(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 September 2010 (23.09.2010)

PCT

(10) International Publication Number
WO 2010/107966 A1

(51) **International Patent Classification**:
A61K 9/20 (2006.01) ***A61K 31/165*** (2006.01)
A61K 47/02 (2006.01) ***A61K 31/41*** (2006.01)

(21) **International Application Number**:
PCT/US2010/027748

(22) **International Filing Date**:
18 March 2010 (18.03.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/161,883 20 March 2009 (20.03.2009) US

(71) **Applicant** *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **BOSE, Sonali** [IN/US]; Novartis, One Health Plaza, East Hanover, NJ 07936 (US). **LI, Shoufeng** [CN/US]; Novartis, One Health Plaza, East Hanover, NJ 07936 (US). **WEN, Hong** [CN/US]; Novartis, One Health Plaza, East Hanover, NJ 07936 (US).

(74) **Agent**: **MATOVCIK, Lisa**; Novartis, Patent Department, One Health Plaza, Bldg. 101, East Hanover, NJ 07936 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2010/107966 A1

(54) **Title**: PHARMACEUTICAL COMPOSITION COMPRISING ALISKIREN

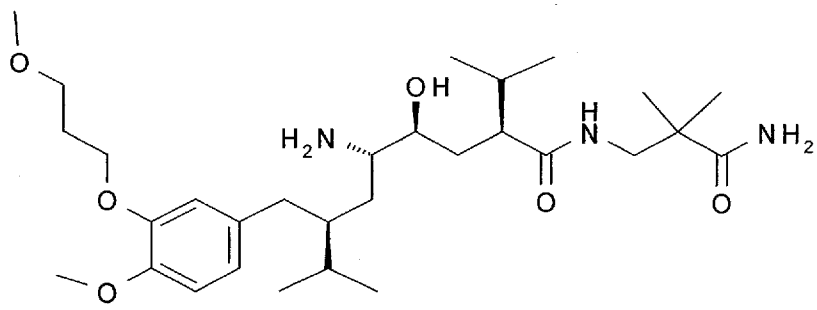
(57) **Abstract**: The present invention relates to a pharmaceutical composition comprising a) a therapeutically effective amount of Aliskiren, or a pharmaceutically acceptable salt thereof, b) a filler; and c) a further specific filler.

PHARMACEUTICAL COMPOSITION COMPRISING ALISKIREN

The present invention relates to pharmaceutical compositions comprising an orally active renin inhibitor, Aliskiren, or a pharmaceutically acceptable salt thereof, as the active ingredients in a suitable carrier. In particular, the present invention provides galenical formulations comprising an orally active renin inhibitor, Aliskiren, or a pharmaceutically acceptable salt thereof, in particular the hemi-fumarate salt of Aliskiren optionally in combination with an angiotensin II antagonist, such as Valsartan. The present invention also relates to the processes for their preparation and to their use as medicaments.

Renin released from the kidneys cleaves angiotensinogen in the circulation to form the decapeptide angiotensin I. This is in turn cleaved by angiotensin converting enzyme in the lungs, kidneys and other organs to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of, e.g., the antihypertensive effect of renin inhibitors. Accordingly, renin inhibitors, or salts thereof, may be employed, e.g., as antihypertensives or for treating congestive heart failure.

The renin inhibitor, Aliskiren, in particular, a hemi-fumarate thereof, is known to be effective in the treatment of reducing blood pressure irrespective of age, sex or race and is also well tolerated. Aliskiren in form of the free base is represented by the following formula



(I)

and chemically defined as 2(*S*),4(*S*),5(*S*),7(*S*)-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide. As described above, most preferred is the hemi-fumarate salt thereof which is specifically disclosed in EP 678503 A as Example 83.

Valsartan is a known Angiotensin receptor blocker (ARB, angiotensin II antagonist) and the combination with Aliskiren is described, e.g. in WO02/40007.

Angiotensin II is a hormone that causes blood vessels to constrict. This, in turn, can result in high blood pressure and strain on the heart. It is known that angiotensin II interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, namely AT1 and AT2, have been identified thus far. In recent times, great efforts have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) are now known to prevent angiotensin II from binding to its receptors in the walls of blood vessels, thereby resulting in lower blood pressure. Because of the inhibition of the AT1 receptor, such antagonists can be used, therefore, as anti-hypertensives or for the treatment of congestive heart failure, among other indications.

Administration of such pharmaceutical agents via the oral route is preferred to parenteral administration because it allow self-administration by patients whereas parenteral formulations have to be administered in most cases by a physician or paramedical personnel.

However, Aliskiren is a drug substance difficult to formulate due to its physicochemical properties and it is not trivial to make oral formulations in the form of tablets in a reliable and robust way, in particular as regards physical properties of the

tablet such as flowability, compression behavior or dissolution rate. For example, Aliskiren has a needle shaped crystallization habit, which has a negative influence on the bulk properties of the drug substance, e.g., flow properties and bulk density. The compression behavior of the drug substance is poor, leading to weak interparticulate bonds and polymorphism changes under pressure. Aliskiren has a strong elastic component that also leads to weakening of interparticulate bonds. The drug substance quality is very variable with effect on the processability of a tablet, e.g., particle size distribution, bulk density, flowability, wetting behavior, surface area and sticking tendency. Moreover, Aliskiren is highly hygroscopic. After contact with water and removal of the water, the drug substance polymorphism changes to an amorphous state, which shows inferior stability compared to the crystalline state.

In addition, in the particular case of high dose of Aliskiren or a pharmaceutically acceptable salt thereof (300 mg or more of the free base per tablet) makes a high drug loading necessary in order to achieve a reasonable tablet size.

The combination of these hurdles makes a standard tablet manufacturing process extremely difficult. A solid oral dosage form of Aliskiren is described in WO2005/089729.

On the other hand, Valsartan has pH dependent solubility whereby it ranges from very slightly soluble in an acidic environment to soluble in a neutral environment of the gastrointestinal tract. Further, development of a patient-convenient oral dosage form of Valsartan is challenging due to its low bulk density.

Moreover, in general the development of oral fixed dose combination formulations using certain active ingredients is challenging. As used herein, "fixed dose combination" refers to a combination of defined doses of two drugs or active ingredients presented in a single dosage unit (e.g. a tablet or a capsule) and administered as such; further as used herein, "free dose combination" refers to a combination of two drugs or active ingredients administered simultaneously but as two distinct dosage units. When formulating oral fixed dose combinations, it is of advantage to provide a patient-convenient dosage form that is bioequivalent to the corresponding free dose combination of the same active ingredients in order to

save time and costs in the development of the fixed dose combination. Development of fixed-dose combinations that are bioequivalent to the free dose combination is challenging due to the multiplicity of hurdles arising from pharmacokinetic and pharmaceutical properties of the drugs sought to be combined.

The difficulties encountered with Aliskiren to prepare oral formulations in the form of tablets in a reliable and robust way are believed to be potentiated when using it in combination with other therapeutic agents, in particular Valsartan for the reasons mentioned above.

In the case where the therapeutic doses of Valsartan and Aliskiren are high, when the two drugs are combined it is highly desired that the amounts of excipients are kept at a minimum to avoid excessively large formulations. Despite that fact, the formulation should still fulfill all of the above requirements.

Accordingly, a suitable and robust galenical formulation overcoming the above problems related to the properties of Aliskiren in particular when formulated together with Valsartan need to be developed.

Surprisingly it has been found that the use of specific fillers enables the preparation of pharmaceutical compositions, in particular in the form of compressed tablets, such as multi-layer tablets, in particular bilayer tablets, overcoming the drawbacks identified above.

Accordingly the present invention provides a pharmaceutical composition comprising

a) a therapeutically effective amount of Aliskiren, or a pharmaceutically acceptable salt thereof,

b) a filler; and

c) one or more, for example one to three, filler differing from the filler b) and independently selected from:

c1) alditols;

c2) mono-, di-, tri-, and polysaccharides; and

c3) a filler having a tapped density in the range of from 0.5 to 1.5 g/cm^3, and

provided that if Indigotin lake is comprised in the composition it is not in an amount of 0.13, 0.2, 0.25 or 0.5 mg per unit dose.

Preferred embodiments are as defined herein and in the subclaims.

In one aspect, the present invention relates to a pharmaceutical composition comprising

a) a therapeutically effective amount of Aliskiren, or a pharmaceutically acceptable salt thereof,

b) a filler; and

c) a filler differing from the filler b) and selected from: c1) alditols, c2) mono-, di-, tri-, and polysaccharides, and c3) a filler having a tapped density in the range of from 0.5 to 1.5 g/cm^3, and

provided that if Indigotin lake is comprised in the composition it is not in an amount of 0.13, 0.2, 0.25 or 0.5 mg per unit dose.

In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising

a) a therapeutically effective amount of Aliskiren, or a pharmaceutically acceptable salt thereof,

b) a filler; and

c) one or more, for example one to three, filler differing from the filler b) and independently selected from c1) alditols or c2) mono-, di-, tri-, and polysaccharides, and

provided that if Indigotin lake is comprised in the composition it is not in an amount of 0.13, 0.2, 0.25 or 0.5 mg per unit dose.

The present invention enables the manufacture of robust galenical formulations, including multi-layer tablets, in particular bilayer tablets.

Throughout the present application, the various terms are as defined below:

Release profile: The term "release" as used herein refers to a process by which the pharmaceutical oral fixed dose combination is brought into contact with a fluid and the fluid transports the drug(s) outside the dosage form into the fluid that surrounds the dosage form. The combination of delivery rate and delivery duration exhibited by a given dosage form in a patient can be described as its in vivo release profile. The release profiles of dosage forms may exhibit different rates and durations of release and may be continuous. Continuous release profiles include release profiles in which one or more active ingredients are released continuously, either at a constant or variable rate.

When two or more components that have different release profiles are combined in one dosage form, the resulting individual release profiles of the two components may be the same or different compared to a dosage form having only one of the components. Thus, the two components can affect each other's release profile leading to a different release profile for each individual component.

A two-component dosage form can exhibit release profiles of the two components that are identical or different to each other. The release profile of a two-component dosage form where each component has a different release profile may be described as "asynchronous". Such a release profile encompasses both (1) different continuous releases where preferably component b) is released at a slower rate than component a), and (2) a profile where one of components a) and b), preferably component b), is released continuous and the other of components a) and b), preferably component a), is modified to be released continuous with a time delay. Also a combination of two release profiles for one drug is possible e.g. 50% of the drug in continuous and 50% of the same drug continuous with a time delay.

Immediate release: For the purposes of the present application, an immediate release formulation is a formulation showing a release of the active substance(s), which is not deliberately modified by a special formulation design or manufacturing method.

Modified release: For the purposes of the present application, a modified release formulation is a formulation showing a release of the active substance(s), which is deliberately modified by a special formulation design or manufacturing method. This modified release can be typically obtained by delaying the time of release of one or both of the components, preferably component a). Typically for the purposes of the present invention, a modified release refers to a release over 5 h, such as a release over 3 h or even shorter. Modified release as used herein is meant to encompass both a different continuous release over time of the two components or a delayed release where one of the components, preferably component a), is released only after a lag time. Such a modified release form may be produced by applying release-modifying coatings, e.g. a diffusion coating, to the drug substance(s) or to a core containing the drug substance(s), or by creating a release-modifying matrix embedding the drug substance(s).

The term "time delay" as used herein refers to the period of time between the administration of a dosage form comprising the composition of the invention and the release of the active ingredient from a particular component thereof.

The term "lag time" as used herein refers to the time between the release of the active ingredient from one component of the dosage form and the release of the active ingredient from another component of the dosage form.

Disintegration: The term “disintegration” as used herein refers to a process where the pharmaceutical oral fixed dose combination, typically by means of a fluid, falls apart into separate particles and is dispersed. Disintegration is achieved when the solid oral dosage form is in a state in which any residue of the solid oral dosage form, except fragments of insoluble coating or capsule shell, if present, remaining on the screen of the test apparatus is a soft mass having no palpably firm core in accordance with USP<701>. The fluid for determining the disintegration property is water, such as tap water or deionized water. The disintegration time is measured by

standard methods known to the person skilled in the art, see the harmonized procedure set forth in the pharmacopeias USP <701> and EP 2.9.1 and JP.

Erosion: The term "erosion" as used herein refers to a process by which the pharmaceutical oral fixed dose combination may be worn away, diminished or deteriorated when placed in an external environment (e.g. dissolution medium, body fluids etc.). In contrast to disintegration, the pharmaceutical oral fixed dose combination is not dispersed by falling apart, rather it is becoming smaller with time as the erosion process proceeds.

Dissolution rate: The term "dissolution" as used herein refers to a process by which a solid substance, here the active ingredients, is dispersed in molecular form in a medium. The dissolution rate of the active ingredients of the pharmaceutical oral fixed dose combination of the invention is defined by the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. The dissolution rate is measured by standard methods known to the person skilled in the art, see the harmonized procedure set forth in the pharmacopeias USP <711> and EP 2.9.3 and JP. For the purposes of this invention, the test is for measuring the dissolution of the individual active ingredients is performed following pharmacopeia USP <711> at pH 4.5 using a paddle stirring element at 75 rpm (rotations per minute). The dissolution medium is preferably a buffer, typically a phosphate buffer, especially one as described in the example "Dissolution Test". The molarity of the buffer is preferably 0.1 M.

Physically separated: The term "physically separated" as defined herein refers to a pharmaceutical composition in the form of a fixed dose combination containing both components a) and d) formulated such that they are not mixed with each other in the same carrier but are separated. This physical separation of the two components a) and d) in one dosage form can be achieved by various means known in the art, e.g. either by formulating the respective components a) and d) into separate layers or shells to obtain, e.g. a bilayer formulation or a dry-coated (core in a shell) tablet, or by using particulate systems (multiparticulates) that comprise particles of different populations of component a) and component d), respectively, to obtain, e.g. capsules, sachets, stickpacks filled with multiparticulates, tablets obtained from

compressing multiparticulates, and minitablets obtained from compressing multiparticulates, such as granules or beads, which can subsequently be filled into capsules. Another form of a physical separation is, for example, a capsule filled with 1) multiparticulates of one of the components and 2) one tablet, several tablets or minitablets obtained from compressing multiparticulates, such as granules or beads, of the other component.

The term "particulate" as used herein refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. When a plurality of particulates is present, these are referred to as multiparticulates. Typically, the particulates have an average size of lower than about 3 mm, preferably between about 1 μm to 3 mm. By " average particle size" it is meant that at least 50% of the particulates have a particle size of less than about the given value, by weight. The particle size may be determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

The term "small tablets" within the scope of this application denotes tablets with an overall size of about 3 to 5 mm.

The term "minitablets" within the scope of this application denotes small tablets with an overall weight of approximately 2 to 30 mg, e.g. approximately 4 to 9 mg, e.g. approximately 7 mg, in their uncoated form. Minitablets are a specific form of multiparticulates as defined herein. They can be prepared as described herein, including preparation from other, smaller multiparticulates, such as granules or beads. The minitablets may have any shape known to the skilled person for tablets, e.g. round e.g. with a diameter of about 1.25 to 3 mm; cyclindrical e.g. having a convex upper face and convex lower face and e.g. with a cylindrical diameter and height independently of each other are from 1 to 3 mm; or biconvex minitablets e.g. whose height and diameter are approximately equal and are from 1.25 to 3 mm.

Preferably, multiparticulates have a controlled release coating. Specifically, if a mixture of multiparticulates component a) and component d) are used, the respective

multiparticulates comprise different controlled release coatings in order to provide different controlled release profiles.

The term "fixed dose combination" refers to a combination of defined doses of two drugs or active ingredients presented in a single dosage unit (e.g. a tablet or a capsule) and administered as such; further as used herein, "free dose combination" refers to a combination of two drugs or active ingredients administered simultaneously but as two distinct dosage units.

The terms "effective amount" or "therapeutically effective amount" refers to the amount of the active ingredient or agent which halts or reduces the progress of diabetic cardiomyopathy, or which otherwise completely or partly cures or acts palliatively on the condition.

The term "prophylactically effective amount" refers to the amount of the active ingredient or agent prevents the onset of diabetic cardiomyopathy.

The term "warm-blooded animal or patient" are used interchangeably herein and include, but are not limited to, humans, dogs, cats, horses, pigs, cows, monkeys, rabbits, mice and laboratory animals. In one embodiment, the mammals are humans.

The term "treatment" means the management and care of a patient for the purpose of preventing, combating or delaying progression of the disease, condition or disorder, preferably for the purpose of combating the disease, condition or disorder, and in particular it also prophylactic treatment.

The terms "prevention"/"preventing" are to be understood as meaning the prophylactic administration of a drug, such as a combined preparation or pharmaceutical composition, to healthy patients to prevent the outbreak of the disease, condition or disorder.

The terms "delay of progression"/"delaying progression" are to be understood as meaning the administration of a drug, such as a combined preparation or

pharmaceutical composition, to patients being in a pre-stage of the disease, condition or disorder.

The terms “drug”, “active substance”, “active ingredient”, “active agent” are to be understood as meaning a compound in free form or in the form of a pharmaceutically acceptable salt, in particular as specified herein.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases, disorders and the like, this is intended to mean one or more single compound(s), salt(s), pharmaceutical composition(s), disease(s), disorder(s) or the like, where the singular or the indefinite article (“a”, “an”) is used, this is intended to include the plural or the singular (“one”).

The term “polysaccharide” as used herein means a polymer made up of saccharide units.

The term "polysaccharide" is defined as being inclusive of homopolymers, copolymers of saccharide monomers and derivatives thereof, and it is inclusive of linear saccharide chains, non-linear saccharide chains and cross-linked saccharide chains.

The term "copolymer" is defined as a polymer derived from more than one species of monomer, including copolymers that are obtained by copolymerization of two monomer species, those obtained from three monomers species ("terpolymers"), those obtained from four monomers species ("quaterpolymers"), etc. The term "copolymer" is further defined as being inclusive of random copolymers and alternating copolymers. The term "random copolymer" is defined as a copolymer comprising molecules in which the probability of finding a given monomeric unit at any given site in the chain is independent of the nature of the adjacent units. The term "alternating copolymer" is defined as a copolymer comprising molecules that include two species of monomeric units in alternating sequence.

The term “homopolysaccharide” as used herein means a polysaccharide made off a single type of saccharide unit. It is inclusive of linear, non-linear and cross-linked polysaccharides, in particular non-linear and cross-linked polysaccharides. In one

embodiment, an homopolysaccharide is a linear polysaccharides wherein the saccharide units are connected via alpha-glycosidic bonds or both alpha- and beta-glycosidic bonds. In another embodiment the term homopolysccharide is a linear polysachharide wherein the saccharide unit is not glucose.

The term "heteropolysaccharide" as used herein means a polysaccharide wherein not all of the saccharide units are the same type. It is inclusive of linear, non-linear and cross-linked heteropolysaccharide.

The term "saccharide unit" as used herein means one saccharide molecule. A saccharide unit is a monomeric unit of a polysaccharide. The term "saccharide" is inclusive of carbohydrates, such as glucose, fructorse or galactose, and derivatives thereof, such as mannuronic acid or guluronic acid.

The term "linear polysaccharide" as used herein means a polysaccharide whose saccharide units are arranged in chain-like fashion with no branches or bridges between the chains.

The term "cross-linked polysaccharide" as used herein means polysaccharide wherein there are bridges linking the polysaccharide chains.

The term "non-linear polysaccharide" or "branched polysaccharide" as used herein means a polysaccharide wherein there are saccharide units having at least one branching point, for example one to three branching points. This term is inclusive of any polysaccharide comprising at least one backbone and at least one terminal branch.

The term "branch" as used herein is inclusive of any saccharide unit or linear polysaccharide which is covalently attached at at least one end to the side group of a branching saccharide unit.

The terms "indigotin LAKE 12196" or "indigotin lake" or "indigotin farBlack" or "indigotin"

refer to a coloring agent, pigment agent or dye commercially available, for example, from UNIVAR LTD and as described, for example, in www.kremer-pigmente.com and in http://www.foodadditivesworld.com/fdc-blue-no2-lake.html.

The pharmaceutical composition in accordance with the present invention is, as defined in claim 1, characterized in that it comprises in addition to components a) and b) a filler as defined as component c) in claim 1. The use of such specific fillers surprisingly overcomes the drawbacks associated with the prior art and enables, in embodiments, the following:

- High loading of component a) (in embodiments 300mg or more per unit dose of a pharmaceutical composition) while maintaining suitable physical and pharmacological properties, as well as the suitability of forming pharmaceutical compositions in the form of compressed tablets, in particular multi-layer tablets, such as bilayer tablets, using conventional equipment.
- Preparation of multi-layer tablets, in particular bilayer tablets, with suitable physical properties, such as friability and hardness, in embodiments even with high hardness, such as from 200 to more than 300 N, such as up to 350 N.
- Maintenance of desired properties for use, such as disintegration time and dissolution profile.

The filler c) to be employed in accordance in the present invention is selected among the groups c1) to c3) as identified in claim 1.

The tapped density for group c3) is determined according to established standards, in particular as measured by USP <616>.. In particular, the tapped density for group c3) is in the range of from 0.5 to 1.5, such as 0.6 to 1.2 g/cm^3.

Preferred embodiments are as follows:

c1): mannitol and sorbitol, most preferably mannitol

c2): lactose, sucrose, dextrose, most preferably lactose

c3): starch, dicalcium phosphate

Particularly preferred are mannitol and lactose. It is further preferred that only one filler c) is present in the pharmaceutical composition of the present invention.

The components a) to c) of the pharmaceutical composition of the present invention are preferably employed in the following weight ratios, based on the total weight of the pharmaceutical composition:

Weight ratio a):c) : of from 20:1 to 1:1, in particular of from 15:1 to 2:1, such as of from 8:1 to 2:1, particularly of from 6:1 to 3:1. These weight ratios are based on the free base of component a) and if a salt is used the weight ratios will be adapted accordingly.

Weight ratio b):c) : of from 10:1 to 1:10, preferably of from 5:1 to 1:5, more preferably of from 4:1 to 2:1.

In another preferred embodiment of the present invention component a) is present in an amount of 10 to 45%, such as 10 to 40%, in one embodiment 15 to 35%, such as 20 to 30% by weight based on the total weight of the pharmaceutical oral fixed dose combination. These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

In a preferred embodiment of the present invention, component a) is present in an amount ranging of from 75 to 300 mg, such as 150 to 300 mg, per unit pharmaceutical oral fixed dose combination, in particular 75, 150 or 300 mg, such as 150 or 300 mg. These amounts are based on the free base of component a) and if a salt is used the amounts will be adapted accordingly.

In another embodiment, component a) is present in an amount of 40% of more, such as 50% or more, such as 60% or more, by weight based on the total weight of the granules comprising component a). These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

In a further embodiment, in a multilayer tablet, according to the present invention, such as a bilayer tablet, component a) is present in an amount of from 40 to 70%, such as 45 to 65%, such as 50 to 65%, by weight based on the total weight of the granules comprising component a). These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

It is further preferred when the pharmaceutical composition of the present invention satisfies both weight ratios, i.e. it is preferred when the weight ration a):c) and b):c) are as defined above, more preferably when both ratios are within the respective preferred ranges as identified above. When the present invention concerns a pharmaceutical composition in the form of a fixed combination of component a) with a second active principle d), which is as defined below, in particular multi-layer tablets, such as a bilayer tablet, the above given weight ratios apply to the part of the fixed dose combination containing component a). e.g. when the pharmaceutical composition is present in the form of a bilayer tablet the weight ratios given above relate to the layer containing component a).

In a further embodiment the present invention overcomes the drawbacks associated with the prior art by providing a specific process for preparing a pharmaceutical composition comprising aliskiren or a pharmaceutically acceptable salt thereof by modifying the known processes for preparing granulates containing aliskiren or a pharmaceutically acceptable salt thereof. This method is defined in claim 14 and a preferred embodiment is given in claim 15.

Surprisingly it has also been found that by a simple process modification, without using new additives, it is possible to provide a granular product containing aliskiren or a pharmaceutically acceptable salt thereof, enabling the preparation of compressed tablets, fixed dose combinations and/or multi-layer tablets, such as bilayer tablets, comprising aliskiren or a pharmaceutically acceptable salt thereof, wherein aliskiren or a pharmaceutically acceptable salt thereof is contained at a higher loading, such as 300 mg (of the free base and if a salt is used the amount will be adapted accordingly) or more per dosage unit,

without encountering difficulties during the manufacture of such products (in particular multi-layer tablets, such as bilayer tablets). The use of a second treatment step of a granulated product containing aliskiren or a pharmaceutically acceptable salt thereof as defined in claim 14 and in particular as defined in claim 15 provides a granular product with highly beneficial properties for preparing products as identified above. Due to the use of the second treatment step prior to the manufacture of a final product, the fine content is reduced and/or the bulk and/or tapped density is increased, which surprisingly enables the formation of pharmaceutical dosage forms with higher loadings of aliskiren or a pharmaceutically acceptable salt thereof even on a large scale, without sacrificing physical or other properties of the dosage form.

Concerning the above identified aspect of the present invention it is emphasized that the preferred embodiments as described herein for the bilayer tablet and the pharmaceutical composition apply also for the novel and inventive process as described above.

As indicated above, the present invention in particular contemplates fixed dose combinations, preferably oral fixed dose combinations of a pharmaceutical composition as defined herein, with a second active principle d) being different from component a). Such as fixed dose combination may be formulated in any desired way, in particular preferred is a multi-layer tablet, such as a bilayer tablet. Component b) of such a fixed dose combination may be selected as desired, preferably however component d) is valsartan or a pharmaceutically acceptable salt thereof. In such a fixed dose combination component d) may be present in the form of a suitable composition, i.e. together with additives as descried herein. It is however preferred that the composition comprising component d) or the respective part of a fixed dose combination does not comprise the filler c) as defined herein for the pharmaceutical composition of the present invention comprising components a) to c).

In the following the present invention will be described in more detail in relation to a multi-layer tablet, in particular a bilayer tablet, comprising as component d) valsartan or a pharmaceutically acceptable salt thereof. This however should not be

construed as a limitation and the embodiments as described here apply likewise to other fixed dose combinations as well as to other embodiments of the pharmaceutical composition of the present invention.

In another preferred embodiment of the present invention component a) is present in an amount of 10 to 45%, such as 10 to 40%, in one embodiment 15 to 35%, such as 20 to 30% by weight based on the total weight of the pharmaceutical oral fixed dose combination. These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

In a preferred embodiment of the present invention, component a) is present in an amount ranging of from 75 to 300 mg, such as 150 to 300 mg, per unit pharmaceutical oral fixed dose combination, in particular 75, 150 or 300 mg, such as 150 or 300 mg. These amounts are based on the free base of component a) and if a salt is used the amounts will be adapted accordingly.

In another embodiment, in a multilayer tablet, according to the present invention, such as a bilayer tablet, component a) is present in an amount of 40% of more, such as 50% or more, such as 60% or more, by weight based on the total weight of the layer comprising component a). These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

In a further embodiment, in a multilayer tablet, according to the present invention, such as a bilayer tablet, component a) is present in an amount of from 40 to 70%, such as 45 to 65%, such as 50 to 65%, by weight based on the total weight of the layer comprising component a). These percentages are based on the free base of component a) and if a salt is used the percentages will be adapted accordingly.

In a preferred embodiment of the present invention, component d) is present in an amount ranging from 8 to 45%, such as 15 to 35%, in particular 20 to 30%, by weight based on the total weight of the pharmaceutical oral fixed dose combination. These percentages are based on the free acid of component d) and if a salt is used the percentages will be adapted accordingly.

It is preferred that component d) is present in an amount ranging from 75 to 350mg, such as 80 mg to 320 mg, such as 160 to 320 mg, per unit dosage form, in particular 80, 160 or 320 mg, such as 160 or 320 mg. These amounts are based on the free acid of component d) and if a salt is used the amounts will be adapted accordingly.

In one embodiment it is preferred to use a high drug load using 300 mg of a) and/or 320 mg of d), most preferably 300/320 mg of a)/d). These amounts are based on the free base of component a) and the free acid of component d), and if salts are used the amounts will be adapted accordingly.

The terms "effective amount" or "therapeutically effective amount" refers to the amount of the active ingredient or agent which halts or reduces the progress of the condition being treated or which otherwise completely or partly cures or acts palliatively on the condition. The terms "drugs", "active substances", active ingredients", "active agents" etc. as used herein refer to components a) and d) unless specified otherwise. Each of component a) or d) can be referred to as a "drug", "active substance", active ingredient", "active agent" etc..

In the above and in the following the term "Aliskiren", if not defined specifically, is to be understood both as the free base and as a salt thereof, especially a pharmaceutically acceptable salt thereof, such as a hemi-fumarate, hydrogen sulfate, orotate or nitrate, most preferably a hemi-fumarate thereof.

Aliskiren, or a pharmaceutically acceptable salt thereof, can, e.g., be prepared in a manner known *per se*, especially as described in EP 678503 A, e.g., in Example 83.

In the following the term "Valsartan", if not defined specifically, is to be understood both as the free base and as a salt thereof, especially a pharmaceutically acceptable salt thereof, as described below.

Valsartan , or a pharmaceutically acceptable salt thereof, can, e.g., be prepared in a manner known *per se*. Preferred salts forms include acid addition salts. The compounds having at least one acid group (e.g., COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases are, e.g., metal salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, calcium or magnesium salts, or

salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, e.g., ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, e.g., mono-, di- or tri-ethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, e.g., for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included. Even more preferred salts are, e.g., selected from the mono-sodium salt in amorphous form; di-sodium salt of Valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Mono-potassium salt of Valsartan in amorphous form; di-potassium salt of Valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Calcium salt of Valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof; magnesium salt of Valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof; calcium/magnesium mixed salt of Valsartan in crystalline form, especially in hydrate form; *bis*-diethylammonium salt of Valsartan in crystalline form, especially in hydrate form; *bis*-dipropylammonium salt of Valsartan in crystalline form, especially in hydrate form; *bis*-dibutylammonium salt of Valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof; mono-*L*-arginine salt of Valsartan in amorphous form; *bis*-*L*-arginine salt of Valsartan in amorphous form; mono-*L*-lysine salt of Valsartan in amorphous form; *bis*-*L*-lysine salt of Valsartan in amorphous form.

Most preferably, Valsartan is used as the free acid.

The fixed dose combination according to the present invention needs to be selected appropriately to show the desired properties, such as dissolution profile. Typically, the fixed dose combination is a solid dosage form.

The oral fixed dose combination of the present invention preferably exhibits release profiles of both components a) and d), more preferably component a) that are

regarded as modified release profiles. The oral fixed dose combination of the present invention preferably exhibits a release profile of component d) that is regarded as an immediate release profile. In a preferred embodiment of the present invention, the release profiles of the two active principles a) and d) of the oral fixed dose combination are asynchronous. In one embodiment, both components are released continuously with an asynchronous release profile, whereby one of the components, preferably component a), is modified to be released at a slower continuous rate. In another embodiment, one of the components, preferably component a), is released with a time delay so as result in a time lag of component a) compared to component d).

Preferably, the pharmaceutical oral fixed dose combination of the present invention is designed in such a way that components a) and d) are physically separated. Typical technologies and formulation principles for pharmaceutical oral fixed dose combinations include multi-layer tablets, such as bilayer tablets.

Thus, the present invention is in particular related to a pharmaceutical oral fixed dose combination in the form of a bilayer tablet.

Bilayer tablets according to the present invention are characterized in that one layer contains component a) and the other layer contains component d). Both layers may be made up of a single phase or one or both layers may comprise an internal and an external phase as known to the skilled person. Preferably both layers comprise an internal and an external phase.

Bilayer tablets can be manufactured by methods known in the art, in particular, the methods described for preparing the individual tablets containing either component a) or component d). Preferably, each of the layers can be prepared using wet or dry granulation. Examples for wet granulation are aqueous or organic wet granulation, in particular organic wet granulation as described below. Preferred examples of dry granulation include roller compaction as described e.g. below. Dry granulation methods are preferred since these circumvent the use of solvents and avoid additional drying steps. For the bilayer tablet of the present invention, the individual layers can be prepared by the same or different processes for example one layer can

be prepared by wet granulation and the second layer can be prepared by roller compaction or, most preferably, both layers can be prepared using roller compaction.

Pharmaceutically acceptable additives suitable for use in the pharmaceutical compositions, in particular in the form of the tablets, such as multi-layer tablets, in particular bilayer tablets, according to the present invention include, without limitation, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and combinations thereof. Preferred pharmaceutically acceptable additives include fillers and binders. The amount of each additive in a pharmaceutical oral fixed dose combination may vary within ranges conventional in the art.

Suitable fillers include, without limitation, microcrystalline cellulose (e.g., cellulose MK GR), low-substituted hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, and combinations thereof, preferably, microcrystalline cellulose, e.g., products available under the registered trade marks AVICEL, FILTRAK, HEWETEN or PHARMACEL. When present, a filler in the layer containing component a) may be employed in an amount ranging from about 1% to about 30%, preferably from about 2% to about 20% by weight of the bilayer tablet (prior to any optional film coating). When present, a filler in the layer containing component d) may be employed in an amount ranging from about 1% to about 40%, preferably from about 10% to about 25% by weight of the bilayer tablet (prior to any optional film coating). Preferably, both layers contain a filler.

Suitable binders include, without limitation, polyvinylpyrrolidone (PVP), such as e.g., PVP K 30 or PVP90F, polyethylene glycols (PEG), e.g., PEG 4000, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, both preferably of medium to high viscosity, , e.g., viscosity grades 3 or 6 cps, pregelatinized starch and combinations thereof.. A most preferred binder is PVP K 30 or PVP90F. A roller compacted layer containing component a) preferably contains the binder in the internal phase and a wet-granulated layer containing component a) preferably contains the binder in the internal and in the external phase. When present, a binder in the layer containing component a) may be employed in an amount ranging from about 0.1% to about 20%, preferably from about 0.5% to about 15%, such as 0.7% to 10%, by weight of the bilayer tablet (prior to any optional film coating).

When present, a binder in the layer containing component d) may be employed in an amount ranging from about 0.1% to about 20%, preferably from about 0.2% to about 10% by weight of the bilayer tablet (prior to any optional film coating).

Suitable lubricants include, without limitation, magnesium stearate, aluminum or calcium silicate, stearic acid, cutina, PEG 4000-8000, talc and combinations thereof, preferably magnesium stearate. When present, a lubricant in the layer containing component a) may be employed in an amount ranging from about 0.1% to about 5%, preferably from about 0.5% to about 3%, by weight of the bilayer tablet (prior to any optional film coating). When present, a lubricant in the layer containing component d) may be employed in an amount ranging from about 0.1% to about 5%, preferably from about 0.5% to about 3%, by weight of the bilayer tablet (prior to any optional film coating). Preferably, both layers contain a lubricant, in each case preferably both in the external and the internal phase.

Suitable disintegrants include, without limitation, carboxymethylcellulose calcium (CMC-Ca), carboxymethylcellulose sodium (CMC-Na), crosslinked PVP (e.g. CROSPOVIDONE, POLYPLASDONE or KOLLIDON XL), alginic acid, sodium alginate and guar gum, most preferably crosslinked PVP (CROSPOVIDONE), crosslinked CMC (Ac-Di-Sol), carboxymethylstarch-Na (PIRIMOJEL and EXPLOTAB). A most preferred disintegrant is crosslinked PVP, preferably PVPPXL. When present, a disintegrant in the layer containing component a) may be employed in an amount ranging from about 0.5% to about 20%, preferably from about 1% to about 3%, by weight of the bilayer tablet (prior to any optional film coating). When present, a disintegrant in the layer containing component d) may be employed in an amount ranging from about 1% to about 20%, preferably from about 2% to about 12%, by weight of the bilayer tablet (prior to any optional film coating). Preferably the disintegrant is absent in the layer containing component a), especially in a roller compacted layer containing component a). A wet granulated layer containing component a) may contain the disintegrant. Preferably layer containing component d) includes a disintegrant.

Suitable glidants include, without limitation, colloidal silicon dioxide (e.g., Aerosil 200), magnesium trisilicate, powdered cellulose, starch, talc and combinations

thereof. When present, a glidant in the layer containing component a) may be employed in an amount ranging from about 00.05% to about 5%, preferably from about 0.1% to about 1%, by weight of the bilayer tablet (prior to any optional film coating). When present, a disintegrant in the layer containing component d) may be employed in an amount ranging from about 0.05% to about 5%, preferably from about 0.1% to about 1%, by weight of the bilayer tablet (prior to any optional film coating).

The pharmaceutical oral fixed dose combinations of the first embodiment of the invention are bilayer tablet pharmaceutical oral fixed dose combinations of low friability. Preferably the friability is not more than 0.8%. The friability is measured by standard methods known to the person skilled in the art, see the harmonized procedure set forth in the pharmacopeias USP <1216> and EP 2.9.7 and JP.

The pharmaceutical oral fixed dose combinations of the first embodiment of the invention are bilayer tablet pharmaceutical oral fixed dose combinations of suitable hardness (the method for determining the hardness should be given) (e.g. an average hardness ranging from about 200 N to about 350 N for bilayer forms). Such an average hardness is determined prior to the application of any film coating on the pharmaceutical oral fixed dose combinations. In that regard, a preferred embodiment of this invention is directed to pharmaceutical oral fixed dose combinations which are film-coated. Suitable film coatings are known and commercially available or can be made according to known methods. Typically the film coating material is a polymeric film coating material comprising materials such as hydroxypropylmethyl cellulose, polyethylene glycol, talc and colorant. Typically, a film coating material is applied in such an amount as to provide a film coating that ranges from about 1% to about 6% by weight of the film-coated tablet.

A further embodiment of the present invention is a process for the manufacture of a bilayer tablet according to the present invention. A bilayer tablet comprising one layer containing component a) and one layer containing component d) can be prepared by the following method, comprising the steps of (1) granulating component a) and pharmaceutically acceptable additives, optionally in the presence of a granulation liquid, to form an Aliskiren granulate; (2) granulating component d) and

pharmaceutically acceptable additives to form a Valsartan granulate; (3) optionally drying resulting respective granulates; (4) sieving; (5) optionally mixing the respective granulates with outer phase excipients; and (6) compressing the Valsartan granulates and the Aliskiren granulates together to form a bilayer tablet. The details regarding the components a) and d) and pharmaceutically acceptable additives, i.e., source, amount, etc., are as set forth above.

In the first step of the method, component a) is granulated with pharmaceutically acceptable additives, optionally in the presence of a granulation liquid, to form an Aliskiren granulate. The granulation liquid can be any liquid or liquid mixture well-known in the granulation art such as ethanol, a mixture of ethanol and water, a mixture of ethanol, water and isopropanol, said mixtures may contain a binder, such as those described herein. The process is then referred to as an organic wet granulation. A preferred mixture of ethanol and water ranges from about 50/50 to about 99/1 (% w/w), most preferably it is about 94/6 (% w/w). A preferred mixture of ethanol, water and isopropanol ranges from about 45/45/5 to about 98/1/1 (% w/w/w), most preferably from about 88.5/5.5/6.0 to about 91.5/4.5/4.0 (% w/w/w). In a preferred embodiment, the granulation is effected by an ethanolic solution of the binder and additional ethanol. Aliskiren granulation can be accomplished by any suitable means. Aliskiren granulation is typically accomplished using the following method (wet granulation) (1) blending component a) and pharmaceutically acceptable additives in the presence of a granulation liquid to form a blended material; (2) drying the blended material, (3) sieving the blended material; and (4) screening the sieved material to isolate the adequate Aliskiren granulate fraction. Alternatively, Aliskiren granulation is accomplished using another method (dry granulation) as follows : (1) blending component a) and pharmaceutically acceptable additives to form a blended material; (2) sieving the blended material; (3) blending the sieved material to form a final blend material; (4) compacting the final blend material to form a compacted material; (5) milling the compacted material to form a milled material; and (6) blending the milled material to form the Aliskiren granulate.

Attention is drawn to the numerous known methods of granulating, drying sieving and mixing employed in the art, e.g., spray granulation in a fluidized bed, wet granulation

in a high-shear mixer, melt granulation, drying in a fluidized-bed dryer, mixing in a free-fall or tumble blender, compressing into tablets on a single-punch or rotary tablet press. The blending steps can be accomplished using any suitable means. Typically the component a) and pharmaceutically acceptable additives are dispatched to a suitable vessel such as a diffusion blender or diffusion mixer. The drying of step can be accomplished using any suitable means, e.g. . The sieving steps can be accomplished using any suitable means, e.g. using oscillating sieving. The screening step can be accomplished using any suitable means. The compacting step can be accomplished using any suitable means. Typically compacting is accomplished using a roller compactor with a compaction force ranging from about 20 kN to about 60 kN, preferably about 35 kN. Compaction may also be carried out by slugging the blended powders into large tablets that are then size-reduced. The milling step can be accomplished using any suitable means. Typically the compacted material is milled through a screening mill. Preferably the milled material is blended, often with a pharmaceutically acceptable additive such as a lubricant, in a diffusion blender.

In the second step of the method, component d) is granulated with pharmaceutically acceptable additives to form a Valsartan granulate. Valsartan granulation can be accomplished by any suitable means. In a preferred embodiment of this invention, Valsartan granulation is accomplished by (1) blending component d) and pharmaceutically acceptable additives to form a blended material; (2) sieving the blended material ; (3) blending the sieved material to form a final blend material; (4) compacting the final blend material to form a compacted material; (5) milling the compacted material to get a milled material; and (6) blending the milled material to form the Valsartan granulate.

The blending of step (1 and 3) can be accomplished using any suitable means. Typically the component d) and pharmaceutically acceptable additives are dispatched to a suitable vessel such as a diffusion blender or diffusion mixer. The sieving of step (2) can be accomplished using any suitable means such as those described above. The compaction of step (4) can be accomplished using any suitable means. For example, typically for component b) compacting is accomplished using a roller compactor with a compaction force ranging from about

20 kN to about 60 kN, preferably about 35 kN. Compaction may also be carried out by slugging the blended powders into large tablets that are then size-reduced. The milling of step (5) can be accomplished using any suitable means. Typically the compacted material is milled through a screening mill. The blending of step (6) can be accomplished using any suitable means. Preferably the milled material is blended, often with a pharmaceutically acceptable additive such as a lubricant, in a diffusion blender.

In a further step of the method, pharmaceutically acceptable additives may be added to the valsartan granulates and/or the aliskiren granulates. This is described as adding additives in the outer phase. The respective Aliskiren and Valsartan granulates are referred to a the inner phase. The additives may be distributed partly in the granulate (in the inner phase) and partly in the outer phase, which is preferably the case in the described invention. Filler, lubricant and glidant (if present), more preferably lubricant, can be distributed partly in the inner and partly in the outer phase, binder (if present) is preferably only part of the inner phase.

In the final step of the method, the Valsartan granulate (including additives) and the Aliskiren granulates (including additives) are compressed together to form a bilayer tablet. Compression can be accomplished using any suitable means. Typically compression is accomplished using a bilayer rotary tablet press. Typical compression force ranges from about 5 kN to about 35 kN. Preferably, the layer containing component d) is pre-compressed and the layer containing component a) is added to the resulting pre-compressed layer and then both layers are compressed.

Optionally, the method comprises the step of film coating the bilayer tablet. The details regarding the film coating material, i.e., components, amounts, etc., are as described above. Film coating can be accomplished using any suitable means. Suitable film coatings are known and commercially available or can be made according to known methods. Typically the film coating material is a polymeric film coating material comprising materials such as hydroxypropylmethyl cellulose, polyethylene glycol, talc and colorant. Typically, a film coating material is applied in

such an amount as to provide a film coating that ranges from about 1% to about 6% by weight of the film-coated tablet.

The resulting formulations in accordance with the present invention show the following advantages:

- A relatively high drug loading may easily be achieved;
- The formulation of pharmaceutical oral fixed dose combinations with sufficient hardness, resistance to friability, disintegration time etc. is possible;
- A robust manufacturing process is achieved;
- Scale-up of formulation and process resulting in a reproducible performance is achieved; and
- Sufficient stability to achieve a reasonable shelf life is achieved.

The invention likewise relates to a process for the preparation of pharmaceutical oral fixed dose combinations as described herein above. Such pharmaceutical oral fixed dose combination may be produced by working up components as defined herein above in the appropriate amounts, to form unit pharmaceutical oral fixed dose combinations.

The pharmaceutical composition as well as the (oral) fixed dose combinations of the present invention are useful for lowering the blood pressure, either systolic or diastolic or both. The conditions for which the instant invention is useful include, without limitation, hypertension (whether of the malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction (such as Alzheimer's) and stroke, headache and chronic heart failure.

The present invention likewise relates to a method of treating hypertension (whether of the malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, e.g., Alzheimer's, stroke, headache and chronic

heart failure comprising administering to an animal, including human patient, in need of such treatment a therapeutically effective pharmaceutical composition or (oral) fixed dose combination according to the present invention.

The present invention likewise relates to the use of a pharmaceutical composition or (oral) fixed dose combination according to the present invention for the manufacture of a medicament for the treatment of hypertension (whether of the malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, e.g., Alzheimer's, stroke, headache and chronic heart failure.

The present invention likewise relates to a pharmaceutical composition for the treatment of hypertension (whether of the malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, e.g., Alzheimer's, stroke, headache and chronic heart failure, comprising a pharmaceutical oral fixed dose combination according to the present invention.

Ultimately, the exact dose of the active agent and the particular formulation to be administered depend on a number of factors, e.g., the condition to be treated, the desired duration of the treatment and the rate of release of the active agent. For example, the amount of the active agent required and the release rate thereof may be determined on the basis of known *in vitro* or *in vivo* techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be

construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Example 1:

Bilayer Tablet Formulation

Compositions of Aliskiren and Valsartan tablets in mg/unit.

The components of the Aliskiren layer were mixed, granulated and optionally compressed as described herein for preparing a roller-compacted Aliskiren layer. The components of the Valsartan layer were mixed, granulated and compressed as described herein. The Valsartan layer was filled into an eccentric tablet press for all bilayer variants and compressed with a compression force of <2.5kN. The Aliskiren layer was added on top of the Valsartan layer and then the tablet core was compressed between 5-40kN to obtain a bilayer tablet core.

Aliskiren/Valsartan 150/160mg	**mg per unit**		*% tablet weight*
Aliskiren layer			
Aliskiren compacted granulate	298.50		48.93
Aliskiren hemifumarate	165.75		*27.17*
Cellulose MK GR	63.975		*10.49*
Mannitol DC	51.00		*8.36*
Indigotin Lake 12196	0.075		*0.01*
PVP XL	9.00		*1.48*
Aerosil 200	2.85		*0.47*
Mg stearate (internal)	5.85		*0.96*
Mg-Stearate (external)	1.50		0.25
Valsartan layer			
Vasartan compacted Granulate *2	307.00		50.33
Valsartan		*160.00*	*26.23*
Cellulose MK GR		*91.50*	*15.00*
PVP XL		*15.50*	*2.54*
L-HPC		*31.00*	*5.08*
Aerosil 200		*3.00*	*0.49*
Mg stearate (internal)		*6.00*	*0.98*
Mg-Stearate (external)	3.00		0.21
	610.00		100.00
Hardness [N] (mean)	270		
Friability 10St. /6.5g 500U.[%]	0.3		

Disintegration Time (min)	16.5

Example 2:

Bilayer Tablet Formulation

Aliskiren/Valsartan 300/320mg	**mg per unit**	*% tablet weight*
Aliskiren layer		
Aliskiren compacted granulate	597.00	48.93
Aliskiren hemifumarate	331.50	*27.17*
Cellulose MK GR	127.95	*10.49*
Mannitol DC	102.00	*8.36*
Indigotin Lake 12196	0.15	*0.01*
PVP XL	18.00	*1.48*
Aerosil 200	5.70	*0.47*
Mg stearate (internal)	11.70	*0.96*
Mg-Stearate (external)	3.00	0.25
Valsartan layer		
Vasartan compacted Granulate *2	614.00	50.33
Valsartan	*320..00*	*26.23*
Cellulose MK GR	*183.00*	*15.00*
PVP XL	*31.00*	*2.54*
L-HPC	*62.00*	*5.08*
Aerosil 200	*6.00*	*0.49*
Mg stearate (internal)	*12.00*	*0.98*
Mg-Stearate (external)	6.00	0.21
	1220.00	100.00
Hardness [N] (mean)	300	
Friability 10St. /6.5g 500U.[%]	0.4	
Disintegration Time (min)	17.1	

Example 3:

Bilayer Tablet Formulation

Aliskiren/Valsartan 300/320mg	**mg per unit**	*% tablet weight*
Aliskiren layer	500.00	44.64
Aliskiren compacted granulate		
Aliskiren hemifumarate	331.5	29.60
Cellulose MK GR	41	3.66
Lactose, Anhydrous DT	80	7.14
Crospovidone	20	1.79
HPC EXF	15	1.34
Aerosil 200	5	0.45
Mg stearate (internal)	5	0.45
Mg-Stearate (external)	2.5	0.22
Valsartan layer	620.00	55.36
Vasartan compacted Granulate *2		
Valsartan	320.00	28.57
Cellulose MK GR	216.00	19.29
Crospovidone XL	60.00	5.36
Aerosil 200	6.00	0.54
Mg stearate (internal)	12.00	1.07
Mg-Stearate (external)	6.00	0.54
	1120.00	100.00
Hardness [N] (mean)	245	
Friability 10St. /6.5g 500U.[%]	0.12	
Disintegration time in min/Valsartan layer	1'00 - 1'30	
Disintegration time in min/Aliskiren layer	19'	

Example 4:

Bilayer Tablet Formulation

	Variant 1		Variant 2		Variant 3	
Aliskiren/Valsartan 300/320mg	**mg per unit**	*% tablet weight*	**mg per unit**	*% tablet weight*	**mg per unit**	*% tablet weight*
Aliskiren layer	600.00	49.18	520	45.61	600	49.18
Aliskiren compacted granulate						
Aliskiren hemifumarate	331.5	27.17	331.5	29.08	331.5	27.17
Cellulose MK GR	172.5	14.14	105.3	9.24	69.3	5.68
Mannitol DC	48	3.93	41.6	3.65	132	10.82
Crospovidone	12	0.98	10.4	0.91	16.2	1.33
HPC EXF	18	1.48	15.6	1.37	30	2.46
Indigotin LAKE 12196 (C)	-	-	-	-	0.6	0.05
Aerosil 200	3	0.25	2.6	0.23	5.7	0.47
Mg stearate (internal)	12	0.98	10.4	0.91	11.7	0.96
Mg-Stearate (external)	3	0.25	2.6	0.23	3	0.25
Valsartan layer	620.00	50.82	620.00	54.39	620.00	50.82
Vasartan compacted Granulate *2						
Valsartan	320	26.23	320	28.07	320	26.23
Cellulose MK GR	152	12.46	152	13.33	152	12.46
PVP XL	62	5.08	62	5.44	62	5.08
L-HPC (low substituted HPC)	62	5.08	62	5.44	62	5.08
Aerosil 200	6	0.49	6	0.53	6	0.49
Mg stearate (internal)	12	0.98	12	1.05	12	0.98
Mg-Stearate (external)	6	0.49	6	0.53	6	0.49
	1220.00	100.00	**1140.00**	100.00	**1220.00**	100.00
Hardness [N] (mean)	288		275		278	
Friability 10St. /6.5g 500U.[%]	0.17		0.37		0.39	
Disintegration time in min/Valsartan layer	1'00 - 1'30		1'00 - 1'30		1'00 - 1'30	
Disintegration time in min/Aliskiren layer	23'		22'		21'30-25'15	

Example 5:

Bilayer Tablet Formulation

	Variant 1		Variant 2		Variant 3	
Aliskiren/Valsartan 300/320mg	**mg per unit**	*% tablet weight*	**mg per unit**	*% tablet weight*	**mg per unit**	*% tablet weight*
Aliskiren layer	600.00	49.18	520.00	45.61	600	49.18
Aliskiren compacted granulate						
Aliskiren hemifumarate	331.5	27.17	331.5	29.08	331.50	27.17
Cellulose MK GR	104.7	8.58	47.84	4.20	88.5	7.25
Mannitol DC	102	8.36	-	-	102.00	8.36
Lactose, Anhdydrous DT	-	-	83.2	7.30	-	
Crospovidone	18	1.48	10.4	0.91	45	3.69
HPC EXF	22.8	1.87	31.2	2.74	12	0.98
Indigotin LAKE 12196 (C)	0.6	0.05	0.6	0.05	0.6	0.05
Aerosil 200	5.7	0.47	4.94	0.43	5.7	0.47
Mg stearate (internal)	11.7	0.96	7.8	0.68	11.7	0.96
Mg-Stearate (external)	3	0.25	2.6	0.23	3	0.25
Valsartan layer	620.00	50.82	620.00	54.39	620.00	50.82
Vasartan compacted Granulate *2						
Valsartan	320	26.23	320	28.07	320	26.23
Cellulose MK GR	152	12.46	152	13.33	152	12.46
PVP XL	62	5.08	62	5.44	62	5.08
L-HPC (low substituted HPC)	62	5.08	62	5.44	62	5.08
Aerosil 200	6	0.49	6	0.53	6	0.49
Mg stearate (internal)	12	0.98	12	1.05	12	0.98
Mg-Stearate (external)	6	0.49	6	0.53	6	0.49
	1220.00	100.00	**1140.00**	100.00	**1220.00**	100.00
Hardness [N] (mean)	300		221		313	
Friability 10St. /6.5g 500U.[%]	0.29		0.20		0.37	
Disintegration time in min/Valsartan layer	1'00 - 1'30		1'00 - 1'30		1'00 - 1'30	
Disintegration time in min/Aliskiren layer	22'45"		24'-26'		18'	

Example 6:

Dissolution Testing

The dissolution property of the formulations in accordance with the present invention were confirmed as follows.

The assembly consists of the following: a covered vessel made of glass or other inert, transparent material; a motor, and a paddle formed from a blade and shaft as the stirring element. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessels at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion.

No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is has the following dimensions and capacities: the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The design of the paddle is as shown in USP <711>, Fig. 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be

attached to dosage units that would otherwise float. Other validated sinker devices may be used.

One liter of a buffered aqueous solution, adjusted to pH 4.5 ± 0.05 (0.1 M Phosphate buffer solution obtained by dissolving 13.61 g of potassium hydrogen phosphate in 750 ml of deionized water and diluted to 1L with deionized water; referred hereinafter as "Dissolution Medium") is placed in the vessel of the apparatus, the apparatus is assembled, the Dissolution Medium is equilibrated to 37 ± 0.5°, and the thermometer is removed. 1 dosage form (e.g. tablet or capsule) is placed on the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately the apparatus is operated at a rate of 75±3 rpm.

Within the time interval specified (e.g. 10, 20, 30, 45, 60, 90 and 120 min.), or at each of the times stated, a specimen(≥ 1 ml) is withdrawn from a zone midway between the surface of the Dissolution Medium and the top of the rotating blade, not less than 1 cm from the vessel wall. [NOTE- the aliquots withdrawn for analysis are replaced with equal volumes of fresh Dissolution Mediums at 37° or, where it can be shown that replacement of the medium is not necessary, the volume change is corrected in the calculation. The vessel is kept covered for the duration of the test, and the temperature of the mixture under test at suitable times is verified.] . The specimen is filtered through a suitable filter, e.g. a 0.45 μm PVDF filter (Millipore) and the first mls (2 to 3 ml) of the filtrate are discarded. The analysis is performed by HPLC or UV detection. The test is repeated at least 6 times. with additional dosage form units.

The examples of bilayer tablets prepared according to the present invention all had suitable dissolution characteristics as set forth in the table below.

	Dissolution profile of Aliskiren at pH 4.5 after 10 min	Dissolution profile of Aliskiren at pH 4.5 after 20 min	Dissolution profile of Valsartan at pH 4.5 after 30 min	Dissolution profile of Valsartan at pH 4.5 after 60 min
Example 1	44.96	98.33	61.15	87.29

Example 2	40.11	76.15	58.89	75.30
Example 3	49.8	86.5	28.66	43.38
Example 4 Variant 1	36.1	63.2	60.96	74.56
Example 4 Variant 2	41.5	69.0	59.89	73.64
Example 4 Variant 3	32.6	57.9	58.05	72.18
Example 5 Variant 1	32.1	59.1	65.4	77.9
Example 5 Variant 2	30.7	59.5	64.8	77.2
Example 5 Variant 3	41.48	71.64	27.23	30.36

Example 7:

Bioequivalence of free combination and fixed-dose combination

An open-label, randomized, two-treatment, crossover, single-dose study to determine the bioequivalence of fixed combination of aliskiren/valsartan 300/320 mg tablet and the free combination of aliskiren 300 mg and valsartan 320 mg was performed in 78 healthy subjects. The fixed combination tablet of 300/320 mg aliskiren/valsartan was bioequivalent to the free combination of 300 mg aliskiren and 2 x 160 mg valsartan capsules. The 90% confidence intervals of geometric mean ratios for AUC/Cmax of both aliskiren and valsartan were contained within the bioequivalence limits of 0.80 – 1.25, which indicates that the test formulation is bioequivalent to the reference formulation. The rate and extent of absorption of aliskiren and valsartan from the fixed combination of 300/320 mg aliskiren/valsartan tablet was similar to that from the free combination of a 300 mg aliskiren tablet and two 160 mg valsartan capsules. Both the free and fixed combinations were safe and well-tolerated.

Pharmacokinetic measurements were performed on blood collected from each subject. A combined LC/MS/MS method was used to detect aliskiren and valsartan in the same plasma sample. The lower limit of quantitation was 0.5 ng/ml for aliskiren and 5.0 ng/ml for valsartan. The PK parameters were determined in plasma, using non-compartmental methods.

Log-transformed $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$ and C_{max} measurements of aliskiren and valsartan were analyzed separately using a linear mixed effects model. The following pharmacokinetic methods were determined for aliskiren and valsartan.

$AUC_{0\text{-tlast}}$: Area under the concentration-time curve from time zero to time tlast, where tlast is the last time point with measurable concentration (ng hr/ml).

$AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve from time zero to infinity (ng hr/ml).

C_{max}: Maximum (peak) plasma concentration (ng/ml).

T_{max}: Time to reach peak or maximum concentration (hr).

$T_{1/2}$: Elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve (hr).

Statistical analysis of PK parameters

The data in the following table shows that AUC and C_{max} were contained within the equivalence limits of 0.8 – 1.25 for both aliskiren and valsartan. This demonstrates that the fixed combination of 300/320 mg aliskiren/valsartan tablet was bioequivalent to the free combination of a 300 mg aliskiren tablet and two 160 mg valsartan capsules.

PK Parameter	**Adjusted geometric means**		**Ratio of geometric means**	
	Test (N)	**Reference (N)**	**Estimate**	**90% Confidence Interval**

Aliskiren				
C_{max} (ng/ml)	159.44 (80)	164.39 (83)	0.97	0.85 – 1.10
$AUC_{0\text{-}tlast}$ (ng hr/ml)	792.13 (79)	797.17 (83)	0.99	0.91 – 1.08
$AUC_{0\text{-}inf}$ (ng hr/ml)	859.32 (77)	860.73 (83)	1.00	0.92 – 1.09
Valsartan				
C_{max} (ng/ml)	3833.28 (80)	3532.28 (83)	1.09	0.98 – 1.20
$AUC_{0\text{-}tlast}$ (ng hr/ml)	31729.8 (79)	29204.2 (83)	1.09	1.01 – 1.17
$AUC_{0\text{-}inf}$ (ng hr/ml)	32657.2 (74)	29529.5 (80)	1.11	1.02 – 1.19

The intra-subject coefficients of variation (CV) for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max} of aliskiren were 33.98%, 33.19% and 51.90%, respectively and the intra-subject CV for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max} of valsartan were 28.56%, 28.33% and 40.37%, respectively.

Aliskiren PK: Free combination and fixed dose combination with valsartan

The mean plasma concentration-time profiles of aliskiren were similar following single oral doses of 300/320 mg aliskiren/valsartan fixed combination tablet compared to those obtained following administration of the free combination of an aliskiren 300 mg tablet and two 160 mg valsartan capsules. The geometric mean ratios (90% CI) for $AUC_{0\text{-}tlast}$ and C_{max} were 0.99 (0.91 – 1.08) and 0.97 (0.85 – 1.10), respectively. The inter-subject variability (% CV) associated with AUC and C_{max} in both treatments was similar. Mean half-life and median T_{max} were also similar between the treatments.

Treatment		$AUC_{0\text{-}inf}$ (ng hr/ml)	$AUC_{0\text{-}tlast}$ (ng hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
Test	N	77	79	80	80	77
	Mean	955.38	879.64	183.79	1.27	33.81
	SD	515.82	478.10	108.01	0.86	9.53
	Min	382.24	353.91	48.70	0.48	17.12
	Median	840.70	772.42	154.50	1.00	32.32
	Max	3839.88	3600.60	595.00	4.00	86.43
	% CV	54	54	59	68	28
Reference	N	83	83	83	83	83
	Mean	1005.32	933.19	202.49	1.16	33.63
	SD	673.71	626.74	144.94	0.83	8.20
	Min	323.16	296.67	46.40	0.47	13.95
	Median	803.29	763.81	163.00	1.00	32.58
	Max	4650.05	4248.63	858.00	4.00	55.40
	% CV	67	67	72	72	24

Valsartan PK: Free combination and fixed dose combination with aliskiren

The mean plasma concentration-time profiles of aliskiren were similar following single oral doses of 300/320 mg aliskiren/valsartan fixed combination tablet compared to

those obtained following administration of the free combination of an aliskiren 300 mg tablet and two 160 mg valsartan capsules. The geometric mean ratios (90% CI) for $AUC_{0\text{-}tlast}$ and C_{max} were 1.09 (1.01 – 1.17) and 1.09 (0.98 – 1.20), respectively. The inter-subject variability (% CV) associated with AUC and C_{max} in both treatments was similar. Mean half-life and median T_{max} were also similar between the treatments.

Treatment		$AUC_{0\text{-}inf}$ (ng hr/ml)	$AUC_{0\text{-}tlast}$ (ng hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
Test	N	74	79	80	80	74
	Mean	35468.81	34421.91	4391.13	3.44	12.41
	SD	13652.96	13676.31	2072.49	1.43	4.94
	Min	6414.57	5911.43	345.00	1.00	5.66
	Median	33919.05	32916.35	4275.00	3.01	11.40
	Max	74819.16	744.8.20	9140.00	12.00	25.68
	% CV	39	40	47	42	40
Reference	N	80	83	83	83	80
	Mean	31845.23	31509.84	3995.08	3.48	11.80
	SD	12262.22	12315.41	1955.46	1.11	5.21
	Min	8766.14	8598.03	797.00	1.50	5.60
	Median	29509.24	29287.13	3670.00	4.00	9.95
	Max	85004.81	84872.17	11800.00	6.02	34.64
	% CV	39	39	49	32	44

What is claimed is:

1. A pharmaceutical composition comprising

a) a therapeutically effective amount of Aliskiren, or a pharmaceutically acceptable salt thereof,

b) a filler; and

c) one or more, for example one to three, filler differing from the filler b) and independently selected from:

c1) alditols;

c2) mono-, di-, tri-, and polysaccharides; and

c3) a filler having a tapped density in the range of from 0.5 to 1.5 g/cm^3, and

provided that if Indigotin lake is comprised in the composition it is not in an amount of 0.13, 0.2, 0.25 or 0.5 mg per unit dose.

2. The pharmaceutical composition according to claim 1, wherein the filler c) is an alditol selected from mannitol and sorbitol.

3. The pharmaceutical composition according to claim 1, wherein the filler c) is a mono- or disaccharide, preferably selected from lactose, sucrose and dextrose.

4. The pharmaceutical composition according to claim 1, wherein the filler c) is selected from the group of compounds c3), preferably starch or dicalcium phosphate.

5. The pharmaceutical composition according to any of the preceding claims in the form of a tablet.

6. The pharmaceutical composition according to any of the preceding claims in the form of a bilayer tablet, comprising one layer containing the pharmaceutical composition according to any of the preceding claims, and a second layer

comprising a pharmaceutically active principle d) being different from component a).

7. The pharmaceutical composition according to claim 6, wherein pharmaceutically active principle d) being different from component a) is valsartan or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition a according to any of the preceding claims, wherein component a) and c) are present in a weight ratio, based on the total weight of the composition, of from 15:1 to 2:1, preferably 8:1 to 2:1, more preferably 6:1 to 3:1.

9. The pharmaceutical composition according to any one of the preceding claims, wherein component b) and c) are present in a weight ratio, based on the total weight of the composition, of from 5:1 to 1:5, preferably 4:1 to 1:2.

10. The pharmaceutical composition according to any one of the preceding claims, comprising 300 mg or more of aliskiren or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical oral fixed dose combination according to any of the preceding claims, wherein component a) is present in an amount of from 40 to 70% by weight based on the total weight of the granules comprising component a).

12. Use of the pharmaceutical composition according to any of the preceding claims for the treatment of hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, headache and chronic heart failure, in particular hypertension.

13. A method for the preparation of a pharmaceutical composition according to any of claims 6 to 11, said method comprising the steps of (1) granulating components a) to c) and pharmaceutically acceptable additives, optionally in the presence of a granulation liquid, to form an Aliskiren granulate; (2) granulating component d) and pharmaceutically acceptable additives to form a Valsartan granulate; (3) optionally

drying resulting respective granulates; (4) sieving; (5) optionally mixing the respective granulates with outer phase excipients; and (6) compressing the Valsartan granulates and the Aliskiren granulates together to form a bilayer tablet.

14. A method for preparing a pharmaceutical composition comprising aliskiren or a pharmaceutically acceptable salt thereof, comprising the steps of (1) granulating aliskiren or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable additives, optionally in the presence of a granulation liquid, to form an Aliskiren granulate; (2) treating the product of step (1) further to increase bulk and or tap density and/or to reduce fine content , and using the product of step (2) for preparing a pharmaceutical dosage form, such as a compressed tablet or one layer of a bilayer tablet.

15. The method of claim 14, wherein the granulation method in step (1) is solvent granulation and the treatment in step (2) is roller compaction.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/027748

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K47/02 A61K31/165 A61K31/41
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/045795 A2 (NOVARTIS AG [CH]; ALTENBURGER RALF [DE]; BABIOLE SAUNIER MAGGY [FR]; B) 9 April 2009 (2009-04-09) page 60; example 3.1	1,2,5, 7-15
X	WO 2005/089729 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; RIGASSI-DIETRICH PETRA GI) 29 September 2005 (2005-09-29) page 3, paragraph 2-4 page 5, paragraph 4 - page 6, paragraph 2 page 8, paragraph 2-6 page 9, paragraph 4 - page 10, paragraph 6 page 13, paragraph 5 - page 14, paragraph 3 page 12, paragraph 1-7; claims 1-20; examples 1,2	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2010	08/07/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Toulacis, C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/027748

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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