bisoprolol mini-granules, perindopril mini-granules and gastro-resistant aspirin tablets.

10 In the fixed pharmaceutical composition comprising bisoprolol, perindopril and aspirin, the aspirin is in the form of gastro-resistant tablets, allowing therapeutic equivalence relative to gastro-resistant tablets of aspirin alone to be obtained.

All the fixed pharmaceutical compositions according to the invention comprise pharmaceutically acceptable salts in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms.

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The present invention relates also to fixed pharmaceutical compositions comprising bisoprolol and its pharmaceutically acceptable salts, perindopril and its pharmaceutically acceptable salts, and either amlodipine and its pharmaceutically acceptable salts or indapamide and its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, in which:

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- the doses of bisoprolol vary from 2.10 to 8.50 mg, expressed in terms of bisoprolol base, or vary from 2.5 mg to 10 mg, expressed in terms of bisoprolol fumarate,
- the doses of perindopril vary from 1.65 mg to 9.512 mg, expressed in terms of perindopril base, or vary from 2.5 mg to 14 mg, expressed in terms of perindopril arginine,
- the doses of amlodipine vary from 2.5 to 10 mg, expressed in terms of amlodipine base, or vary from 3.47 mg to 13.89 mg, expressed in terms of amlodipine besylate,
- the doses of indapamide vary from 0.625 mg to 2.5 mg, expressed in terms of indapamide base,
- the doses of aspirin are from 75 mg to 150 mg, expressed in terms of aspirin base.

Preferably, in the fixed pharmaceutical compositions according to the invention, the doses:

- of bisoprolol fumarate are 2.5 mg, 5 mg and 10 mg,
- of perindopril arginine are 2.5 mg, 3.5 mg, 5 mg, 7 mg, 10 mg and 14 mg,
- of amlodipine besylate are 2.5 mg, 5 mg and 10 mg,
- 5 - of indapamide are 0.625 mg, 1.25 mg, 1.5 mg and 2.5 mg, and
- of aspirin are 75 mg, 100 mg and 150 mg.

The fixed pharmaceutical compositions according to the invention that are most particularly preferred are the pharmaceutical compositions comprising:

- a) 5 mg of bisoprolol fumarate and 5 mg or 10 mg of perindopril arginine,
 - 10 b) 10 mg of bisoprolol fumarate and 5 mg or 10 mg of perindopril arginine,
- and each additionally comprise
- i) either 5 mg or 10 mg of amlodipine besylate
 - ii) or 1.25 mg or 2.5 mg of indapamide,
 - iii) or 100 mg of aspirin.

15 The fixed pharmaceutical compositions according to the invention that are yet more preferably preferred are the pharmaceutical compositions comprising:

- i) 5 mg of bisoprolol fumarate, 5 mg of perindopril arginine and
 - a. either 5 mg of amlodipine besylate,
 - b. or 1.25 mg of indapamide,
 - 20 c. or 100 mg of aspirin
- ii) 5 mg of bisoprolol fumarate, 10 mg of perindopril arginine and
 - a. either 5 mg of amlodipine besylate,
 - b. or 2.5 mg of indapamide,
 - c. or 100 mg of aspirin
- 25 iii) 5 mg of bisoprolol fumarate, 10 mg of perindopril arginine and 10 mg of amlodipine besylate
- iv) 10 mg of bisoprolol fumarate, 10 mg of perindopril arginine and
 - a. either 10 mg of amlodipine besylate,
 - b. or 2.5 mg of indapamide
 - 30 c. or 100 mg of aspirin
- v) 10 mg of bisoprolol fumarate, 5 mg of perindopril arginine and
 - a. either 1.25 mg of indapamide

b. or 100 mg of aspirin.

The above-mentioned fixed pharmaceutical compositions according to the invention all comprise one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms.

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In addition to bisoprolol, perindopril, amlodipine, indapamide and aspirin, said pharmaceutical compositions contain one or more excipients or carriers chosen from diluents, lubricants, binders, disintegrators, surfactants, enteric coatings, absorbents, colourings, sweeteners, etc.

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There may be mentioned by way of non-limiting example:

- ♦ *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- ♦ *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- 15 ♦ *for the binders*: magnesium aluminium silicate, starch, gelatin, tragacanth, cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinylpyrrolidone,
- ♦ *for the disintegrators*: agar, starch, alginic acid and its sodium salt, effervescent mixtures, carboxymethylcellulose salts, carboxymethyl starch salts, polyvinylpyrrolidone
- 20 derivatives.

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The dosage used varies according to the age of the patient, the nature of the disorder, and any associated pathologies and treatments. It is always 1 tablet/day and can be adjusted especially depending on the condition of the patient in order to stabilise the cardiovascular parameters at the correct values.

The examples which follow illustrate the invention and do not limit it in any way.

Examples

30 In the examples which follow, the preparation of the mini-granules according to the invention is carried out in accordance with techniques known to the person skilled in the art.

Example 1: Preparation of bisoprolol mini-granules

Bisoprolol fumarate and hypromellose are mixed in purified water. The suspension previously obtained is then sprayed onto microcrystalline cellulose to form bisoprolol mini-granules.

Table 1 – 5 and 10 mg immediate-release bisoprolol mini-granules

Dosages (mg)	5	10
Components	Quantity (mg)	Quantity (mg)
Bisoprolol fumarate	5	10
Hypromellose, type 2910	0.556	1.112
Microcrystalline cellulose, type CP-305	54.444	108.888
Total mass	60	120

5 Example 2: Preparation of perindopril mini-granules

Perindopril arginine and hydroxypropylcellulose are mixed in purified water. The suspension previously obtained is then sprayed onto sugar spheres to form perindopril mini-granules.

Table 2 – 5 and 10 mg immediate-release perindopril mini-granules

Dosages (mg)	5	10
Components	Quantity (mg)	Quantity (mg)
Perindopril arginine	5	10
Hydroxypropylcellulose	2.145	4.29
Sugar mini-granules	22.855	45.71
Total mass	30	60

10 Example 3: Preparation of amlodipine mini-granules

Amlodipine besylate and hypromellose are mixed in purified water. The suspension previously obtained is then sprayed onto microcrystalline cellulose to form amlodipine mini-granules.

Table 3 – 5 and 10 mg immediate-release amlodipine mini-granules

Dosages (mg)	5	10
Components	Quantity (mg)	Quantity (mg)
Amlodipine besylate <i>corresponding in terms of base to</i>	6.935 5	13.87 10
Hypromellose, type 2910	0.775	1.55
Microcrystalline cellulose, mini-granules	52.29	104.58
Total mass	60	120

Example 4: Preparation of indapamide mini-granules

Indapamide and hypromellose are mixed in purified water. The suspension previously obtained is then sprayed onto microcrystalline cellulose to form indapamide mini-granules.

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Table 4 – 1.25 and 2.5 mg immediate-release indapamide mini-granules

Dosages (mg)	1.25	2.5
Components	Quantity (mg)	Quantity (mg)
Indapamide	1.25	2.5
Hypromellose, type 2910	0.14	0.28
Microcrystalline cellulose, type CP-305	28.61	57.22
Total mass	30	60

Example 5: Preparation of gastro-resistant aspirin tablets

A first mixture is formed with acetylsalicylic acid, microcrystalline cellulose and maize starch, which mixture is then sieved a first time and then mixed again. In a second stage, microcrystalline cellulose is mixed with anhydrous colloidal silica and sodium stearyl fumarate, and the mixture is then sieved. The first mixture is then added, the whole is mixed, and the tablets are formed by conventional techniques known to the person skilled in the art.

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The coating suspension is obtained by mixing talc, Ariavit Ponceau, triethyl citrate, methacrylic acid-ethyl acrylate copolymer (1:1) and purified water. The tablet is then coated

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with the coating suspension by techniques known to the person skilled in the art.

Table 5 – 100 mg gastro-resistant acetylsalicylic acid tablet

Components	Quantity (mg)
<i>Tablet</i>	
Acetylsalicylic acid	100
Microcrystalline cellulose	14.1
Maize starch	12
Sodium stearyl fumarate	2.6
Anhydrous colloidal silica	1.3
<i>Coating</i>	
Methacrylic acid-ethyl acrylate copolymer (1:1)	11.767
Triethyl citrate	1.76
Talc	1.47
Ariavit Ponceau 36002 Edicol Ponceau 4R	0.003
Total mass	145

The following capsules were prepared in accordance with the invention.

Example 6: Capsules comprising bisoprolol, perindopril and amlodipine

5 The bisoprolol mini-granules obtained according to Example 1, the immediate-release perindopril mini-granules obtained according to Example 2 and the immediate-release amlodipine mini-granules obtained according to Example 3 are each lubricated by techniques known to the person skilled in the art. The capsules are then filled with the lubricated mini-granules by techniques known to the person skilled in the art.

Table 6 – Compositions of capsules comprising bisoprolol, perindopril and amlodipine

Dosages (mg) Components	Bisoprolol / perindopril / amlodipine			
	5/5/5	5/10/5	5/10/10	10/10/10
Quantity per capsule (mg)				
<u>Immediate-release bisoprolol mini-granules</u>	60	60	60	120
Bisoprolol fumarate	5	5	5	10
Hypromellose, type 2910	0.558	0.558	0.558	1.116
Microcrystalline cellulose, type CP-305	54.444	54.444	54.444	108.888
<u>Immediate-release perindopril mini-granules</u>	30	60	60	60
Perindopril arginine	5	10	10	10
Hydroxypropylcellulose	2.145	4.29	4.29	4.29

Dosages (mg) Components	Bisoprolol / perindopril / amlodipine			
	5/5/5	5/10/5	5/10/10	10/10/10
	Quantity per capsule (mg)			
Sugar spheres	22.855	45.71	45.71	45.71
Talc	0.75	0.9	1.2	1.5
<u>Immediate-release amlodipine mini-granules</u>	60	60	120	120
Amlodipine besylate	6.935	6.935	13.87	13.87
<i>corresponding in terms of base to</i>	5	5	10	10
Hypromellose, type 2910	0.774	0.774	1.548	1.548
Microcrystalline cellulose, type CP-305	52.29	52.29	104.58	104.58
Total mass	150.75	180.9	241.2	301.5
Capsule (number)	1	1	1	1

Example 7: Capsules comprising bisoprolol, perindopril and indapamide

In accordance with the same process as that of Example 6, the capsule is filled with immediate-release bisoprolol mini-granules according to Example 1, immediate-release perindopril mini-granules according to Example 2 and indapamide mini-granules according to Example 4.

Table 7 – Compositions of capsules comprising bisoprolol, perindopril and indapamide

Dosages (mg) Components	Bisoprolol / perindopril / indapamide			
	5/5/1.25	5/10/2.35	10/5/1.25	10/10/2.5
	Quantity per capsule (mg)			
<u>Immediate-release bisoprolol mini-granules</u>	60	120	60	120
Bisoprolol fumarate	5	10	5	10
Hypromellose, type 2910	0.558	1.116	0.558	1.116
Microcrystalline cellulose, type CP-305	54.444	108.888	54.444	108.888
<u>Immediate-release perindopril mini-granules</u>	30	60	30	60
Perindopril arginine	5	10	5	10
Hydroxypropylcellulose	2.145	4.29	2.145	4.29
Sugar spheres	22.855	45.71	22.855	45.71
Talc	0.6	1.2	0.6	1.2
<u>Immediate-release indapamide mini-granules</u>	30	60	30	60
Indapamide	1.25	1.25	1.25	2.5
Hypromellose, type 2910	0.138	0.276	0.138	0.276
Microcrystalline cellulose, type CP-305	28.61	57.22	28.61	57.22

Dosages (mg) Components	Bisoprolol / perindopril / indapamide			
	5/5/1.25	5/10/2.35	10/5/1.25	10/10/2.5
	Quantity per capsule (mg)			
Total mass	120.6	241.2	120.6	241.2
Capsule (number)	1	1	1	1

Example 8: Capsules comprising bisoprolol, perindopril and aspirin

In accordance with the same process as that of Example 6, the capsule is filled with
 5 immediate-release bisoprolol mini-granules according to Example 1, immediate-release
 perindopril mini-granules according to Example 2 and gastro-resistant aspirin tablets
 according to Example 5.

Table 8 – Compositions of capsules comprising bisoprolol, perindopril and aspirin

Dosages (mg) Components	Bisoprolol / perindopril / aspirin			
	5/5/100	5/10/100	10/5/100	10/10/100
	Quantity per capsule (mg)			
<u>Immediate-release bisoprolol mini-granules</u>	60	60	120	120
Bisoprolol fumarate	5	5	10	10
Hypromellose, type 2910	0.558	0.558	1.116	1.116
Microcrystalline cellulose, type CP-305	54.444	54.444	108.888	108.888
<u>Immediate-release perindopril mini-granules</u>	30	60	30	60
Perindopril arginine	5	10	5	10
Hydroxypropylcellulose	2.145	4.29	2.145	4.29
Sugar spheres	22.855	45.71	22.855	45.71
Talc	0.45	0.6	0.75	0.9
<u>Gastro-resistant acetylsalicylic acid tablet</u>	145	145	145	145
<i>Tablet</i>				
Acetylsalicylic acid	100	100	100	100
Microcrystalline cellulose	14.1	14.1	14.1	14.1
Maize starch	12	12	12	12
Sodium stearyl fumarate	2.6	2.6	2.6	2.6
Anhydrous colloidal silica	1.3	1.3	1.3	1.3
<i>Coating</i>				
Methacrylic acid-ethyl acrylate copolymer (1:1)	11.76	11.76	11.76	11.76
Triethyl citrate	1.76	1.76	1.76	1.76
Talc	1.47	1.47	1.47	1.47
Ariavit Ponceau 36002 Edicol Ponceau 4R	0.003	0.003	0.003	0.003
Total mass	235.45	265.6	295.75	325.9
Capsule (number)	1	1	1	1

CLAIMS

1. Fixed pharmaceutical composition comprising bisoprolol and its pharmaceutically acceptable salts, perindopril and its pharmaceutically acceptable salts and either:
 - amlodipine and its pharmaceutically acceptable salts, or
 - 5 - indapamide and its pharmaceutically acceptable salts, or
 - acetylsalicylic acid and its pharmaceutically acceptable salts,in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms.
- 10 2. Fixed pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is a capsule.
3. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein:
 - bisoprolol and its pharmaceutically acceptable salts or
 - perindopril and its pharmaceutically acceptable salts or
 - 15 - amlodipine and its pharmaceutically acceptable salts or
 - indapamide and its pharmaceutically acceptable saltsare each in the form of mini-granules.
4. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein aspirin and its pharmaceutically acceptable salts is in the form of a gastro-resistant tablet.
- 20 5. Fixed pharmaceutical composition according to any one of claims 1 to 4, wherein bisoprolol is in the form of bisoprolol fumarate.
6. Fixed pharmaceutical composition according to any one of claims 1 to 4, wherein perindopril is in the form of perindopril *tert*-butylamine or perindopril arginine and more preferably in the form of perindopril arginine.
- 25 7. Fixed pharmaceutical composition according to any one of claims 1 to 4, wherein amlodipine is in the form of amlodipine besylate.
8. Fixed pharmaceutical composition according to any one of claims 1 to 7, wherein:

- the doses of bisoprolol vary from 2.10 mg to 8.50 mg, expressed in terms of bisoprolol base, or from 2.5 to 10 mg, expressed in terms of bisoprolol fumarate,
 - the doses of perindopril vary from 1.65 mg to 9.512 mg, expressed in terms of perindopril base, or from 2.5 mg to 14 mg, expressed in terms of perindopril arginine,
 - 5 - the doses of amlodipine vary from 2.5 to 10 mg, expressed in terms of amlodipine base, or from 3.47 mg to 13.89 mg, expressed in terms of amlodipine besylate,
 - the doses of indapamide vary from 0.625 mg to 2.5 mg, expressed in terms of indapamide base,
 - the doses of aspirin are from 75 mg to 150 mg, expressed in terms of aspirin base.
- 10 9. Fixed pharmaceutical composition according to any one of claims 1 to 8, wherein the doses:
- of bisoprolol fumarate are 5 mg and 10 mg,
 - of perindopril arginine are 5 mg and 10 mg,
 - of amlodipine are 5 mg and 10 mg,
 - 15 - of indapamide besylate are 1.25 mg and 2.5 mg, and
 - of aspirin is 100 mg.
10. Fixed pharmaceutical compositions according to any one of claims 1 to 9 for use in the treatment or prevention of cardiovascular diseases.
- 20 11. Fixed pharmaceutical compositions according to claim 10, characterised in that the cardiovascular diseases are selected from arterial hypertension and stable coronary artery disease.