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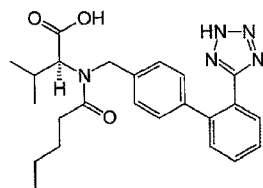
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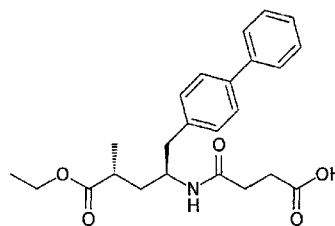
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(54) **Title:** A PHARMACEUTICAL COMPOSITION CONTAINING VALSARTAN AND SACUBITRIL AND METHODS FOR PREPARATION AND STABILIZATION THEREOF



(I)



(II)

(57) **Abstract:** The invention relates to orally administered compositions containing Valsartan of formula (I), systematic name (S)-3-methyl-2-((N-([2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl)methyl]-pentanamido)butanoic acid, or its pharmaceutically acceptable salts, and Sacubitril of formula (II), systematic name (2R,4S)-5-(biphenyl-4-yl)-4-[(3-carboxypropionyl)amino]-2-methyl-pentanoic acid ethyl ester, or its pharmaceutically acceptable salts with suitable pharmaceutical excipients, and also to preparation and stabilization thereof, wherein the composition is stored in a pharmaceutical package where an inert atmosphere is maintained by means of nitrogen.

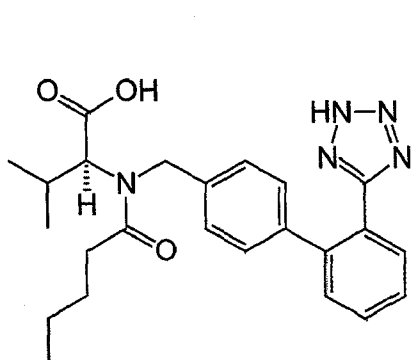
A pharmaceutical composition containing Valsartan and Sacubitril and methods for preparation and stabilization thereof

Technical Field

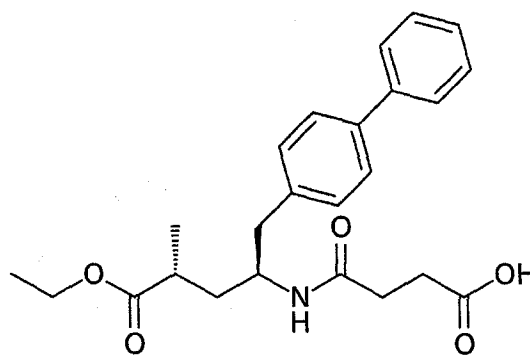
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The invention relates to pharmaceutical compositions in the form of tablets suitable for oral administration, containing Valsartan of formula (I), systematic name (*S*)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid, or its pharmaceutically acceptable salts, in combination with Sacubitril of formula (II), systematic name (2*R*,4*S*)-5-(biphenyl-4-yl)-4-[(3-carboxypropionyl)amino]-2-methylpentanoic acid ethyl ester, or its pharmaceutically acceptable salts, as well as methods for preparation and stabilization thereof.

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(I)



(II)

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Background Art

The combination of Valsartan and Sacubitril is a novel combination of drugs against hypertension and heart failure. A pharmaceutical composition of Valsartan or its pharmaceutically acceptable salts with NEP inhibitors in the presence of pharmaceutically acceptable excipients for the treatment of hypertension is described in the patent application WO03059345. The original product comprises a cocrystal of Valsartan disodium salt with the sodium salt of Sacubitril and two and half molecules of water, referred to as LCZ 696. The summary formula of the cocrystal LCZ 696 is $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5 H_2O$. Synthesis of this cocrystal and its formulations are described in the patent applications: WO2007056546, WO 2009061713 and EP2217205.

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Pharmaceutical products available in the market contain this cocrystal. The total dose of the preparation is up to 400 mg of the active ingredient in the dosage form.

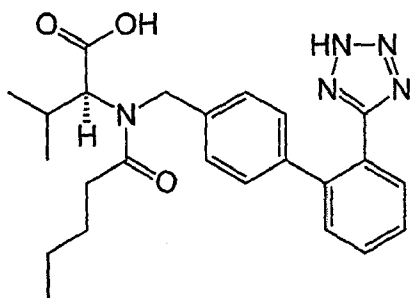
Depending on the preparation conditions, Valsartan may form both an amorphous structure and various types of crystalline forms. The patent applications WO2002006253, WO2004083192, WO2007017897, US20080261959, WO2003089417, WO2006076561, WO2003066606 and WO200206253 describe several types of solid forms of Valsartan or its pharmaceutically acceptable salts. These forms differ from each other with their crystal arrangement and their physical properties, especially solubility and bioavailability.

Preparation of Sacubitril was described in the publication J. Med. Chem. **1995**, 38, 1689-1700 and the patent application EP0555175 describes synthesis of this molecule and its sodium salt. The patent applications WO2009061713, EP2217205 describe solid pharmaceutical compositions of the LCZ 696 cocrystal for oral administration with common pharmaceutical excipients. The sodium salts of Sacubitril and Valsartan are present in it in the form of the LCZ 696 cocrystal mentioned above. It should be possible to prepare these pharmaceutical compositions both with direct tableting and by means of dry granulation - compaction or briquetting.

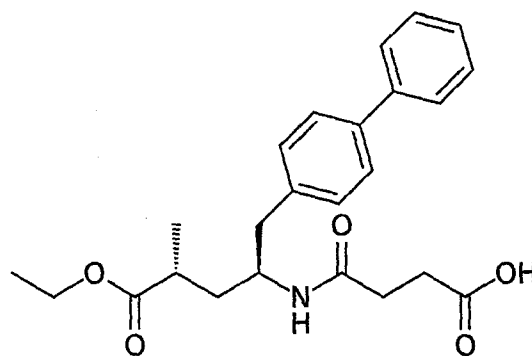
Disclosure of Invention

A combination of Sacubitril and Valsartan or their pharmaceutically acceptable salts represents the basis of the new product for hypertension treatment. Valsartan is classified as BCS II – its solubility is strongly influenced by pH and it is easy to absorb. Valsartan is not a problematic substance from the point of view of stability in the dosage form. Dosage forms containing Valsartan do not exhibit a considerable increase of impurities during storage under various loads.

This invention provides a pharmaceutical composition containing Valsartan of formula (I), systematic name (*S*)-3-methyl-2-(*N*-{[2'-(2*H*-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}-pentanamido)butanoic acid, or its pharmaceutically acceptable salts, and Sacubitril of formula (II), systematic name (2*R*,4*S*)-5-(biphenyl-4-yl)-4-[(3-carboxypropionyl)amino]-2-methylpentanoic acid ethyl ester, or its pharmaceutically acceptable salts, with suitable pharmaceutical excipients.



(I)



(II)

The invention further provides a pharmaceutical composition containing a mixture of Valsartan free acid and Sacubitril free acid with suitable pharmaceutical excipients.

- 5 The invention further provides a pharmaceutical composition containing a mixture of Valsartan free acid and the calcium salt of Sacubitril with suitable pharmaceutical excipients. The invention further provides a pharmaceutical composition containing a mixture of Valsartan free acid and the sodium salt of Sacubitril with suitable pharmaceutical excipients. The invention further provides a pharmaceutical composition containing a mixture of
- 10 Valsartan free acid and the cyclohexylammonium salt of Sacubitril with suitable pharmaceutical excipients. The invention further provides a pharmaceutical composition containing a mixture of the sodium salt of Valsartan and the calcium salt of Sacubitril with suitable pharmaceutical excipients. The invention further provides a pharmaceutical composition containing a mixture of the sodium salt of Valsartan and the sodium salt of
- 15 Sacubitril with suitable pharmaceutical excipients. The invention further provides a pharmaceutical composition containing a mixture of the sodium salt of Valsartan and the cyclohexylammonium salt of Sacubitril with suitable pharmaceutical excipients.

The invention further provides a pharmaceutical composition containing Valsartan or its pharmaceutically acceptable salts and Sacubitril or its pharmaceutically acceptable salts, at

20 least one excipient being selected from the group of fillers, binders, disintegrants, lubricants, surfactants and/or glidants. A preferred embodiment of the above mentioned pharmaceutical composition is such that at least one excipient from the group of fillers is selected from the group comprising: microcrystalline cellulose, meglumine, lactose, mannitol, sorbitol, xylitol, trehalose, carbonate salts, colloidal silica, fructose and other common pharmaceutical fillers.

- 25 Another preferred embodiment of the above mentioned pharmaceutical composition is such that at least one excipient from the group of disintegrants is selected from the group

comprising: sodium salt of croscarmellose, crospovidone, starch and its derivatives and other common pharmaceutical disintegrants.

Another preferred embodiment of the above mentioned pharmaceutical composition is such that it further contains at least one excipient from the group of lubricants, selected from the group comprising: magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate, glycerol dibehenate, talc and other common pharmaceutical lubricants. Still another preferred embodiment of the above mentioned pharmaceutical composition is such that it further contains at least one excipient for local pH adjustment, such as meglumine, Na_2HPO_4 , $\text{Mg}(\text{OH})_2$, sodium hydroxide, carbonates, potassium citrate, sodium citrate and other pharmaceutically acceptable alkalizing salts.

The invention further provides a pharmaceutical composition, which is in a form suitable for oral administration. In a preferred embodiment, the pharmaceutical composition contains Valsartan or its pharmaceutically acceptable salts and Sacubitril or its pharmaceutically acceptable salts in a composition where individual active ingredients are physically separated from each other.

In a preferred embodiment, it is a pharmaceutical composition that is in the form of a tablet. Further, it is a pharmaceutical composition where individual active ingredients are contained in a single-layered tablet. In a preferred embodiment it is a pharmaceutical composition where the active ingredients are separated from each other in a double-layered tablet. Another object of this invention is a pharmaceutical composition characterized in that the content of the active ingredient is 10 wt.% to 70 wt.%, preferably 15 wt.% to 50 wt.%.

In another aspect, this invention provides a method for preparation of the pharmaceutical composition containing Valsartan or its pharmaceutically acceptable salts and Sacubitril or its pharmaceutically acceptable salts, characterized in that the method comprises at least one processing method selected from the group: wet granulation, dry granulation, admixing the mixture to the tableting matter, fluid drying, fluid granulation, compaction, briquetting, direct tableting or a combination of these methods. The invention further provides a method for preparation, where Valsartan or its pharmaceutically acceptable salt and Sacubitril or its pharmaceutically acceptable salt are sieved together with at least one pharmaceutically acceptable excipient and tableted by means of direct tableting. The invention further provides a method for preparation comprising steps where a) Valsartan or its pharmaceutically acceptable salt is granulated together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water, b) Sacubitril or its pharmaceutically acceptable salt

is directly admixed to the granulate of Valsartan from step a) together with at least one pharmaceutically acceptable excipient, and c) the tableting matter prepared this way is tabletted. The invention further provides a method for preparation, characterized in that it comprises the following steps: a) Valsartan or its pharmaceutically acceptable salt is processed
5 by fluid granulation together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water, b) Sacubitril or its pharmaceutically acceptable salt is compacted together with at least one pharmaceutically acceptable excipient, and c) the granulate of Valsartan and compactate of Sacubitril are mixed and tabletted into a single-layered tablet. The invention further provides a method for preparation, characterized in that it
10 comprises the following steps: a) Valsartan or its pharmaceutically acceptable salt is granulated together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water, b) Sacubitril or its pharmaceutically acceptable salt is compacted together with at least one pharmaceutically acceptable excipient, and c) the tableting matter containing Valsartan and Sacubitril is tabletted into a double-layered tablet with separated
15 active ingredients. In a preferred embodiment, the preparation method is characterized in that Sacubitril is in the form of the free acid, sodium salt, calcium salt, potassium salt, magnesium salt or cyclohexylammonium salt. In another preferred embodiment, the preparation method is characterized in that Valsartan is in the form of the free acid, sodium salt, calcium salt, potassium salt or magnesium salt. In another preferred embodiment, the preparation method is
20 characterized in that at least one pharmaceutically acceptable excipient is selected from the group comprising a filler, binder, disintegrant, lubricant, surfactant and/or glidant and/or any combinations thereof. In another preferred embodiment, the method is characterized in that at least one excipient from the group of fillers is selected from the group comprising: microcrystalline cellulose, meglumine, lactose, mannitol, sorbitol, xylitol, trehalose, carbonate
25 salts, colloidal silica, fructose and other common pharmaceutical fillers. In still another preferred embodiment, the preparation method is characterized in that at least one excipient from the group of disintegrants is selected from the group comprising: sodium salt of croscarmellose, crospovidone, starch and its derivatives and other common pharmaceutical disintegrants. In still another preferred embodiment, the preparation method is characterized in
30 that it further contains at least one excipient from the group of lubricants, selected from the group comprising: magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate, glycerol dibehenate, talc and other common pharmaceutical lubricants. In still another preferred embodiment, the preparation method is characterized in that it further contains at

least one excipient for local pH adjustment, such as meglumine, Na₂HPO₄, Mg(OH)₂, sodium hydroxide, carbonates, potassium citrate, sodium citrate and other pharmaceutically acceptable alkalizing salts.

In a further aspect, this invention provides a method for stabilization of a pharmaceutical composition containing Valsartan of formula I, systematic name (*S*)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid, or its pharmaceutically acceptable salts, and Sacubitril of formula II, systematic name (2*R*,4*S*)-5-(biphenyl-4-yl)-4-[(3-carboxypropionyl)amino]-2-methylpentanoic acid ethyl ester, or its pharmaceutically acceptable salts with suitable pharmaceutical excipients, wherein the composition is stored in a pharmaceutical package where an inert atmosphere is maintained by means of nitrogen.

In the free acid form, Sacubitril is difficult to isolate in the solid state. This substance is unstable at higher temperatures or when exposed to higher relative humidity. The formulations described in this patent are stable dosage forms that contain Valsartan and Sacubitril or their pharmaceutically acceptable salts as separate components, namely in a single-layered or double-layered tablet. The dose of the preparation varies from 20 to 400 mg of Valsartan and from 20 to 400 mg of Sacubitril. The content of each dosage form in the tablet varies in the range from 10 to 70 wt.%. Not only direct tableting, but also wet granulation and dry granulation are used for the preparation of these dosage forms.

During a stability study of the product combining Sacubitril and Valsartan, sensitivity of Sacubitril to the surrounding environment has surprisingly been discovered. The rate of development of impurities in a preparation that was packed in an atmosphere containing oxygen (air) was limiting with respect to the storage conditions and shelf life of the product. This combination would thus have a reduced service life for therapeutic purposes, or its storage at temperatures higher than 25°C would be substantially limited. Packing of tablets under a nitrogen atmosphere prevents access of air to the final product, significantly reducing the rate of development of impurities of Sacubitril, namely under the conditions of accelerated stability tests – 40°C, which considerably increases the shelf life of the preparation and its storage will not be limited by temperatures throughout its useful life. This property is especially important in countries with a higher average temperature such as the countries of the equatorial and subtropical belts.

The pharmaceutical package of the composition is a blister pack whose material is selected from the group of the type: OPA/ALU/PVC, PVC/ACLAR/PVC, PVC, PVC/PE/PVDC, PVC/PVDC, PVC/PVDC, where OPA stands for oriented polyamide film, ALU stands for

aluminium, PVC stands for polyvinyl chloride, ACLAR stands for poly-chloro-tri-fluoro-ethylene, PVDC stands for polyvinylidene chloride a PE stands for polyethylene. The cavities in the blister packs filled with tablets were welded with aluminium foil.

5 Detailed description of the invention

An advantage of the combination of Valsartan and Sacubitril or its pharmaceutically acceptable salts thereof in one tablet as separate substances is that the preparation of the dosage form is shorter and simpler and the demanding production of the cocrystal is avoided. But at the same time, the described product retains the properties of the original product – i.e. releasing of the active ingredients and their stability. The formulation of both the single-layered and double-layered tablet with the active ingredients Valsartan and Sacubitril separated, prevents excessive degradation of Sacubitril at higher temperatures, increasing the stability of the product. Thanks to this, the storage conditions of the drug do not need to be modified.

Examples

The purpose of the following examples is to further elucidate the invention without limiting its scope.

Formulations containing a combination of Valsartan and Sacubitril and their pharmaceutically acceptable salts

Example 1

Constituent	Function
Sacubitril free acid	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant

Magnesium stearate	Lubricant
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Sacubitril free acid and Valsartan free acid were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture was sieved through a sieve and tableted.

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Example 2

Constituent	Function
Sacubitril sodium salt	Active pharmaceutical ingredient
Valsartan sodium salt	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

Sacubitril sodium salt and Valsartan sodium salt were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture was sieved through a sieve and tableted.

10

Example 3

Constituent	Function
Sacubitril cyclohexylammonium salt	Active pharmaceutical ingredient
Valsartan sodium salt	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

Sacubitril cyclohexylammonium salt and Valsartan sodium salt were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture was sieved through a sieve and tabletted.

5

Example 4

Constituent	Function
Sacubitril sodium salt	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical ingredient
Prosolv	Filler
Sodium hydrogen carbonate	Filler
Sorbitol	Filler
Povidone	Binder
Pre-gelatinized starch	Binder
Crospovidone	Disintegrant
Colloidal silica	Glidant
Sodium lauryl sulphate	Wetting agent
Sodium stearyl fumarate	Lubricant

Valsartan free acid was granulated together with Prosoiv, lauryl sulphate, sorbitol, povidone and crospovidone. Purified water was used as the granulating solvent. The dried granulate was sieved. Sacubitril sodium salt was admixed to the granulate of Valsartan free acid together with sodium hydrogen carbonate, crospovidone, pre-gelatinized starch, sodium stearyl fumarate and colloidal silica. The tableting matter prepared this way was tabletted into single-layered tablets.

10

15 **Example 5**

Constituent	Function
Sacubitril calcium salt	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical

	ingredient
Microcrystalline cellulose	Filler
Prosolv	Filler
Sodium hydrogen carbonate	Filler
Sorbitol	Filler
Povidone	Binder
Pre-gelatinized starch	Binder
Crospovidone	Disintegrant
Colloidal silica	Glidant
Sodium lauryl sulphate	Wetting agent
Sodium stearyl fumarate	Lubricant

- 5 Valsartan free acid was processed by means of fluid granulation together with Prosolv, sodium lauryl sulphate, sorbitol, povidone and crospovidone. Purified water was used as the granulating solvent. The dried granulate was sieved. Sacubitril calcium salt was compacted and sieved together with microcrystalline cellulose, colloidal silica, crospovidone, sodium stearyl fumarate and pre-gelatinized starch. The granulate of Valsartan and compactate of Sacubitril is mixed together with sodium hydrogen carbonate, crospovidone, colloidal silica and sodium stearyl fumarate. The mixture prepared this way was tabletted.

10 *Example 6*

Constituent	Function
Sacubitril cyclohexylammonium salt	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Prosolv	Filler
Sorbitol	Filler
Povidone	Binder
Pre-gelatinized starch	Binder
Crospovidone	Disintegrant

Colloidal silica	Glidant
Sodium lauryl sulphate	Wetting agent
Sodium stearyl fumarate	Lubricant

Valsartan free acid was granulated together with Prosolv, sodium lauryl sulphate, sorbitol, povidone and crospovidone. Purified water was used as the granulating solvent. The dried granulate was sieved and microcrystalline cellulose, colloidal silica, crospovidone and sodium stearyl fumarate were admixed to it. Sacubitril cyclohexylammonium salt was compacted together with microcrystalline cellulose, colloidal silica, crospovidone, sodium stearyl fumarate and pre-gelatinized starch and mixed with sieved microcrystalline cellulose, colloidal silica, crospovidone, sodium stearyl fumarate. The tableting matters containing Valsartan free acid and Sacubitril cyclohexylammonium salt were tabletted into double-layered tablets with separated active ingredients.

Example 7

Constituent	Function
Sacubitril sodium salt	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

Sacubitril sodium salt and Valsartan free acid were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture was sieved through a sieve and tabletted.

Example 8

Constituent	Function
Sacubitril calcium salt	Active pharmaceutical ingredient
Valsartan sodium salt	Active pharmaceutical ingredient
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

Sacubitril calcium salt and Valsartan sodium salt were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture

5 was sieved through a sieve and tabletted.

Example 9

Constituent	Function
Sacubitril sodium salt	Active pharmaceutical ingredient
Valsartan free acid	Active pharmaceutical ingredient
Meglumine	Filler and excipient for local pH adjustment
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

Sacubitril sodium salt, Valsartan free acid and meglumine were mixed together with microcrystalline cellulose, sodium salt of croscarmellose, colloidal silica and magnesium stearate. The mixture was sieved through a sieve and tabletted.

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Example 10

Constituent	Function
Sacubitril free acid	Active pharmaceutical ingredient
Valsartan disodium salt	Active pharmaceutical ingredient
Sodium hydrogen carbonate	Filler / excipient for local pH adjustment
Microcrystalline cellulose	Filler
Sodium salt of croscarmellose	Disintegrant
Colloidal silica	Glidant
Magnesium stearate	Lubricant

- 5 The final dosage forms containing a combination of Sacubitril and Valsartan, produced by means of granulation, compaction, direct tableting and combinations of individual processes, tabletted as single-layered as well as double-layered tablets, were packed into blister packs under an air or nitrogen atmosphere. The dosage forms packed this way were subjected to stability tests under the following conditions: - 40°C, 75% relative humidity
- 10 The stability tests were conducted with different packages:
- OPA 25/ALU 45/PVC 100
PVC 127/ACLAR 76/PVC 127
PVC 250
PVC 250/PE 25/PVDC 90
- 15 PVC 250/PVDC 40
PVC 250/PVDC 120,
- wherein OPA is oriented polyamide film (Nylon), ALU is aluminium, PVC is polyvinyl chloride, ACLAR is poly-chloro-tri-fluoro-ethylene, PVDC is polyvinylidene chloride and PE is polyethylene.

The cavities in the blister packs filled with tablets were welded with aluminium foil with the thickness of 0.02 mm. The stability study took 3 months. In one-month intervals, the development of impurities of Sacubitril and Valsartan was checked in the dosage forms.

5 Results of the stability measurements

The results of the analyses of total amounts of impurities for Sacubitril and for Valsartan are summarized in the tables below. In the tables, the packing materials are identified with a number according to the following key:

1 - OPA 25/ALU 45/PVC 100

10 2 - PVC 127/ACLAR 76/PVC 127

3 - PVC 250

4 - PVC 250/PE 25/PVDC 90

5 - PVC 250/PVDC 40

6 - PVC 250/PVDC 120

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Table 1: Total amount of impurities in the formulation - packing under an air atmosphere – 3 months

Formulation	Packing material					
	1	2	3	4	5	6
Example 1	<0.05 %	<0.05 %	0.35 %	0.15 %	0.20 %	0.20 %
Example 2	<0.05 %	<0.05 %	0.25 %	0.13 %	0.15 %	0.15 %
Example 3	<0.05 %	<0.05 %	0.38 %	0.18 %	0.22 %	0.18 %
Example 8	0.07 %	0.09 %	0.50 %	0.28 %	0.25 %	0.20 %
Example 10	<0.05 %	<0.05 %	0.20 %	0.09 %	0.16 %	0.09 %

20 Table 2: Total amount of impurities in the formulation - packing under a nitrogen atmosphere

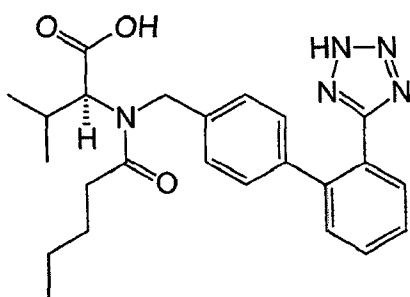
Formulation	Packing material					
	1	2	3	4	5	6
Example 1	<0.05 %	<0.05 %	n/a	<0.05 %	n/a	0.08 %
Example 2	<0.05 %	<0.05 %	n/a	<0.05 %	n/a	<0.05 %
Example 3	<0.05 %	<0.05 %	n/a	0.07 %	n/a	0.09 %

Example 8	<0.05 %	<0.05 %	n/a	0.15 %	n/a	0.15 %
Example 10	<0.05 %	<0.05 %	n/a	<0.05 %	n/a	<0.05 %

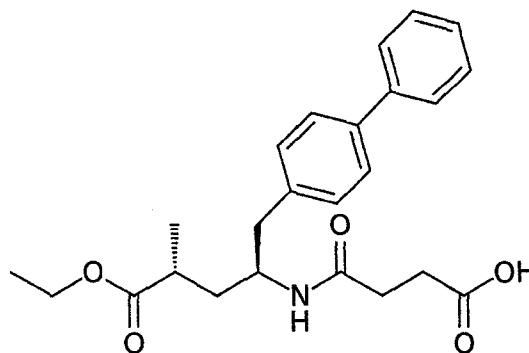
The above mentioned data clearly show that the formulations are very sensitive to air humidity. If the formulation is packed in packing materials that prevent access of atmospheric humidity, such as the above mentioned materials 1 and 2, stable behaviour of the proposed composition is achieved. If permeable packing materials (3) are used, the proposed formulations are not stable. Stability can also be supported by packing the products under a nitrogen atmosphere. In the case of the packing materials identified with nos. 3 and 5, due to their permeability for gases and water vapour, packing under a nitrogen atmosphere was not tested.

CLAIMS

1. A pharmaceutical composition, containing Valsartan of formula I, systematic name (*S*)-3-methyl-2-(*N*-{[2'-(2*H*-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido)butanoic acid, or its pharmaceutically acceptable salts, and Sacubitril of formula II, systematic name (2*R*,4*S*)-5-(biphenyl-4-yl)-4-[(3-carboxypropionyl)amino]-2-methylpentanoic acid ethyl ester, or its pharmaceutically acceptable salts, with suitable pharmaceutical excipients.



(I)



(II)

2. The pharmaceutical composition according to claim 1, characterized in that it contains a mixture of Valsartan free acid and Sacubitril free acid with suitable pharmaceutical excipients.
3. The pharmaceutical composition according to claim 2, characterized in that it contains a mixture of Valsartan free acid and the calcium salt of Sacubitril with suitable pharmaceutical excipients.
4. The pharmaceutical composition according to claim 2, characterized in that it contains a mixture of Valsartan free acid and the sodium salt of Sacubitril with suitable pharmaceutical excipients.
5. The pharmaceutical composition according to claim 2, characterized in that it contains a mixture of Valsartan free acid and the cyclohexylammonium salt of Sacubitril with suitable pharmaceutical excipients.
6. The pharmaceutical composition according to claim 1, characterized in that it contains a mixture of the sodium salt of Valsartan and calcium salt of Sacubitril with suitable pharmaceutical excipients.

7. The pharmaceutical composition according to claim 1, characterized in that it contains a mixture of the sodium salt of Valsartan and sodium salt of Sacubitril with suitable pharmaceutical excipients.
8. The pharmaceutical composition according to claim 1, characterized in that it contains a mixture of the sodium salt of Valsartan and cyclohexylammonium salt of Sacubitril with suitable pharmaceutical excipients.
9. The pharmaceutical composition according to any one of the preceding claims, characterized in that it contains at least one excipient from the group of fillers, binders, disintegrants, lubricants, surfactants, excipients for local pH adjustment or glidants.
10. The pharmaceutical composition according to any one of the preceding claims, characterized in that at least one excipient from the group of fillers is selected from the group comprising: microcrystalline cellulose, meglumine, lactose, mannitol, sorbitol, xylitol, trehalose, carbonate salts, colloidal silica, fructose and other common pharmaceutical fillers.
11. The pharmaceutical composition according to any one of the preceding claims, characterized in that at least one excipient from the group of disintegrants is selected from the group comprising: sodium salt of croscarmellose, crospovidone, starch and its derivatives and other common pharmaceutical disintegrants.
12. The pharmaceutical composition according to any one of the preceding claims, characterized in that it further contains at least one excipient from the group of lubricants, selected from the group comprising: magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate, glycerol dibehenate, talc and other common pharmaceutical lubricants.
13. The pharmaceutical composition according to any one of the preceding claims, characterized in that it further contains at least one excipient for local pH adjustment, such as meglumine, Na_2HPO_4 , $\text{Mg}(\text{OH})_2$, sodium hydroxide, carbonates, potassium citrate, sodium citrate and other pharmaceutically acceptable alkalizing salts.
14. The pharmaceutical composition according to any one of the preceding claims, characterized in that it is in a form suitable for oral administration.

15. The pharmaceutical composition according to claim 14, characterized in that Valsartan or its pharmaceutically acceptable salts and Sacubitril or its pharmaceutically acceptable salts are separated from each other in the composition.
16. The pharmaceutical composition according to any one of the preceding claims, characterized in that it is in the tablet form.
17. The pharmaceutical composition according to claim 16, characterized in that the active ingredients are contained in a single-layered tablet.
18. The pharmaceutical composition according to claim 16, characterized in that the active ingredients are separated from each other in a double-layered tablet.
19. The pharmaceutical composition according to any one of the preceding claims, characterized in that the content of the active ingredient is 10 wt.% to 70 wt.%, preferably 15 wt.% to 50 wt.%.
20. A method for preparation of the pharmaceutical composition containing Valsartan or its pharmaceutically acceptable salts and Sacubitril or its pharmaceutically acceptable salts as defined in claims 1 to 19, characterized in that it comprises at least one processing method selected from the group: wet granulation, dry granulation, admixing the mixture to the tableting matter, fluid drying, fluid granulation, compaction, briquetting, direct tableting or a combination of these methods.
21. The method according to claim 20, characterized in that Valsartan or its pharmaceutically acceptable salt and Sacubitril or its pharmaceutically acceptable salt are sieved together with at least one pharmaceutically acceptable excipient and tableted by means of direct tableting.
22. The method according to claim 20, characterized in that comprises the following step:
 - a) Valsartan or its pharmaceutically acceptable salt is granulated together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water,
 - b) Sacubitril or its pharmaceutically acceptable salt is directly admixed to the granulate of Valsartan from step a) together with at least one pharmaceutically acceptable excipient,
 - c) the tableting matter prepared this way is tableted.
23. The method according to claim 20, characterized in that it comprises the following step:

- a) Valsartan or its pharmaceutically acceptable salt is processed by means of fluid granulation together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water,
 - b) Sacubitril or its pharmaceutically acceptable salt is compacted together with at least one pharmaceutically acceptable excipient,
 - c) the granulate of Valsartan and the compactate of Sacubitril are mixed and tableted into a single-layered tablet.
24. The method according to claim 20, characterized in that comprises the following step:
- a) Valsartan or its pharmaceutically acceptable salt is granulated together with at least one pharmaceutically acceptable excipient with the use of a solvent, preferably water,
 - b) Sacubitril or its pharmaceutically acceptable salt is compacted together with at least one pharmaceutically acceptable excipient,
 - c) the tableting matter containing Valsartan and Sacubitril are tableted into a double-layered tablet with the active ingredients separated.
25. The method according to any one of claims 20 to 24, characterized in that Sacubitril is in the form of the free acid, sodium salt, calcium salt, potassium salt, magnesium salt or cyclohexylammonium salt.
26. The method according to any one of claims 20 to 24, characterized in that Valsartan is in the form of the free acid, sodium salt, calcium salt, potassium salt or magnesium salt.
27. The method according to any one of claims 20 to 26, characterized in that at least one pharmaceutically acceptable excipient is selected from the group comprising a filler, binder, disintegrant, lubricant, surfactant and/or glidant and/or any combinations thereof.
28. The method according to claim 27, characterized in that at least one excipient from the group of fillers is selected from the group comprising: microcrystalline cellulose, meglumine, lactose, mannitol, sorbitol, xylitol, trehalose, carbonate salts, colloidal silica, fructose and other common pharmaceutical fillers.
29. The method according to claim 27, characterized in that at least one excipient from the group of disintegrants is selected from the group comprising: sodium salt of croscarmellose, crospovidone, starch and its derivatives and other common pharmaceutical disintegrants.

30. The according to claim 27, characterized in that at least one excipient from the group of lubricants is selected from the group comprising: magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate, glycerol dibehenate, talc and other common pharmaceutical lubricants.
31. The method according to claim 27, characterized in that it further contains at least one excipient for local pH adjustment, such as meglumine, Na_2HPO_4 , $\text{Mg}(\text{OH})_2$, sodium hydroxide, carbonates, potassium citrate, sodium citrate and other pharmaceutically acceptable alkalizing salts.
32. A method for stabilization of a pharmaceutical composition in the form of tablets suitable for oral administration, containing Sacubitril or its pharmaceutically acceptable salt in a mixture with Valsartan or its pharmaceutically acceptable salt and one or more other auxiliary substances, characterized in that the composition is stored in a pharmaceutical package where an inert atmosphere is maintained.
33. The method according to claim 32, characterized in that the inert atmosphere is maintained by means of nitrogen.
34. The method according to claim 33, characterized in that the pharmaceutical package is a blister pack.
35. The method according to claim 34, characterized in that the packing material of the blister pack is selected from the group of the type: OPA/ALU/PVC, PVC/ACLAR/PVC, PVC, PVC/PE/PVDC, PVC/PVDC, PVC/PVDC, where OPA stands for oriented polyamide film, ALU stands for aluminium, PVC stands for polyvinyl chloride, ACLAR stands for poly-chloro-tri-fluoro-ethylene, PVDC stands for polyvinylidene chloride a PE stands for polyethylene.
36. The method according to claim 35, characterized in that the cavities in the blister packs filled with tablets have been welded with aluminium foil.
37. The method according to any one of claims 32-36, characterized in that the pharmaceutical composition contains 1 to 40 wt.% of Valsartan, further 1 to 40 wt.% of Sacubitril and one or more other auxiliary substances.
38. The method according to claim 37, characterized in that the pharmaceutical composition contains 5 to 20% by weight of Valsartan, further 5 to 20 wt.% of Sacubitril and one or more other auxiliary substances.

39. The method according to claim 38, characterized in that the one or more other auxiliary substances is selected from the group comprising a filler, binder, disintegrant, lubricant, surfactant and/or glidant and/or any combinations thereof.
40. The method according to claim 39, characterized in that at least one excipient from the group of fillers is selected from the group comprising: microcrystalline cellulose, meglumine, lactose, mannitol, sorbitol, xylitol, trehalose, carbonate salts, colloidal silica, fructose and other common pharmaceutical fillers.
41. The method according to claim 39, characterized in that at least one excipient from the group of disintegrants is selected from the group comprising: sodium salt of croscarmellose, crospovidone, starch and its derivatives and other common pharmaceutical disintegrants.
42. The method according to claim 39, characterized in that at least one excipient from the group of lubricants is selected from the group comprising: magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate, glycerol dibehenate, talc and other common pharmaceutical lubricants.
43. The method according to claim 39, characterized in that the pharmaceutical composition further contains at least one excipient for local pH adjustment, such as meglumine, Na_2HPO_4 , $\text{Mg}(\text{OH})_2$, sodium hydroxide, carbonates, potassium citrate, sodium citrate and other pharmaceutically acceptable alkalizing salts.
44. The method according to one of claims 32-43, characterized in that the active ingredient Sacubitril is selected from Sacubitril free acid, Sacubitril sodium salt, Sacubitril cyclohexylammonium salt, Sacubitril potassium salt or Sacubitril calcium salt.
45. The method according to one of claims 32-44, characterized in that the active ingredient Valsartan is selected from Valsartan free acid, Valsartan sodium salt or Valsartan disodium salt.

INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2016/000079

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/20 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 practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, 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	WO 2009/061713 A1 (NOVARTIS AG [CH]; AL-FAYOUMI SULIMAN [US]; HU JIAHUI [US]; KUMARAPERUM) 14 May 2009 (2009-05-14) claims 13, 15 examples 1-6 -----	1-45
A,P	WO 2016/049663 A1 (CRYSTAL PHARMATECH INC [US]; CRYSTAL PHARMATECH CO LTD [CN]; SUZHOU PE) 31 March 2016 (2016-03-31) examples 17, 18 -----	1-45



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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