

PHARMACEUTICAL COMPOSITION COMPRISING AN HMG-CoA REDUCTASE INHIBITOR AND AN ACE INHIBITOR

Technical field

5 The present invention relates to a fixed pharmaceutical composition comprising an HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor and an antihypertensive agent, and to the use of said composition in the treatment and prevention of cardiovascular diseases.

Prior art/context of the invention

10 Cardiovascular diseases are the leading cause of death in developed countries and in developing countries, which represents approximately one third of all deaths in the world. Deaths associated with cardiovascular diseases are expected to increase to 23.3 million in 2030.

15 In Europe, cardiovascular diseases are the main 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).

20 The development of coronary artery diseases is due to the global effect of modifiable and non-modifiable risk factors. These risk factors include hypertension, dyslipidaemia, excess weight and obesity, diabetes, a sedentary lifestyle, smoking, alcohol, a more or less high salt intake, family history of hypertension and premature cardiovascular disease, age, sex, and psychological factors such as anxiety and depression. The coexistence of these risk factors
25 increases the morbidity and the mortality rates significantly.

People with a past history of MI and cerebrovascular accident (CVA) are most at risk of other coronary and cerebral events. There is considerable scientific evidence that specific interventions allow the risk of other vascular events in patients having an MI to be reduced. In

particular, acetylsalicylic acid, or aspirin, at low doses of from 75 to 150 mg is considered to be the cornerstone of the pharmacological prevention of arterial thrombosis.

Stable coronary artery diseases associated with dyslipidaemia, as well as other risk factors, can increase the risk of cardiovascular disease. Dyslipidaemia is a modifiable cardiovascular risk factor which is of great importance in the prevention of cardiovascular diseases. A high level of total cholesterol (TC) and low-density lipoproteins (LDL) have received most attention, in particular because they can be modified by changes in lifestyle and by medication.

Clinical studies in primary prevention and secondary prevention show that reducing total cholesterol and low-density lipoprotein cholesterol (LDL-C) with statins can prevent cardiovascular diseases.

Interestingly, the treatment of a single risk factor can reduce cardiovascular events by approximately 30%, while the treatment of multiple risk factors can reduce the risk of cardiovascular diseases by more than 50%.

Chronic 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 on the basis of the proportion of days of treatment covered of less than 0.80.

Non-compliance with cardioprotective medication is widespread among outpatients suffering from coronaropathy and is associated with a wide range of undesirable effects, including all-cause and cardiovascular mortality, cardiovascular hospitalisations and revascularisation procedures. Likewise, stopping taking low-dose acetylsalicylic acid increases the risk of non-fatal MI or death by coronary artery disease by more than 50% in primary-care patients with a past history of ischaemic events. Non-compliance with medication was the most common reason for stopping treatment.

A meta-analysis of five 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).

It is within this context that the present invention proposes to develop a new fixed combination comprising a statin and at least one antihypertensive chosen from a CEI such as perindopril or a diuretic such as indapamide optionally with another active ingredient chosen from a non-steroidal anti-inflammatory drug (NSAID) such as acetylsalicylic acid.

In the prior art there are a number of documents which describe associations between statins, antihypertensives and/or aspirin.

Patent application WO 99/11259 describes a therapeutic combination comprising amlodipine and atorvastatin in the treatment of hypertension, hyperlipidaemia, angina pectoris, atherosclerosis and cardiac risk management.

Patent application WO 99/11260 describes a combined therapy comprising atorvastatin and an antihypertensive agent in the treatment of hypertension, hyperlipidaemia, angina pectoris, atherosclerosis and cardiac risk management. The antihypertensives mentioned include calcium channel inhibitors, ACE inhibitors, A-II antagonists, diuretics, beta-adrenergic receptor blockers, vasodilators and alpha-adrenergic receptor blockers.

These two applications make no mention of the problems of interactions or degradation which may exist within a fixed pharmaceutical composition of two active ingredients or more.

Patent application WO 03/092729 describes a stable pharmaceutical formulation containing a statin combined with an ACE inhibitor, which formulation comprises at least one stabilising

agent for the statin and at least one stabilising agent for the ACE inhibitor and in which the statin and the ACE inhibitor are separated by a layer or membrane made of a compatible physiologically inert material having a neutral pH.

ACE inhibitors are compounds which are sensitive to degradation reactions which are promoted in the presence of acids or bases. That application solves the problem of the decomposition or degradation of ACE inhibitors in the presence of statins by developing a stable pharmaceutical composition in which the quantity of active ingredients does not vary over time and the active ingredients of which do not decompose at all or decompose only very little.

Patent application WO 99/47123 describes a pharmaceutical composition comprising a statin-based cholesterol-lowering agent and aspirin in a formulation designed to minimise statin:aspirin interaction, wherein (i) the statin and the aspirin are formulated as a single bilayer tablet and wherein the aspirin is present in a first layer and the statin is present in a second layer; or (ii) the pharmaceutical composition is in the form of a capsule containing aspirin granules and statin granules. That application solves the problem of interactions between the active ingredients.

Patent application WO 2011/096665 describes a complex formulation for the prevention and treatment of cardiovascular diseases comprising a) aspirin coated with a barrier of a hydrophobic additive, and b) an HMG-CoA reductase inhibitor. That application solves the problem of the instability of HMG-CoA reductase, which is unstable in an acidic medium.

Patent application WO 2012/002919 describes a pharmaceutical composition in the form of a tablet or capsule comprising atorvastatin and aspirin, it being possible for each of these active ingredients to be in the form of tablets, mini-tablets, micro-tablets, microcapsules, granules and/or powder, which composition can be used in the prevention or treatment of cardiovascular diseases. The doses of aspirin vary from 1 to 500 mg, preferably from 1 to 300 mg and more preferably from 1 to 150 mg. The doses of atorvastatin are from 1 to 200 mg, preferably from 1 to 150 mg and more preferably from 1 to 100 mg/dose. The formulation according to that application solves the problem of interactions of the active ingredients with one another. The examples which are described are pharmaceutical

formulations comprising either aspirin tablets and atorvastatin granules or aspirin tablets and atorvastatin granules in capsules.

Patent application WO 2012/011882 describes a pharmaceutical composition comprising atorvastatin and aspirin, each of these active ingredients being in powder form, which composition can be used in the prevention or treatment of cardiovascular diseases. The object of that application is to provide a pharmaceutical formulation which combines both aspirin and atorvastatin and which has good bioavailability and does not exhibit chemical degradation. But also a formulation in which atorvastatin is sufficiently soluble in water.

Patent application WO 2012/081905 describes a pharmaceutical formulation for the prevention and treatment of cardiovascular diseases which comprises on the one hand an HMG-CoA reductase inhibitor and a basic additive and on the other hand aspirin with an enteric coating layer. The HMG-CoA reductase inhibitor can be formulated in the form of powder, granules, pellets or mini-tablets and the aspirin can be formulated in the form of granules pellets or mini-tablets.

Patent application WO 2012/124973 describes a pharmaceutical composition for the treatment of cardiovascular diseases comprising atorvastatin in the form of mini-tablets and aspirin in the form of mini-tablets or mini-granules having an enteric coating, thus reducing interactions between the two active ingredients while optimising the therapeutic effect and the storage stability.

Patent application WO 03/020243 describes a pharmaceutical composition which can be in the form of a capsule, comprising an agent which lowers the cholesterol level, which is a statin, a CEI and aspirin, in which at least one of the components is separated from the two others. The components can be in the form of pellets or granules. That application describes a pharmaceutical composition which is a multilayer tablet comprising a first prolonged-release layer of lovastatin, a second prolonged-release layer of enalapril, a separation layer formed of excipients, and an immediate-release layer of aspirin. That application also describes a pharmaceutical composition comprising lovastatin granules, enalapril granules and an immediate-release aspirin matrix which are mixed to form a tablet obtained by compression.

Finally, that application describes a pharmaceutical composition in the form of tablets or capsules comprising a plurality of active ingredients including lovastatin, enalapril and aspirin, all in immediate-release form, which is obtained by mixing the powders, which mixture is then introduced into a capsule.

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That application also addresses the problem of interactions between the various active ingredients within a fixed pharmaceutical composition, but also possible interactions between the active ingredients and the excipients. However, the various active ingredients each have a different release profile.

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Patent application WO 2004/080488 describes pharmaceutical compositions containing acetylsalicylic acid, an HMG-CoA reductase inhibitor and optionally an antihypertensive for the primary prevention of cardiovascular diseases. That application describes examples comprising

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- aspirin, atorvastatin and optionally amlodipine, and
- aspirin, simvastatin and perindopril.

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Patent application WO 2009/118359 describes a pharmaceutical composition in capsule form for the prevention of cardiovascular diseases, which comprises film-coated acetylsalicylic acid tablets, film-coated simvastatin or pravastatin tablets and film-coated lisinopril, ramipril or perindopril tablets. The examples described in that application comprise 100 mg of acetylsalicylic acid, 20 mg of simvastatin, and ramipril (2.5; 5 or 10 mg) or lisinopril (20 mg).

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Patent application WO 2014/195421 describes an oral formulation for the treatment of cardiovascular diseases, comprising an HMG-CoA reductase inhibitor which is a statin and acetylsalicylic acid and in which interactions between the two active ingredients are minimised. In that formulation, the two active ingredients are in the form of a coated unit dose. The oral formulation may further contain a renin-angiotensin system inhibitor which is an ACE inhibitor such as perindopril, for example.

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Summary of the invention

The present invention relates to a fixed pharmaceutical composition comprising an HMG-CoA reductase inhibitor and an antihypertensive.

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More especially, the present invention relates to a fixed pharmaceutical composition comprising an HMG-CoA inhibitor and at least one antihypertensive chosen from an angiotensin converting enzyme inhibitor (CEI), a diuretic and optionally an NSAID.

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

- the HMG-CoA inhibitor is atorvastatin or an addition salt thereof with a pharmaceutically acceptable acid, their hydrates and crystalline forms, and
- 15 - the CEI is perindopril or an addition salt thereof with a pharmaceutically acceptable acid or base, their hydrates and crystalline forms.

The present invention relates also to a fixed pharmaceutical composition comprising, in addition to the HMG-CoA reductase inhibitor and the CEI, another active ingredient chosen from:

- 20 - an NSAID or
- a diuretic.

The present invention relates further to the use of these fixed pharmaceutical compositions in the treatment and prevention of cardiovascular diseases and more especially the prevention of coronary events in patients with a past history of myocardial infarction and/or of
25 revascularisation in association with primary hypercholesterolaemia or mixed hyperlipidaemia.

The HMG-CoA reductase inhibitor that is preferably used is atorvastatin or an addition salt thereof with a pharmaceutically acceptable acid or base, and more especially the calcium or
30 sodium salt thereof, 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 the *tert*-butylamine, tosylate or arginine salts thereof, their hydrates and crystalline forms.

- 5 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.

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.

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Detailed description of the invention

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

- The present invention relates also to a fixed pharmaceutical composition comprising, in addition to atorvastatin and perindopril, acetylsalicylic acid, also called aspirin, or its
20 pharmaceutically acceptable salts, their hydrates and crystalline forms, and to the use of said composition in the prevention and treatment of cardiovascular diseases.

- The present invention relates also to a fixed pharmaceutical composition comprising, in addition to atorvastatin and perindopril, indapamide or its pharmaceutically acceptable salts,
25 their hydrates and crystalline forms, and to the use of said composition in the prevention and treatment of cardiovascular diseases.

- Cardiovascular diseases are more precisely understood as being the prevention of coronary events in patients with a past history of myocardial infarction and/or of revascularisation in
30 association with primary hypercholesterolaemia or mixed hyperlipidaemia.

A fixed pharmaceutical composition has the advantage of permitting both a reduction in manufacturing costs, but above all better compliance with the treatment on the part of patients and consequently better control of their pathology.

5 In the present invention, the fixed pharmaceutical composition of at least two active ingredients, which are 1) atorvastatin and 2) perindopril, which belong to different therapeutic classes having complementary effects, therefore has the advantage of targeting several risk factors which are responsible for cardiovascular diseases with a single dose.

10 The present invention is also a fixed therapeutic combination of at least three active ingredients which belong to different therapeutic classes having complementary effects, which are 1) atorvastatin, 2) perindopril and also:

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

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The use of these fixed therapeutic combinations:

- atorvastatin + perindopril,
- atorvastatin + perindopril + acetylsalicylic acid, and
- atorvastatin + perindopril + indapamide

20 is the prevention of coronary events in patients with a past history of myocardial infarction and/or of revascularisation in association with primary hypercholesterolaemia or mixed hyperlipidaemia as a substitution therapy in adult patients controlled concurrently by monotherapy with atorvastatin, perindopril and/or the active ingredients a) to d) at the same doses as are present in the fixed pharmaceutical composition.

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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 for patients receiving
30 medicaments separately and thus improve compliance by limiting the number of tablets.

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

- 5 Atorvastatin forms part of a group of medicaments called HMG-CoA reductase inhibitors or statins. Atorvastatin reduces the concentration of low-density lipoproteins (LDL) and triglycerides in the blood while increasing the concentration of high-density lipoprotein (HDL). Atorvastatin in the form of the calcium trihydrate salt is marketed under the name Tahor® or Lipitor® and the corresponding pharmaceutical composition is described in patent application WO 94/16693. Atorvastatin is indicated for:
- 10
- the treatment of hypercholesterolaemia as an adjunct to diet for reducing high levels of total cholesterol (Chol-T), LDL-cholesterol (LDL-C), apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia, including familial hypercholesterolaemia, or mixed hyperlipidaemias,
 - 15 - the prevention of cardiovascular events in patients at high risk of having a first cardiovascular event, as an adjunct to the correction of the other risk factors.

- 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 the degradation of vasodilatory bradykinin to an inactive heptapeptide. Perindopril in the form of the arginine salt is marketed under the name Coversyl® and is indicated for:
- 20
- the treatment of arterial hypertension,
 - reducing the risk of cardiac events in patients with a past history of myocardial infarction and/or revascularisation, and
 - 25 - the treatment of symptomatic heart failure.

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

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

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
15 nonetheless necessary in order to stabilise one or other of the active ingredients.

The use of acetylsalicylic acid to reduce the risk of myocardial infarction and the use of statins to lower the cholesterol level and prevent or treat cardiovascular and cerebrovascular diseases are very well documented. In fact, it is not unusual for patients who have a high
20 cholesterol level and who are considered to be at risk of "having" a myocardial infarction to take both a statin and acetylsalicylic acid. However, the use of both statins and acetylsalicylic acid requires particular precautions in order to minimise the interactions between these two medicaments because it is well known from the prior art that HMG-CoA reductase inhibitors decompose in the presence of acetylsalicylic acid. The interactions include physical and
25 chemical incompatibilities but also side effects.

In addition, statins are sensitive to factors such as heat, humidity, low pH and light. In particular, atorvastatin is converted into lactone, which is the result of an intramolecular esterification reaction. The major degradation products which are produced during the
30 decomposition of statins are lactones and oxidation products, which reduce the stability of atorvastatin and accordingly its half-life.

Atorvastatin is a molecule which decomposes quite easily and requires the use of a stabilising agent, which in the formulation of Tahor® is calcium carbonate. This formulation of Tahor® is described especially in patent EP 0 680 320.

- 5 Surprisingly, by mixing perindopril with atorvastatin and by formulating the mixture on the basis of the formulation of Tahor®, that is to say in the presence of calcium carbonate, the Applicant realised that the calcium carbonate modifies the human pharmacokinetics of perindopril, making it difficult to achieve the bioequivalence of the formulation of perindopril in the fixed combination "perindopril + atorvastatin".
- 10 In fact, in an interaction study of the fixed combination "atorvastatin 40 mg + perindopril arginine 10 mg" versus atorvastatin 40 mg on its own and perindopril arginine 10 mg on its own, the Applicant has shown that the C_{max} (which is the maximum concentration of product present in the blood after administration) of perindopril in bitherapy was modified.

Parameters (ng/ml)	Atorvastatin	
	Atorvastatin + perindopril	Atorvastatin
C _{max}	14	14
	Perindopril	
	Atorvastatin + perindopril	Perindopril
C _{max}	102	76

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Thus, the ratio between perindopril administered in the fixed combination "atorvastatin + perindopril" and perindopril administered on its own is more than 130%.

- It is therefore necessary to separate these two active ingredients physically in order to obtain a stable fixed pharmaceutical composition of atorvastatin and perindopril.
- 20

The present invention solves this problem by developing a fixed pharmaceutical composition in capsule form comprising atorvastatin mini-granules and perindopril mini-granules.

- 25 It is known from the prior art that aspirin degrades HMG-CoA reductase inhibitors. In a compatibility study of the different active ingredients, the Applicant was able to show that, when the 3 active ingredients are on their own, there is no degradation, including when atorvastatin and perindopril are formulated together. By contrast, when aspirin is added to the

"atorvastatin + perindopril" mixture, the 3 active ingredients degrade, as shown by the table below.

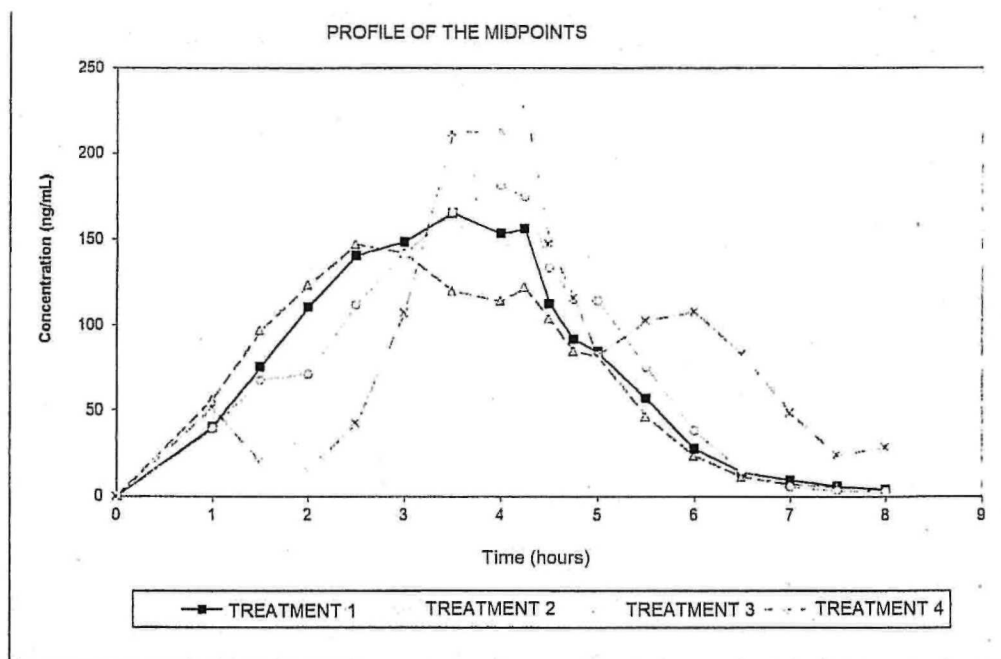
Table A: Compatibility study of the active ingredients

Active ingredients	Known impurities of perindopril	Known impurities of aspirin	Known impurities of atorvastatin
Aspirin	-	1.4364	-
Atorvastatin	-	-	1.170
Perindopril	1.120	-	-
Atorvastatin + perindopril	0.830	-	0.560
Atorvastatin + perindopril + Aspirin	38.881	15.668	5.784

Therefore, in the fixed pharmaceutical composition according to the invention which comprises atorvastatin, perindopril and aspirin, it is necessary to separate the aspirin from the atorvastatin and the perindopril. The Applicant has therefore developed a fixed pharmaceutical composition in capsule form comprising atorvastatin mini-granules, perindopril mini-granules and gastro-resistant aspirin mini-granules.

However, in this fixed pharmaceutical composition, the gastro-resistant aspirin mini-granules are not bioequivalent to the gastro-resistant aspirin tablets present on the market, as shown by the Applicant (see figure hereinbelow – treatment 4).

In this study, it can be seen that the profile of treatment 4 is different from the profiles of treatments 1 to 3, thus showing a difference between the gastro-resistant aspirin tablet and the gastro-resistant aspirin mini-granules.



Treatment 1:

- 1 capsule of atorvastatin calcium mini-granules without calcium carbonate
- 5 • 1 capsule of perindopril arginine mini-granules
- 1 capsule of gastro-resistant aspirin mini-granules

Treatment 2:

- 1 capsule of atorvastatin calcium mini-granules with calcium carbonate – process of mixing the calcium carbonate without grinding
- 10 • 1 capsule of perindopril arginine mini-granules
- 1 capsule of gastro-resistant aspirin mini-granules

Treatment 3:

- 1 capsule of atorvastatin calcium mini-granules with calcium carbonate – process of mixing the calcium carbonate with grinding
- 15 • 1 capsule of perindopril arginine mini-granules
- 1 capsule of gastro-resistant aspirin mini-granules

Treatment 4:

- 1 Tahor® tablet
- 1 Coversyl® tablet
- 20 • 1 gastro-resistant aspirin tablet

The present invention solves the problem by developing a fixed pharmaceutical composition comprising atorvastatin, perindopril and aspirin, 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.

The present invention therefore proposes a fixed pharmaceutical composition in capsule form comprising atorvastatin mini-granules, perindopril mini-granules and gastro-resistant aspirin tablets. This composition therefore has the advantage of being bioequivalent to the gastro-resistant aspirin tablet on its own and of having no interactions between the 3 active ingredients or with the excipients.

In the same manner and for the same reasons as mentioned hereinbefore, the present invention comprises a fixed pharmaceutical composition comprising:

A) atorvastatin mini-granules, perindopril mini-granules and indapamide mini-granules.

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.

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

- the doses of atorvastatin vary from 10 mg to 80 mg, expressed in terms of atorvastatin base, or vary from 10.80 mg to 86.80 mg, expressed in terms of atorvastatin calcium trihydrate, and
- 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 present invention relates also to fixed pharmaceutical compositions further comprising aspirin and its pharmaceutically acceptable salts or amlodipine and its pharmaceutically

acceptable salts or indapamide and its pharmaceutically acceptable salts or bisoprolol and its pharmaceutically acceptable salts, in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms wherein:

- the doses of aspirin are from 75 mg to 150 mg, expressed in terms of aspirin base,
- 5 - the doses of indapamide vary from 0.625 mg to 2.5 mg, expressed in terms of indapamide base.

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

- of atorvastatin calcium are 10 mg, 20 mg, 40 mg and 80 mg,
- of perindopril arginine are 2.5 mg, 3.5 mg, 5 mg, 7 mg, 10 mg and 14 mg,
- 10 - of aspirin are 75 mg, 100 mg and 150 mg, and
- of indapamide are 0.625 mg, 1.25 mg, 1.5 mg and 2.5 mg.

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

- a) 10 mg of atorvastatin calcium and 2.5 mg, 5 mg or 10 mg of perindopril arginine,
- 15 b) 20 mg of atorvastatin calcium and 2.5 mg, 5 mg or 10 mg of perindopril arginine,
- c) 40 mg of atorvastatin calcium and 2.5 mg, 5 mg or 10 mg of perindopril arginine.

The fixed pharmaceutical compositions according to the invention as described in a), b) or c) may each further contain 75 mg, 100 mg or 150 mg of aspirin.

20 The fixed pharmaceutical compositions according to the invention as described in a), b) or c) may each further contain 1.5 mg or 2.5 mg of indapamide.

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

- i) 10 mg of atorvastatin calcium and 5 mg or 10 mg of perindopril arginine,
- ii) 20 mg of atorvastatin calcium and 5 mg or 10 mg of perindopril arginine,
- 25 iii) 40 mg of atorvastatin calcium and 5 mg or 10 mg of perindopril arginine,
- iv) 100 mg of aspirin and
 - a. 20 mg of atorvastatin calcium and 5 mg or 10 mg of perindopril arginine;
 - b. 40 mg of atorvastatin calcium and 5 or 10 mg of perindopril arginine,

- v) 1.25 mg of indapamide, 5 mg of perindopril arginine and 10 mg, 20 mg or 40 mg of atorvastatin calcium,
- vi) 2.5 mg of indapamide and 10 mg of perindopril arginine and 10 mg, 20 mg or 40 mg of atorvastatin calcium.

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

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

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

- ♦ *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- 15 ♦ *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 polyvinylpyrrolidone,
- 20 ♦ *for the disintegrators*: agar, starch, alginic acid and its sodium salt, effervescent mixtures, carboxymethylcellulose salts, carboxymethyl starch salts, polyvinylpyrrolidone derivatives.

25 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

Method for the preparation of the pharmaceutical compositions according to the invention.

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

5 Example 1: Preparation of the atorvastatin mini-granules

Atorvastatin calcium and calcium carbonate are mixed in purified water. Sodium croscarmellose and polysorbate 80 are then added. The suspension previously obtained is then sprayed onto sugar spheres to form the atorvastatin mini-granules.

Table 1 – 20 and 40 mg immediate-release atorvastatin mini-granules

Components	20 mg	40 mg
	Quantity (mg)	Quantity (mg)
Atorvastatin calcium <i>corresponding in terms of base to</i>	21.64 20	43.28 40
Calcium carbonate	21.64	43.28
Hydroxypropylcellulose	4.32	8.64
Polysorbate 80	2.48	4.96
Sodium croscarmellose	1.915	3.83
Sugar spheres	28.01	56.02
Total mass	80	160

10 Example 2: Preparation of the perindopril mini-granules

Perindopril arginine and hydroxypropylcellulose are mixed in purified water. The suspension previously obtained is then sprayed onto sugar spheres to form the 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 spheres	22.855	45.71
Talc	2.2	2.2
Total mass	30	60

Example 3: Preparation of the 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.

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

Table 3 – 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)	11.76
Triethyl citrate	1.76
Talc	1.47
Ariavit Ponceau 36002 Edicol Ponceau 4R	0.003
Total mass	145

Example 4: Preparation of the indapamide mini-granules

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

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	0.138	0.276
Microcrystalline cellulose, type CP-305	28.61	57.22
Total mass	30	60

The following capsules were prepared according to the invention.

Example 5: Capsules comprising atorvastatin and perindopril

5 The immediate-release atorvastatin mini-granules obtained according to Example 1 and the immediate-release perindopril mini-granules obtained according to Example 2 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 5 – Compositions of capsules comprising atorvastatin and perindopril

Dosages (mg)	Atorvastatin / perindopril			
	20/5	20/10	40/5	40/10
Components	Quantity per capsule (mg)			
<u>Immediate-release atorvastatin mini-granules</u>	80	80	160	160
Atorvastatin calcium	21.64	21.64	43.28	43.28
<i>corresponding in terms of base to</i>	20	20	40	40
Calcium carbonate	21.64	21.64	43.28	43.28
Hydroxypropylcellulose	4.32	4.32	8.64	8.64
Polysorbate 80	2.48	2.48	4.96	4.96
Sodium croscarmellose	1.915	1.915	3.83	3.83
Sugar spheres	28.01	28.01	56.02	56.02
<u>Immediate-release perindopril mini-granules</u>	30	60	30	60
Perindopril arginine	5	10	5	10
Hydroxypropylcellulose	2.145	4.29	2.15	4.29
Sugar spheres	22.855	45.71	22.86	45.71
Talc	2.2	2.2	2.2	2.2
Total mass	112.2	142.2	192.2	222.2
Capsule (number)	1	1	1	1

Example 6: Capsules comprising atorvastatin, perindopril and aspirin

In accordance with the same process as that of Example 5, the capsule is filled with immediate-release atorvastatin mini-granules, immediate-release perindopril mini-granules and gastro-resistant acetylsalicylic acid tablets obtained according to Example 3.

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Table 6 – Compositions of capsules comprising atorvastatin, perindopril and acetylsalicylic acid

Dosages (mg) Components	Atorvastatin / perindopril / acetylsalicylic acid			
	20/5/100	20/10/100	40/5/100	40/10/100
	Quantity per capsule (mg)			
<u>Immediate-release atorvastatin mini-granules</u>	80	80	160	160
Atorvastatin calcium <i>corresponding in terms of base to</i>	21.64 20	21.64 20	43.28 40	43.28 40
Calcium carbonate	21.64	21.64	43.28	43.28
Hydroxypropylcellulose	4.32	4.32	8.64	8.64
Polysorbate 80	2.48	2.48	4.96	4.96
Sodium croscarmellose	1.915	1.915	3.83	3.83
Sugar spheres	28.01	28.01	56.02	56.02
<u>Immediate-release perindopril mini-granules</u>	30	60	30	60
Perindopril arginine	5	10	5	10
Hydroxypropylcellulose	2.145	4.29	2.15	4.29
Sugar spheres	22.855	45.71	22.86	45.71
Talc	2.2	2.2	2.2	2.2
<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	257.2	287.2	337.2	367.2
Capsule (number)	1	1	1	1

Example 7: Capsules comprising atorvastatin, perindopril and indapamide

The capsules of Example 7 are obtained in the same manner as the capsules of Example 5, by further adding immediate-release indapamide mini-granules obtained according to Example 4.

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

Dosages (mg)	Atorvastatin / perindopril / indapamide					
	10/5/1.25	10/10/2.5	20/5/1.25	20/10/2.5	40/5/1.25	40/10/2.5
Components	Quantity per capsule (mg)					
<u>Immediate-release atorvastatin mini-granules</u>	40	40	80	80	160	160
Atorvastatin calcium	10.82	10.82	21.64	21.64	43.28	43.28
<i>corresponding in terms of base to</i>	10	10	20	20	40	40
Calcium carbonate	10.82	10.82	21.64	21.64	43.28	43.28
Hydroxypropylcellulose	2.16	2.16	4.32	4.32	8.64	8.64
Polysorbate 80	1.25	1.25	2.48	2.48	4.96	4.96
Sodium croscarmellose	0.9575	0.9575	1.915	1.915	3.83	3.83
Sugar spheres	14.005	14.005	28.01	28.01	56.02	56.02
<u>Immediate-release perindopril mini-granules</u>	30	60	30	60	30	60
Perindopril arginine	5	10	5	10	5	10
Hydroxypropylcellulose	2.145	4.29	2.145	4.29	2.145	4.29
Sugar spheres	22.855	45.71	22.855	45.71	22.855	45.71
Talc	2.2	2.2	2.2	2.2	2.2	2.2
<u>Immediate-release indapamide mini-granules</u>	30	60	30	60	30	60
Indapamide	1.25	2.5	1.25	2.5	1.25	2.5
Hypromellose, type 2910	0.138	0.276	0.138	0.276	0.138	0.276
Microcrystalline cellulose, type CP-305	28.61	57.22	28.61	57.22	28.61	57.22
Total mass	102.2	162.2	142.2	202.2	222.2	282.2
Capsule (number)	1	1	1	1	1	1

CLAIMS

1. Fixed pharmaceutical composition comprising atorvastatin and its pharmaceutically acceptable salts and perindopril and its pharmaceutically acceptable salts in combination with one or more pharmaceutically acceptable excipients, their hydrates and their crystalline forms.
2. Fixed pharmaceutical composition according to claim 1, further comprising aspirin 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.
3. Fixed pharmaceutical composition according to either claim 1 or claim 2, wherein the pharmaceutical composition is a capsule.
4. Fixed pharmaceutical composition according to any one of claims 1 to 3, wherein:
 - the atorvastatin and its pharmaceutically acceptable salts or
 - the perindopril and its pharmaceutically acceptable salts or
 - the indapamide and its pharmaceutically acceptable saltsare each in the form of mini-granules.
5. Fixed pharmaceutical composition according to either claim 2 or claim 3, wherein the aspirin and its pharmaceutically acceptable salts are in the form of a gastro-resistant tablet.
6. Fixed pharmaceutical composition according to any one of claims 1 to 5, wherein the atorvastatin is in the form of atorvastatin calcium.
7. Fixed pharmaceutical composition according to any one of claims 1 to 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 atorvastatin vary from 10 mg to 80 mg, expressed in terms of atorvastatin base, or from 10.80 mg to 86.80 mg, expressed in terms of atorvastatin calcium trihydrate,

- 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,

- the doses of aspirin are from 75 mg to 150 mg, expressed in terms of aspirin base,

- the doses of indapamide vary from 0.625 mg to 2.5 mg, expressed in terms of indapamide base.

9. Fixed pharmaceutical composition according to any one of claims 1 to 8, wherein the doses:

- of atorvastatin calcium are 10 mg, 20 mg, 40 mg and 80 mg,

- of perindopril arginine are 2.5 mg, 3.5 mg, 5 mg, 7 mg, 10 mg and 14 mg,

- of aspirin are 75 mg, 100 mg and 150 mg,

- of indapamide are 0.625 mg, 1.25 mg, 1.5 mg and 2.5 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 coronary events in patients with a past history of myocardial infarction and/or of revascularisation in association with primary hypercholesterolaemia or mixed hyperlipidaemia.