PHARMACEUTICAL COMPOSITION COMPRISING A BETA BLOCKER AND AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR

Technical field

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

More especially, the present invention relates to a fixed pharmaceutical composition comprising a beta blocker and an angiotensin enzyme converting inhibitor (CEI) wherein:

- the beta blocker is bisoprolol or an addition salt thereof with a pharmaceutically acceptable acid, their hydrates and crystalline forms, and
- the converting enzyme inhibitor is perindopril or an addition salt thereof with a pharmaceutically acceptable acid or base, their hydrates and crystalline forms.

Prior art/context of the invention

Cardiovascular diseases are the leading cause of death both in developed countries and in developing countries, they are responsible for one third of deaths.

Hypertension, coronary artery disease and chronic heart failure 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 often require long-term combination therapies. This fosters patients' non-adherence to their treatment, thus leading to poor control of their pathologies.

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.

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 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.

For the treatment of chronic heart failure (reduced ejection fraction): beta blockers and CEIs are complementary and are recommended in all patients suffering from systolic heart failure. Moreover, they are both recognised as being cardioprotective in heart failure patients and post infarction.

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, coronary artery disease and heart failure.

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 with perindopril, followed by atenolol.

The doses of perindopril and bisoprolol that are most co-prescribed in the three target indications of the association, namely hypertension, stable coronary artery disease and chronic heart failure,

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, I 11, 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, stable coronary artery disease and chronic heart failure.

Summary of the invention

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

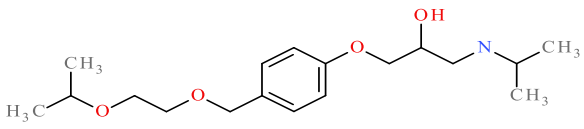
The beta blocker that is preferably used is bisoprolol or an addition salt thereof with a pharmaceutically acceptable acid or base, and more especially its fumarate salt, their hydrates and crystalline forms.

The angiotensin converting enzyme inhibitor that is preferably used is perindopril or an addition salt thereof with a pharmaceutically acceptable acid or base, and more especially its *tert*-butylamine, tosylate or arginine salts, their hydrates and crystalline forms.

Detailed description of the invention

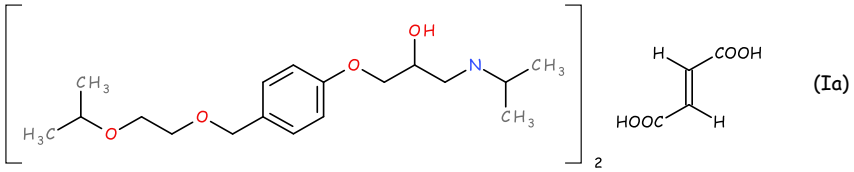
The present invention relates to a fixed pharmaceutical composition comprising bisoprolol or pharmaceutically acceptable salts thereof, their hydrates and crystalline forms, and perindopril or pharmaceutically acceptable salts thereof, their hydrates and crystalline forms, and to the use of said composition in the treatment or prevention of cardiovascular diseases and more especially the treatment or prevention of arterial hypertension, stable coronary artery disease or chronic heart failure.

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



(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):



(Ia)

Bisoprolol fumarate, which is marketed under the name Cardensiel®, is indicated in the treatment of stable chronic heart failure with reduction of left systolic ventricular function, as a supplement to converting enzyme inhibitors (CEIs) and diuretics and, optionally, digitalis 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:

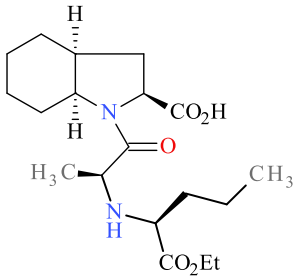
Lodoz®	Per tablet (in mg)		
Bisoprolol fumarate	2.5	5	10
Hydrochlorothiazide	6.25	6.25	6.25

(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

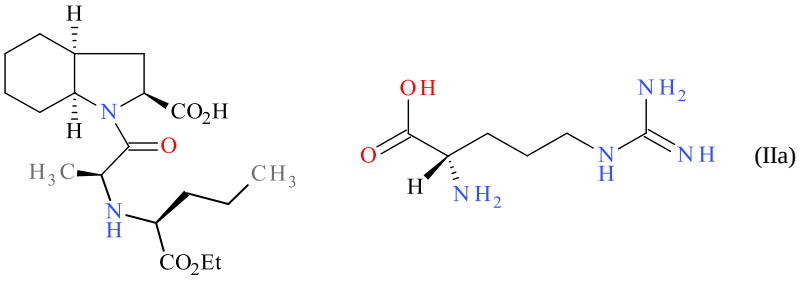
Patent application EP 2 359 815 describes the association of bisoprolol fumarate and amlodipine besilate and the use thereof in the treatment of hypertension and angina pectoris. The pharmaceutical composition comprising bisoprolol and amlodipine is either a monolayer tablet obtained by conventional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

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



(II)

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, 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:



(IIa)

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 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 besilate 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 besilate: 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

Another fixed association with perindopril which has just obtained marketing authorisation (MA)

in Europe is Triplixam®.

The association of perindopril arginine, indapamide and amlodipine besilate 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 besilate: 6.935 mg/tab. containing 5 mg amlodipine or 13.870 mg/tab. containing 10 mg amlodipine)					

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.

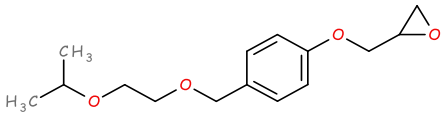
To date and to our knowledge, there is no fixed pharmaceutical combination which combines both a beta blocker and a CEI. There is therefore a real need, for patients suffering from cardiovascular diseases such as arterial hypertension, stable coronary artery disease or chronic heart failure, to have the benefit of such a fixed pharmaceutical composition.

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.

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 or perindopril alone, they may contain impurities and/or 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-isopropoxy-

ethoxy)methyl]phenoxy]-2,3-epoxypropane of formula (Ib):



(Ib)

This impurity epoxibiso is always present in the starting material.

When the two 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.

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.

The applicant therefore first envisaged a fixed pharmaceutical composition of bisoprolol and perindopril in the form of a monolayer tablet.

In the first instance, in order to carry out the invention, the applicant envisaged a fixed pharmaceutical composition of bisoprolol and perindopril in the form of a monolayer tablet obtained by direct compression (Example A) or by wet granulation (Example B). Surprisingly, the applicant found that the formulations tested did not give satisfactory results from the point of view of dosage (Table 2) and/or of stability (Table 3).

Table 2: Content of active ingredients in the monolayer tablets obtained by direct compression

Compression step/ sampling level	**Bisoprolol fumarate content (in %)**	**Perindopril arginine content (in %)**	**Specifications (in %)**
Start of compression	102.40	109.20	95 - 105
Middle of compression	97.60	97.20	
End of compression	95.20	92.80	

These results were obtained from non-film-coated tablets containing a dose of 1.25 mg of bisoprolol and 2.5 mg of perindopril arginine salt. The tablets were taken directly at the outlet of the tablet press and at different times during the compression.

The active ingredient content was analysed by assaying the two active ingredients by liquid chromatography with UV detection, either by high performance liquid chromatography (HPLC) on an Inertsil® C8 column (length 15 cm, diameter: 4.6 mm; porosity 150A; particle size 5 micrometres) or by ultra performance liquid chromatography (UPLC) on a Kinetec® C8 column (length 10 cm, diameter: 3.0 mm; porosity 100A; particle size 2.6 micrometres).

The analyses of the monolayer tablets revealed a non-conformity at the start and at the end of compression, with a pronounced fall in the active ingredient content at the end of compression (Table 2). Analysis of the monolayer tablets obtained by wet granulation was found to comply with the specifications, namely a dose of active ingredients of between 95 and 105% of the theoretical dose.

Since the monolayer tablets obtained by direct compression did not comply with the specifications, while the monolayer tablets obtained by wet granulation complied as regards the active ingredient content, the applicant studied the stability only of the monolayer tablets obtained by wet granulation (Table 3).

The analyses carried out showed the formation of numerous known and unknown degradation products over time when the monolayer tablets are obtained by wet granulation (Table 3).

Table 3: Stability of the monolayer tablets obtained by wet granulation after 6 months at 40°C/75% RH

	Quantity in %		
Dosage	**x mg bisoprolol fumarate / y mg perindopril arginine tab.**		
	10/10 mg tab. (T0)	**10/10 mg tab. (T6)**	**Specifications (in %)**
Bisoprolol fumarate impurities (in %)			
Total impurities*	0.2	4.7	≤ 6.00
Perindopril arginine impurities (in %)			
Total impurities*	0.5	5.20	≤ 5.00

* impurities = degradation products + unknown impurities

These results were obtained starting from film-coated tablets packaged in 30-tablet containers and then placed in ovens, the temperature and humidity of which are controlled.

The monolayer tablets obtained by wet granulation contain the correct dose of active ingredients. As regards the content of bisoprolol impurities, the total quantity of impurities was multiplied by more than 20 between T0 and T6 months, with the emergence of 9 unknown impurities, of which 6 were off-specification.

For perindopril, although no unknown impurity is present, the total quantity of impurities was multiplied by 10 between T0 and T6 months and exceeded the specification limit.

All in all, these results show the instability over time of the fixed pharmaceutical composition, the monolayer tablet obtained by wet granulation.

Wholly surprisingly, the applicant realised that physically separating the bisoprolol and the perindopril in a fixed pharmaceutical composition allowed a solution to the above-mentioned disadvantages to be proposed.

There are various ways of physically separating two or more active ingredients in a fixed pharmaceutical composition.

Either it is possible to produce a fixed pharmaceutical composition which is a bilayer tablet wherein each of the layers comprises one of the two active ingredients. A first layer comprises bisoprolol on its own and a second layer comprises perindopril on its own. This fixed pharmaceutical composition limits contact between the bisoprolol and the perindopril to the interface between the two layers. Although there is potentially an interaction between the two layers, it is very weak and should not lead to high degradation rates.

Or it is possible to produce a fixed pharmaceutical composition which is a trilayer tablet comprising, in addition to the two distinct layers, a separation layer between the bisoprolol layer and the perindopril layer.

Another solution consists in producing a fixed pharmaceutical composition which is a capsule in which the two active ingredients are in the form of bisoprolol granules and perindopril granules, bisoprolol tablets and perindopril tablets, or a mixture of the two, namely tablets of one of the active ingredients and granules of the other of the active ingredients.

One aspect of the invention is, therefore, a fixed pharmaceutical composition comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof, alone or in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms.

According to another aspect of the invention, the fixed pharmaceutical composition is a bilayer tablet, a trilayer tablet or a capsule.

Preferably, the fixed pharmaceutical composition is a bilayer tablet wherein each of the layers comprises one of the two active ingredients.

Yet another aspect of the invention is a fixed pharmaceutical composition which is a trilayer tablet which is the bilayer tablet further comprising a separation layer between the two layers comprising the two active ingredients.

Yet another aspect of the invention is a fixed pharmaceutical composition which is a capsule containing granules or tablets or a mixture of granules and tablets of each of the two active ingredients.

Another aspect of the invention is a fixed pharmaceutical composition in which the bisoprolol is preferably in the form of bisoprolol fumarate.

Yet another aspect of the invention is a fixed pharmaceutical composition in which the perindopril is preferably in the form of perindopril *tert*-butylamine or perindopril arginine and yet more preferably in the form of perindopril arginine.

The present invention relates also to fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof, alone or in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, wherein:

- the doses of bisoprolol are 1.05 mg and 8.50 mg, expressed in terms of bisoprolol base, or between 1.25 and 10 mg, expressed in terms of bisoprolol fumarate, and

- the doses of perindopril are 1.65 and 6.80 mg, expressed in terms of perindopril base, or between 2.5 and 10 mg, expressed in terms of perindopril arginine.

Preferably, in the fixed pharmaceutical compositions, the doses of bisoprolol fumarate are 2.5 mg, 5 mg and 10 mg and the doses of perindopril arginine are 2.5 mg, 5 mg and 10 mg.

Yet more preferably, in the fixed pharmaceutical compositions, the doses are as follows:

a) 2.5 mg of bisoprolol fumarate and 2.5 mg of perindopril arginine
b) 2.5 mg of bisoprolol fumarate and 5 mg of perindopril arginine
c) 5 mg of bisoprolol fumarate and 5 mg of perindopril arginine
d) 5 mg of bisoprolol fumarate and 10 mg of perindopril arginine
e) 10 mg of bisoprolol fumarate and 5 mg of perindopril arginine
f) 10 mg of bisoprolol fumarate and 10 mg of perindopril arginine.

The present invention relates also to fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, for use in the treatment or prevention of cardiovascular diseases.

Preferably, the present invention relates also to fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, for use in the treatment of cardiovascular diseases.

Preferably, the present invention relates also to fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, for use in the prevention of cardiovascular diseases.

Yet another aspect of the invention is the use of fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients,

their hydrates and their crystalline forms, in the treatment or prevention of arterial hypertension, stable coronary artery disease or chronic heart failure.

Yet another aspect of the invention is the use of fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, in the treatment or prevention of arterial hypertension.

Yet another aspect of the invention is the use of fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, in the treatment or prevention of stable coronary artery disease.

Yet another aspect of the invention is the use of fixed pharmaceutical compositions comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, in the treatment or prevention of chronic heart failure.

In addition to the beta blocker and the angiotensin converting enzyme inhibitor (CEI), said pharmaceutical compositions comprise one or more excipients or carriers chosen from diluents, lubricants, binders, disintegrators, absorbents, colourings, sweeteners, etc.

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,
- *for the binders*: magnesium aluminium silicate, starch, gelatin, tragacanth, cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and polyvinyl-pyrrolidone,
- *for the disintegrators*: agar, starch, alginic acid and its sodium salt, effervescent mixtures, carboxymethylcellulose salts, carboxymethyl starch salts, polyvinylpyrrolidone derivatives.

The dosage used varies according to the age of the patient, the nature of the disorder, and any associated pathologies and treatments.

For hypertension and stable coronary artery disease, the usual dosage of bisoprolol is 5 mg/day. The dose can be increased to 10 mg/day if necessary. The maximum recommended dose is 20 mg/day. In the case of chronic heart failure, a dose titration phase is necessary, with an initial dose of 1.25 mg/day, which is increased gradually according to the patient's tolerance to reach the maintenance dose of 10 mg/day. The maximum recommended dose is 10 mg/day.

The usual dosage of perindopril arginine salt ranges from 2.5 mg to 10 mg/day (2 mg to 8 mg/day for perindopril *tert*-butylamine salt), with a recommended initial dosage of 5 mg/day, which can be increased to 10 mg/day, for arterial hypertension and stable coronary artery disease and an initial dosage of 2.5 mg/day, which can be increased to 5 mg/day, in the case of heart failure.

The following examples illustrate the invention without limiting it in any way.

Examples

Examples A and B are comparative.

Example A: Monolayer tablet containing a dose of 10/10 mg, obtained by direct compression

Formula	**In %**	**In mg per tablet**
Bisoprolol fumarate	4.17	10.00
Perindopril arginine	4.17	10.00
Calcium carbonate/starch	56.63	131.11
Microcrystalline cellulose (PH 102)	33.33	80.00
Sodium carboxymethyl starch	3.00	7.20
Anhydrous colloidal silica	0.20	0.48
Magnesium stearate	0.50	1.20
Total	**100**	**240**

Example B: Monolayer tablet containing a dose of 10/10 mg, obtained by wet granulation

Formula	**In %**	**In mg per tablet**
Bisoprolol fumarate	4.17	10.00
Perindopril arginine	4.17	10.00
Microcrystalline cellulose	15.00	36.00

Calcium carbonate	29.63	71.12
Purified water	qs	qs
Microcrystalline cellulose (PH 102)	33.33	80.00
Sodium carboxymethyl starch	3.00	7.20
Anhydrous colloidal silica	0.20	0.48
Magnesium stearate	0.50	1.20
Total	**100**	**240**

The examples which follow form part of the invention.

Example 1: Formula for the four dosages of the bilayer tablets

Example 1a: Bilayer tablets containing a dose of 5 mg of bisoprolol and 5 mg of perindopril

Example 1b: Bilayer tablets containing a dose of 5 mg of bisoprolol and 10 mg of perindopril

Example 1c: Bilayer tablets containing a dose of 10 mg of bisoprolol and 5 mg of perindopril

Example 1d: Bilayer tablets containing a dose of 10 mg of bisoprolol and 10 mg of perindopril

Dosage	**Quantity in %**			
	x mg bisoprolol fumarate / y mg perindopril arginine tab.			
	5/5 mg tab.	**5/10 mg tab.**	**10/5 mg tab.**	**10/10 mg tab.**
Bisoprolol fumarate layer				
Bisoprolol fumarate	4.03	2.68	5.37	4.03
Microcrystalline cellulose	16.11	10.74	21.48	16.11
Calcium carbonate	18.45	12.30	24.60	18.45
Maize starch	7.73	5.15	10.31	7.73
Sodium carboxymethyl starch	1.45	0.97	1.93	1.45
Anhydrous colloidal silica	0.19	0.13	0.26	0.19
Magnesium stearate	0.36	0.24	0.48	0.36
Perindopril arginine layer				
Perindopril arginine	4.03	5.37	2.68	4.03
Microcrystalline cellulose	16.11	21.48	10.74	16.11
Calcium carbonate	18.45	24.60	12.30	18.45
Pregelatinised maize starch	7.73	10.31	5.15	7.73
Croscarmellose sodium	1.45	1.93	0.97	1.45
Anhydrous colloidal silica	0.19	0.26	0.13	0.19
Magnesium stearate	0.36	0.48	0.24	0.36
Film-coated tablet				
Brown coating premix 5943	3.25	3.25	3.25	3.25
Macrogol 6000	0.10	0.10	0.10	0.10

Film-coating and smoothing process

The process of film-coating and smoothing the uncoated tablet consists principally of 2 steps, which are: a) the film-coating step then b) the smoothing step.

The techniques used are conventional film-coating and smoothing techniques known to the person skilled in the art.

Example 2: Divisible film-coated tablet

Among the fixed pharmaceutical compositions described in Example 1, two (Examples 1a and 1b) have a break-line or score line. The fixed pharmaceutical compositions in question are those comprising:

a) Example 1a: 5 mg of bisoprolol fumarate and 5 mg of perindopril arginine, and
b) Example 1b: 5 mg of bisoprolol fumarate and 10 mg of perindopril arginine.

x mg bisoprolol/y mg perindopril tab.			
5/5 tab.	**5/10 tab.**	**10/5 tab.**	**10/10 tab.**
Brown film-coated tablet			
Elliptical Divisible	Elliptical Divisible	Round	Elliptical

The advantage of the score line is that it is possible to provide patients with the following doses:

a) 2.5 mg of bisoprolol fumarate and 2.5 mg of perindopril arginine, and
b) 2.5 mg of bisoprolol fumarate and 5 mg de perindopril arginine.

The fixed pharmaceutical compositions of bisoprolol and perindopril according to the invention (Examples 1 and 2) thus make it possible to provide patients with at least 71% of the co-prescriptions of the compounds taken individually.

Results of stability at 6 months of the bilayer tablets

The results of stability of the bilayer tablets at 6 months were obtained starting from the film-coated tablets packaged in 30-tablet containers and then placed in ovens, the temperature and humidity (RH) of which were controlled. These parameters are 40°C for the temperature and 75% for the humidity.

Separation of the two active ingredients made it possible to correct the problems of underdosage of

active ingredients encountered with the monolayer tablet and especially to obtain a pharmaceutical form that is stable over time (Table 5).

Table 5: Comparison of the results of stability at 6 months - 40°C/75% RH of the monolayer tablets and bilayer tablets containing a dose of 10/10 mg

	Quantity in %		
Dosage	**Monolayer tablet** (Example B)	**Bilayer tablet** (Example 1d)	**Specifications (in %)**
Bisoprolol fumarate impurities* (in %)			
Total impurities	4.70	0.20	≤ 6.00
Perindopril arginine impurities* (in %)			
Total impurities	5.20	0.30	≤ 5.00

* impurities = degradation products + unknown impurities

The stability studies showed a considerable reduction in the total quantity of degradation impurities for bisoprolol fumarate and perindopril arginine and, for bisoprolol fumarate, a sharp reduction in the number of unknown impurities.

The total quantity of impurities for a tablet containing a dose of 10/10 mg changed from 4.70% in the monolayer tablet to 0.20% in the bilayer tablet for bisoprolol and from 5.20% in the monolayer tablet to 0.30% in the bilayer tablet for perindopril.

Example 3: Trilayer tablet with a separation layer

The trilayer tablet was produced in the same manner as the bilayer tablet by taking the tablets of Examples 1a to 1d and further adding a separation layer between the bisoprolol layer and the perindopril layer. This separation layer comprises a mixture of lactose and magnesium stearate.

Example 4: Capsules of bisoprolol and perindopril

The pharmaceutical composition for a capsule containing 10 mg of bisoprolol fumarate in the form of granules and 10 mg of perindopril arginine salt in the form of granules is as follows:

a) Granules of 10 mg of bisoprolol fumarate

Bisoprolol fumarate..... 10 mg

Hydroxypropylmethylcellulose..... 1.1 mg

Sugar spheres..... 88.89 mg

b) Granules of 10 mg of perindopril arginine salt

Perindopril arginine salt ..... 10 mg

Hydroxypropylcellulose ..... 4.25 mg

Sugar spheres..... 45.70 mg.

CLAIMS

1. Fixed pharmaceutical composition comprising bisoprolol and pharmaceutically acceptable salts thereof and perindopril and pharmaceutically acceptable salts thereof in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms, wherein the bisoprolol and the perindopril are physically separated.

2. Fixed pharmaceutical composition according to claim 1 which is a bilayer tablet in which a first layer comprises bisoprolol and a second layer comprises perindopril, a trilayer tablet in which, in addition to the two distinct layers, there is a separation layer, or a capsule containing bisoprolol granules and perindopril granules, bisoprolol tablets and perindopril tablets or tablets of one of the active ingredients and granules of the other of the active ingredients.

3. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein the pharmaceutical composition is a bilayer tablet in which a first layer comprises bisoprolol and a second layer comprises perindopril.

4. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein the pharmaceutical composition is a trilayer tablet in which, in addition to the two distinct layers, there is a separation layer.

5. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein the pharmaceutical composition is a capsule containing bisoprolol granules and perindopril granules, bisoprolol tablets and perindopril tablets or tablets of one of the active ingredients and granules of the other of the active ingredients.

6. Fixed pharmaceutical composition according to any one of claims 1 to 5, wherein the bisoprolol is in the form of bisoprolol fumarate.

7. Fixed pharmaceutical composition according to either claim 1 or claim 5, wherein the perindopril is in the form of perindopril *tert*-butylamine or perindopril arginine and more preferably in the form of perindopril arginine.

8. Fixed pharmaceutical composition according to any one of claims 1 to 7, wherein:

- the doses of bisoprolol are 1.05 mg and 8.50 mg, expressed in terms of bisoprolol base, or between 1.25 and 10 mg, expressed in terms of bisoprolol fumarate, and
- the doses of perindopril are 1.65 and 6.80 mg, expressed in terms of perindopril base, or between 2.5 and 10 mg, expressed in terms of perindopril arginine.

9. Fixed pharmaceutical composition according to any one of claims 1 to 8, wherein the doses of bisoprolol fumarate are 2.5 mg, 5 mg and 10 mg and the doses of perindopril arginine are 2.5 mg, 5 mg and 10 mg.

10. Fixed pharmaceutical compositions according to any one of claims 1 to 9 for use in the treatment or prevention of cardiovascular diseases.

11. Fixed pharmaceutical compositions according to claim 10, characterised in that the cardiovascular diseases are chosen from arterial hypertension, stable coronary artery disease and chronic heart failure.