Court File No.: T- -26

FEDERAL COURT

B E TW E E N:

NOVARTIS PHARMACEUTICALS CANADA INC and NOVARTIS AG

Plaintiffs

- and -

ZYDUS LIFESCIENCES LIMITED

Defendant

STATEMENT OF CLAIM

TO THE DEFENDANT:

A LEGAL PROCEEDING HAS BEEN COMMENCED AGAINST YOU by the Plaintiff. The claim made against you is set out in the following pages.

IF YOU WISH TO DEFEND THIS PROCEEDING, you or a solicitor acting for you are required to prepare a statement of defence in Form 171B prescribed by the Federal Courts Rules, serve it on the plaintiff's solicitor or, if the plaintiff does not have a solicitor, serve it on the plaintiff, and file it, with proof of service, at a local office of this Court

> WITHIN 30 DAYS after the day on which this statement of claim is served on you, if you are served in Canada or the United States; or
>
> WITHIN 60 DAYS after the day on which this statement of claim is served on you, if you are served outside Canada and the United States.
>
> TEN ADDITIONAL DAYS are provided for the filing and service of the statement of defence if you or a solicitor acting for you serves and files a notice of intention to respond in Form 204.1 prescribed by the Federal Courts Rules.

Copies of the *Federal Courts Rules*, information concerning the local offices of the Court and other necessary information may be obtained on request to the

Administrator of this Court at Ottawa (telephone 613-992-4238) or at any local office.

IF YOU FAIL TO DEFEND THIS PROCEEDING, judgment may be given against you in your absence and without further notice to you.

Issued on: February 20, 2026
Issued by: Nicholas Dempster (Registry Officer)
Address of Local Office: 90 Sparks Street/rue Sparks Ottawa, Ontario K1P 5R5

Date: February 20, 2026 Issued by (Registry Officer)

Address of local office: 90 Sparks Street
Ottawa, ON K1A 0H9

TO: **ZYDUS LIFESCIENCES LIMITED**
c/o **Aitken Klee LLP**
Lesley Caswell
180 Elgin Street, Suite 1400
Ottawa, ON K2P 2K3

Defendant

AND TO: **AITKEN KLEE LLP**
180 Elgin St., Suite 1400
Ottawa, ON K2P 2K6

Lesley Caswell
Tel: 613-903-5033
Email: lcaswell@aitkenklee.com

Solicitors for the Defendant

CLAIM

1. The Plaintiffs claim:

(a) a declaration, pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations* ("***Regulations***"), that the making, constructing, using, and/or selling of ZDS-SACUBITRIL AND VALSARTAN (the "**Zydus Product**") in accordance with the Defendant Zydus Lifesciences Limited's ("**Zydus**") Abbreviated New Drug Submission filed under Submission Number 301464 (the "**Zydus ANDS**") would directly infringe or induce the infringement of:

(i) the "**511 Asserted Claims**", namely claims 1-6, 8-13, 15, 22, 26 and 30 of Canadian Patent 2,590,511 (the "**511 Patent**");

(ii) the "**598 Asserted Claims**", namely claims 1-7 and 9-21 of Canadian Patent 2,703,598 (the "**598 Patent**");

(b) A permanent injunction restraining the Defendant, by itself or through any other person, company, partnership or business with which it may be associated or affiliated, or which may be under its authority, direction or control, whether directly or indirectly, from conducting any activity in respect of the Zydus Product that infringes, or induces others to infringe, the 511 Asserted Claims and the 598 Asserted Claims;

(c) an order requiring the Defendant to deliver up to the Plaintiffs or to destroy under oath, at the Plaintiffs' election, all sacubitril/valsartan products, including but not limited to any intermediates, bulk product and finished product thereof, in the Defendant's power, possession or control that would offend the injunction sought in subparagraph (b) above;

(d) the Plaintiffs' costs in this action pursuant to section 6.12 of the *Regulations* on the highest scale; and

(e) such further and other relief as this Court may permit and deem just, including relief that may be available under the *Patent Act*, as permitted by subsection 6(4) of the *Regulations*.

THE PARTIES

2. The Plaintiff Novartis Pharmaceuticals Canada Inc. ("**Novartis Canada**") is a corporation incorporated under the laws of Canada, with a registered head office at 700 Rue St-Hubert, suite 100, Montreal, Quebec, H2Y 0C1.

3. The Plaintiff Novartis AG is a corporation incorporated under the laws of Switzerland, with a principal address of CH-4056 Basel Switzerland.

4. The Plaintiffs Novartis Canada and Novartis AG are collectively referred to as "**Novartis**".

5. Novartis AG is the registered owner of the 511 and 598 Patents and is thus made a party to this proceeding pursuant to subsection 6(2) of the *Regulations* and subsection 55(3) of the *Patent Act*.

6. Novartis Canada markets and sells innovative pharmaceutical products, including ENTRESTO®, in Canada. Novartis Canada is the "first person" as contemplated under the *Regulations*.

7. The Defendant, Zydus Lifesciences Limited, manufactures generic pharmaceutical products and has an office at Plant Number 26 to 29 and 31, Dabhasa Umaraya Road, Village Dabhasa, Vadodara, Gujarat, 391440, India.

8. Zydus has prepared and filed an ANDS for the Zydus Product and is seeking approval to market a generic copy of Novartis Canada's ENTRESTO® product as set out below. Zydus is a "second person" as contemplated under the *Regulations*.

ENTRESTO®

9. Novartis Canada markets and sells ENTRESTO® in Canada pursuant to a Notice of Compliance ("**NOC**") issued by the Minister of Health for tablets containing 24.3mg sacubitril and 25.7mg valsartan (as sacubitril valsartan sodium hydrate complex), 48.6mg sacubitril and 51.4mg valsartan (as sacubitril valsartan sodium hydrate complex), and 97.2mg sacubitril and 102.8mg valsartan (as sacubitril valsartan sodium hydrate complex), which have Drug Identification Numbers ("DINs") 02446928, 02446936, and 02446944, respectfully.

10. ENTRESTO® is a film-coated immediate release oral tablet that contains a crystalline salt complex of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively.

11. ENTRESTO® also contains the following excipients: colloidal silicon dioxide, crospovidone, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose and talc.

12. ENTRESTO® is approved for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalisation.

THE 511 PATENT

13. The 511 Patent is entitled "PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR".

14. A copy of the 511 Patent is attached to this claim as Appendix "A".

15. The 511 Patent was issued by the Canadian Patent Office on January 8, 2013, filed in Canada on November 8, 2006, and published on May 18, 2007.

16. The named inventors of the 511 Patent are Lili Feng, Sven Erik Godtfredsen, Piotr Karpinski, Paul Allen Sutton, Mahavir Prashad, Michael J. Girgis, Bin Hu, Yugang Liu, and Thomas J. Blacklock.

17. The 511 Patent claims priority from:

(a) United States Application Number 60/735,093, filed November 9, 2005;

(b) United States Application Number 60/735,541, filed November 10, 2005;

(c) United States Application Number 60/789,332, filed April 4, 2006;

(d) United States Application Number 60/822,086, filed August 11, 2006;

18. The 511 Patent is presumed valid pursuant to subsection 43(2) of the *Patent Act* and is in good standing. The 511 Patent will remain in full force and effect until November 8, 2026.

19. The 511 Patent is included on the Patent Register maintained by the Minister of Health pursuant to sections 3 and 4 of the *Regulations* in connection with a NOC in the name of Novartis Canada.

20. The 511 Patent contains 30 claims. The claims of the 511 Patent read:

1. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate in the solid form.

2. The compound of claim 1 in the crystalline form.

3. The compound of claim 1 or 2, which is an asymmetric unit comprising six each of $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$, wherein the molecular mass of each $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$ is 957.99 and wherein each of $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$ comprises an ARB moiety and a NEPi moiety, 3 sodium atoms, and 2.5

water molecules, wherein said ARB moiety is a (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine molecular moiety and said NEPi moiety is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester molecular moiety.

4. The compound of claim 1, 2 or 3, characterized by an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm^{-1})(± 2 cm^{-1}): 2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

5. The compound of any one of claims 1 to 4 characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals:

d in [Å] (± 0.1 Å): 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w).

6. A dual-acting compound obtained by:

(i) dissolving (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a suitable solvent;

(ii) dissolving a basic compound of Na in a suitable solvent;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) - (iii), as the first method, followed by steps (iva) - (via) by:

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

7. The compound of claim 6 wherein the suitable solvent in steps (i), and/or (va) is acetone.

8. The compound of claim 6 or 7 wherein the basic compound of Na is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

9. The compound of any one of claims 6 to 8 in the crystalline form.

10. The compound of any one of claims 6 to 9 in the form of a hydrate.

11. A pharmaceutical composition comprising

(a) the compound according to any one of claims 1 to 10; and

(b) at least one pharmaceutically acceptable additive.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable additive is a diluent or filler, a disintegrant, a glidant, a lubricant, a binder, or a colorant, or any combination thereof.

13. A method of preparing the compound according to any one of claims 1 to 5, said method comprising the steps of:

(i) dissolving (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a suitable solvent;

(ii) dissolving a basic compound of Na in a suitable solvent;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the compound; or alternatively

obtaining the compound by exchanging the solvent(s) employed in steps (i) - (iii), as the first method, followed by steps (iva) - (via) by:

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the compound.

14. The method of claim 13 wherein the suitable solvent in steps (i) and/or (va) is acetone.

15. The method of claim 13 or 14, wherein the basic compound of Na is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

16. Use of a compound according to any one of claims 1 to 10 for the preparation of a medicament for the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart failure, left ventricular dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scieroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

17. The use according to claim 16 for the treatment of hypertension.

21. The use according to claim 16 for the treatment of acute heart failure.

22. The use according to claim 16 for the treatment of chronic heart failure.

23. Use of a compound according to any one of claims 1 to 10 for the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart failure, left ventricular dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

24. The use according to claim 23 for the treatment of hypertension.

25. The use according to claim 23 for the treatment of acute heart failure.

26. The use according to claim 23 for the treatment of chronic heart failure.

27. The pharmaceutical composition according to claim 11 or 12 for use in the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart failure, left ventricular dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary

renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

28. The pharmaceutical composition according to claim 11 or 12 for the treatment of hypertension.

29. The pharmaceutical composition according to claim 11 or 12 for the treatment of acute heart failure.

30. The pharmaceutical composition according to claim 11 or 12 for the treatment of chronic heart failure.

THE 598 PATENT

21. The 598 Patent is entitled “DUAL-ACTING PHARMACEUTICAL COMPOSITIONS BASED ON SUPERSTRUCTURES OF ANGIOTENSIN RECEPTOR ANTAGONIST/BLOCKER (ARB) AND NEUTRAL ENDOPEPTIDASE (NEP) INHIBITOR”.

22. A copy of the 598 Patent is attached to this claim as Appendix “B”.

23. The 598 Patent was issued by the Canadian Patent Office on August 9, 2016, filed in Canada on November 4, 2008, and published on May 14, 2009.

24. The named inventors of the 598 Patent are Suliman Al-Fayoumi, Jiahui Hu, Natrajan Kumaraperumal, Alan Edward Royce, Colleen Ruegger, and Erika Aina Zannou.

25. The 598 Patent claims priority from United States Application Number 60/985,668, filed November 6, 2007.

26. The 598 Patent is presumed valid pursuant to section 43(2) of the *Patent Act* and is in good standing. The 598 Patent will remain in full force and effect until November 4, 2028.

27. The 598 Patent is included on the Patent Register maintained by the Minister of Health pursuant to sections 3 and 4 of the *Regulations* in connection with a NOC in the name of Novartis Canada.

28. The 598 Patent contains 21 claims. The claims of the 598 Patent read:

1. A solid oral dosage form comprising:

(a) the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate in a concentration from about 4% to about 90% by weight of the composition; and

(b) at least one pharmaceutically acceptable excipient,

wherein the compound is present in a dose strength of 40, 50, 100, 200 or 400 mg corresponding to the respective combined amount of valsartan free acid and (2*R*,4*S*)-5-biphenyl-4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a 1:1 ratio per unit dosage form.

2. The solid oral dosage form of claim 1, wherein said solid oral dosage form comprises trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)-propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate in a concentration from 4% to 60% by weight of the composition.

3. The solid oral dosage form of claim 1, wherein said solid oral dosage form is a tablet.

4. The solid oral dosage form of claim 3, wherein said tablet is an immediate-release formulation.

5. The solid oral dosage form of claim 3, wherein the compound is present in a dose strength of 40, 50, 100, 200 or 400 mg and the tablet is a roller compacted tablet.

6. The solid oral dosage form of claim 1, wherein the pharmaceutically acceptable excipients comprise (i) microcrystalline cellulose, (ii) hydroxypropylcellulose, (iii) Crospovidone, (iv) Mg, Ca or Al stearate, (v) anhydrous colloidal silica and (v) talc.

7. The solid oral dosage form according to claim 6, wherein Mg stearate is employed in amounts of 1.0 to 6.0% by weight, anhydrous colloidal silica is employed in an amount of from 0.1 to 2% by weight, microcrystalline cellulose is present in an amount of 10 to 30% by weight, and crospovidone is present in an amount of 1 to 20% by weight.

8. A process for making a solid oral dosage form according to claim 1 comprising the steps of

(a) mixing the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate with at least one pharmaceutically acceptable excipient to form a blend;

(b) directly compressing said blend into a solid oral dosage form.

9. A process for making a solid oral dosage form according to claim 5 comprising the steps of

(a) mixing the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate with at least one pharmaceutically acceptable excipient to form a blend;

(b) compacting said blend; and

(c) compressing the final blend into a solid oral dosage form.

10. A process according to claim 9 comprising the additional step of mixing the compacted blend as obtained in step b) with further pharmaceutically acceptable excipients.

11. A process for making a solid oral dosage form according to claim 5 comprising the steps of

(a) sieving the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate and pharmaceutically acceptable excipients to form a sieved material;

(b) blending the sieved material to form a blended material;

(c) compacting the blended material to form a compacted material;

(d) milling the compacted material to form a milled material; and

(e) compressing the final mixture to form a tablet.

12. A process according to claim 11 comprising the additional step of blending the milled material obtained in step d) with further pharmaceutically acceptable excipients to form a final mixture.

13. A process according to claim 11 or 12 comprising the additional step of applying a film coat to the tablet obtain in step e) in order to obtain film coated tablets.

14. The solid oral dosage form according to claim 1, wherein the solid oral dosage form exhibits an *in vitro* dissolution profile, such that after 30 min, a mean of about 10% to a mean of about 100 % (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

15. The solid oral dosage form according to claim 1, wherein the solid oral dosage form exhibits an *in vitro* dissolution profile, such that after 30 min, a

mean of at least 40% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

16. The solid oral dosage form according to claim 1, wherein the solid oral dosage exhibits an *in vitro* dissolution profile, such that after 10 min, a mean of at least 40% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

17. The solid oral dosage form according to claim 1, wherein

(i) the compound is present in an amount of about 100 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released, or

(ii) the compound is present in an amount of about 200 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released; or

(iii) the compound is present in an amount of about 400 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 40% of valsartan free acid, is released, after 20 min, a mean of about 70% of valsartan free acid, is released, after 30 min, a mean of about 90% of valsartan free acid, is released.

18. The solid oral dosage form according to claim 1 that delivers a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, and a carrier medium, wherein the oral dosage form provides a rate of absorption of valsartan free acid with a t_{max} of 1 to 2.2 h following administration of a single dose of said dosage form and / or provides a dose-normalized mean plasma exposure (AUC_{0-24}) of 230 to 400

ng•h/mL/mg-equivalent following administration of a single dose of said dosage form.

19. The solid oral dosage form according to claim 1 for the preparation of a medicament for increasing the rate of absorption and / or exposure of valsartan free acid.

20. The process according to claim 9, wherein the compacting in step (b) is roller compacting.

21. The process according to claim 11, wherein the compacting in step (c) is roller compacting.

THE ZYDUS NOA

29. On January 6, 2026, Zydus caused to be served a letter purporting to be a notice of allegation ("**Zydus NOA**") pursuant to the *Regulations* on Novartis Canada in respect of the Zydus Product and the 511 Patent and 598 Patent.

30. The Zydus NOA states that Zydus has filed an Abbreviated New Drug Submission filed under Submission Number 301464 with the Minister of Health, seeking a NOC from Health Canada for the Zydus Product in strengths of 24/26 mg sacubitril/valsartan, 49/51 mg sacubitril/valsartan, and 97/103 mg sacubitril/valsartan. The Zydus NOA further states that Zydus has compared the Zydus Product to Novartis Canada's ENTRESTO® sacubitril valsartan sodium hydrate complex film-coated tablet of the same strengths.

INFRINGEMENT

31. Zydus has, without the consent of Novartis, filed an ANDS with the Minister comparing the Zydus Product to ENTRESTO® for the purpose of obtaining an NOC for the Zydus Product. The filing of the Zydus ANDS and the work underlying the Zydus ANDS indicates Zydus's clear and present intention to make or have made for it (in Canada or abroad), construct, use, sell, offer for sale, market, distribute, import and/or export the Zydus Product in accordance

with the Zydus ANDS. Such activity constitutes infringement of the 511 Asserted Claims and 598 Asserted Claims.

32. The Zydus Product, if made, manufactured, used, sold, offered for sale, marketed, distributed, imported or exported, in accordance with the Zydus ANDS will infringe, directly or indirectly, each of the 511 Asserted Claims and 598 Asserted Claims.

33. The Zydus Product will be an immediate-release tablet solid oral dosage form comprising, in whole or in part, the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate ("sacubitril valsartan sodium hydrate complex") in a concentration from about 4% to about 60% by weight of the composition and at least one pharmaceutically acceptable excipient.

34. The Zydus Product will contain material that in the Zydus Product can convert to sacubitril valsartan sodium hydrate complex during its making, processing or storage. The active pharmaceutical material used by or for Zydus to make the Zydus Product can also convert to sacubitril valsartan sodium hydrate complex during and under the conditions of its making, processing or storage.

35. Sacubitril valsartan sodium hydrate complex in solid form, including in crystalline form, is formed during the manufacturing process of the Zydus Product and during the manufacturing process used to make sacubitril valsartan sodium hydrate complex.

36. The Zydus Product will contain sacubitril valsartan sodium hydrate complex in a dosage strength of 50, 100 or 200 mg corresponding to the respective combined amount of valsartan free acid and (2*R*,4*S*)-5-biphenyl-4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester ("**sacubitril**") in a 1:1: ratio per unit dosage form.

37. The Zydus Product will contain sacubitril valsartan sodium hydrate complex in a solid crystalline form. Crystalline sacubitril valsartan sodium hydrate complex will be present in the Zydus Product.

38. The sacubitril valsartan sodium hydrate complex of the Zydus Product will be an asymmetric unit comprising six each of $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$, wherein the molecular mass of each $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$ is 957.99 and wherein each of $C_{48}H_{55}N_6O_8Na_3 \cdot 2.5\ H_2O$ comprises an ARB moiety and a NEPi moiety, 3 sodium atoms, and 2.5 water molecules, wherein said ARB moiety is a (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine molecular moiety and said NEPi moiety is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester molecular moiety.

39. The sacubitril valsartan sodium hydrate complex of the Zydus Product will further be characterized by an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm^{-1})(± 2 cm^{-1}): 2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

40. The sacubitril valsartan sodium hydrate complex of the Zydus Product will further be characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals: d in [Å] (± 0.1 Å): 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w).

41. The Zydus Product will contain a dual acting compound, in the form of a crystalline hydrate, obtained by the following steps, or an obvious equivalent thereto:

(a) dissolving (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a suitable solvent;

(b) dissolving NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO in a suitable solvent;

(c) combining the solutions;

(d) precipitating the solid, and drying same to obtain the dual-acting compound; or alternatively evaporating the resulting solution to dryness;

(e) re-dissolving the solid in a suitable solvent;

(f) precipitating the solid and drying same to obtain the dual-acting compound.

42. The Zydus Product will further comprise a diluent or filler, a disintegrant, a glidant, a lubricant, a binder and a colorant. In particular, the Zydus Product will comprise (i) microcrystalline cellulose in an amount of 10 to 30% by weight, (ii) hydroxypropylcellulose, (iii) crospovidone in an amount of 1 to 20% by weight, (iv) Mg stearate in an amount of 1.0 to 6.0% by weight, (v) anhydrous colloidal silica in an amount of 0.1 to 2% by weight, and (v) talc.

43. The Zydus Product will be made by a process comprising the steps of:

(a) sieving the sacubitril valsartan sodium hydrate complex with pharmaceutically acceptable excipients to form a sieved material;

(b) blending the sieved material to form a blended material;

(c) compacting the blended material by roller compacting to form a compacted material;

(d) milling the compacted material to form a milled material;

(e) blending the milled material with further pharmaceutically acceptable excipients to form a final mixture;

(f) compressing the final mixture to form a tablet; and

(g) applying a film coat to the tablet to obtain film coated tablets.

44. The Zydus Product will exhibit an *in vitro* dissolution profile, such that after 30 minutes, a mean of about 10% to a mean of about 100% (by weight), and more particularly at least 40% (by weight), of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

45. The Zydus Product will further exhibit an *in vitro* dissolution profile, such that after 10 minutes, a mean of about 40% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

46. The Zydus Product, including when present in an amount of about 100 mg per unit dosage form and about 200 mg per unit dosage form, will further exhibit an *in vitro* dissolution profile, such that after 10 minutes, a mean of about 50% of valsartan free acid, is released, after 20 minutes, a mean of about 85% of valsartan free acid, is released, and after 30 minutes, a mean of about 95% of valsartan free acid is released.

47. The Zydus Product will deliver a therapeutically effective amount of valsartan free acid or a pharmaceutically acceptable salt thereof, and a carrier medium, and will provide a rate of absorption of valsartan free acid with a t_{max} of 1 to 2.2 h and / or provide a dose-normalized mean plasma exposure (AUC_{0-24}) of 230 to 400 ng•h/mL/mg-equivalent following administration of a single dose of the Zydus Product.

48. The Zydus Product will increase the rate of absorption and / or exposure of valsartan free acid and will be sold as a medicament for increasing the rate of absorption and / or exposure of valsartan free acid.

49. Further, the Zydus Product will be made, manufactured, used, sold, offered for sale, marketed, distributed, imported or exported for, and will contain a compound for use in, the treatment or prevention of chronic heart failure.

50. Zydus will market and position the Zydus Product as fully substitutable for ENTRESTO®. Zydus will use, offer for sale, sell, market and distribute the Zydus Product to wholesalers, physicians, pharmacies, pharmacists, and patients as an alternative to ENTRESTO®, for use in the treatment or prevention of chronic heart failure.

51. Zydus will knowingly and intentionally exert its influence over formularies, wholesalers, pharmacies, physicians, pharmacists, and patients through its marketing, advertising, rebates, and the Product Monograph for the Zydus Product. Zydus's representations to formularies, wholesalers, pharmacies, physicians, pharmacists, and patients will cause the Zydus Product to be used and sold for use in the treatment or prevention of chronic heart failure.

52. The Zydus Product, if approved, will therefore be prescribed, dispensed, administered, and provided to patients by doctors, pharmacists, and hospitals for use in the treatment or prevention of chronic heart failure.

53. Novartis is unaware of the full extent of Zydus's infringing activities and/or intended infringing activities. Full particulars of all such activities are within the knowledge of Zydus.

DAMAGES TO THE PLAINTIFFS

54. Zydus, by reason of its aforementioned acts, will make a profit and Novartis will suffer damages in the event that Zydus is permitted to market and sell the Zydus Product during the periods in which the 511 Patent and 598 Patent are in force. Should Zydus be permitted to market and sell the Zydus Product during these periods, Novartis expects to suffer losses, exclusive of interest and costs, in excess of $50,000.

55. Should Zydus enter the market with its Zydus Product, Novartis reserves the right to amend this claim, including by adding any other persons claiming under the patentee, and by seeking any and all relief available, including under the *Patent Act* in respect of same, including without limitation a claim for compensatory, punitive, and exemplary damage, and/or an accounting of profits, at Novartis' election.

PLACE OF TRIAL

56. The Plaintiffs propose that this action be tried at Ottawa, Ontario.

Dated at Ottawa, Ontario, this 20th day of February, 2026.

Gowling WLG (Canada) LLP
Barristers & Solicitors
160 Elgin Street, Suite 2600
Ottawa, Ontario K1P 1C3

John Norman
john.norman@ca.gowlingwlg.com
Alex Gloor
alex.gloor@ca.gowlingwlg.com
Adam Heckman
adam.heckman@ca.gowlingwlg.com
Jenny Hepditch
jenny.hepditch@ca.gowlingwlg,com

Tel: 613-233-1781
Fax: 613-563-9869

Solicitors for the Plaintiffs

Appendix “ A ”

Canadian Patent No. 2,590,511

Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2590511 C 2013/01/08

(11)(21) 2 590 511

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2006/11/08
(87) Date publication PCT/PCT Publication Date: 2007/05/18
(45) Date de délivrance/Issue Date: 2013/01/08
(85) Entrée phase nationale/National Entry: 2007/06/11
(86) N° demande PCT/PCT Application No.: US 2006/043710
(87) N° publication PCT/PCT Publication No.: 2007/056546
(30) Priorités/Priorities: 2005/11/09 (US60/735,093); 2005/11/10 (US60/735,541); 2006/04/04 (US60/789,332); 2006/08/11 (US60/822,086)

(51) Cl.Int./Int.Cl. *C07D 257/04* (2006.01), *A61K 31/216* (2006.01), *A61K 31/41* (2006.01), *A61P 9/12* (2006.01), *C07C 233/47* (2006.01)

(72) Inventeurs/Inventors:
FENG, LILI, US;
GODTFREDSEN, SVEN ERIK, US;
KARPINSKI, PIOTR, US;
SUTTON, PAUL ALLEN, US;
PRASHAD, MAHAVIR, US;
GIRGIS, MICHAEL J., US;
...

(73) Propriétaire/Owner:
NOVARTIS AG, CH

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : COMBINAISON PHARMACEUTIQUES D'UN ANTAGONISTE DE RECEPTEUR D'ANGIOTENSINE ET D'UN INHIBITEUR DE NEP

(54) Title: PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR

(57) Abrégé/Abstract:
A specific combination, linked pro-drug or a compound of an angiotensin receptor antagonist and a NEPi are used in the treatment of hypertension.

CA 2590511 C 2013/01/08
(11)(21) 2 590 511
(13) C

(72) Inventeurs(suite)/Inventors(continued): HU, BIN, US; LIU, YUGANG, US; BLACKLOCK, THOMAS J., US

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 May 2007 (18.05.2007)

PCT

(10) International Publication Number
WO 2007/056546 A1

(51) International Patent Classification:
A61K 31/216 (2006.01) *A61P 9/00* (2006.01)
A61K 31/41 (2006.01) *A61P 9/10* (2006.01)
A61P 3/10 (2006.01)

(21) International Application Number:
PCT/US2006/043710

(22) International Filing Date:
8 November 2006 (08.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/735,093	9 November 2005 (09.11.2005)	US
60/735,541	10 November 2005 (10.11.2005)	US
60/789,332	4 April 2006 (04.04.2006)	US
60/822,086	11 August 2006 (11.08.2006)	US

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

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FENG, Lili** [CN/US]; 2600 Rachel Terrace, Apartment 20, Pine Brook, NJ 07058 (US). **GODTFREDSEN, Sven, Erik** [DK/US]; 188 Riveredge Drive, Chatham, NJ 07928 (US). **KARPINSKI, Piotr** [US/US]; 25 Terrace Parkway, Lincoln Park, NJ 07035 (US). **SUTTON, Paul, Allen** [US/US]; 34 Irvington Road, Parsippany, NJ 07054 (US). **PRASHAD, Mahavir** [US/US]; 27 Davenport Road, Montville, NJ 07045 (US). **GIRGIS, Michael, J.** [US/US]; 21 Springbrook Road West, Montville, NJ 07045 (US). **HU, Bin** [CN/US]; 226 West End Avenue, Green Brook, NJ 08812 (US). **LIU, Yugang** [US/US]; 57 Huntley Way, Bridgewater, NJ 08807 (US).

(74) Agent: **FERRARO, Gregory, D.**; Novartis, Corporate Intellectual Property, One Health Plaza, Building 104, East Hanover, NJ 07936 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR

(57) **Abstract:** A specific combination, linked pro-drug or a compound of an angiotensin receptor antagonist and a NEPi are used in the treatment of hypertension.

WO 2007/056546 A1

21489-10714

Pharmaceutical Combinations of an Angiotensin Receptor Antagonist and an NEP Inhibitor

Background of the Invention

Field of the Invention

The present invention is directed to dual-acting compounds and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular a dual acting molecule wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding, or supramolecular complexes of angiotensin receptor blockers and neutral endopeptidase inhibitors, also described as linked pro-drugs, such as mixed salts or co-crystals, as well as to pharmaceutical combinations containing such a dual-acting compound or combination, methods of preparing such dual-acting compounds and methods of treating a subject with such a dual-acting compound or combination. Specifically, the invention is directed to a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule.

Related Background Art

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.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see *Pharmacol Rev*, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see

J Hypertens, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see *J Clin Pharmacol*, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see *Peptides*, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see *Lancet*, Vol. 365, p. 217 (2005); and *Hypertension*, Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for efficacious combination therapy which does not have deleterious side effects.

Summary of the Invention

In a first aspect, the present invention is directed to a dual-acting compound, such as a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation.

The present invention is also directed to a dual-acting compound, such as a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The present invention is also directed to a combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

In preferred embodiments, the angiotensin receptor antagonist and NEPi have acidic groups which facilitate formation of the dual acting compound, such as the supramolecular complex of the present invention.

Preferably, the angiotensin receptor antagonist is selected from the group consisting of valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan, saprisartan, tasosartan, elisartan and combinations thereof.

In preferred embodiments, the NEPi is selected from the group consisting of: SQ 28,603; *N*-[*N*-[1(*S*)-carboxyl-3-phenylpropyl]-(*S*)-phenylalanyl]-(*S*)-isoserine; *N*-[*N*-[((1*S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine; *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid ethyl ester; (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-*oxo*-3-phenylpropyl]amino]benzoic acid; 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2*S*-(2-methoxyethoxymethyl)propanoic acid; *N*-((2*S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; *N*-(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine; (*S*)-(2-biphenyl-4-yl)-1-(1*H*-tetrazol-5-yl)ethylamino) methylphosphonic acid; (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl; *N*-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine; *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; *N*-[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; *N*-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine; *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(R)-alanine; *N*-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine; *N*-[1-[[1(*S*)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-methionine; *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine; *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(*S*)-isoserine;

N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester; 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof. Preferably, the dual-acting compound or combination , in particular the supramolecular complex, is a mixed salt or a co-crystal. It is also preferred that the linked pro-drug is a mixed salt or a co-crystal.

In a second aspect, the present invention is directed to pharmaceutical composition comprising

(a) the aforementioned dual-acting compound or combination, such as the aforementioned complex; and

(b) at least one pharmaceutically acceptable additive.

The present invention is also directed to pharmaceutical compositions comprising a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

(c) at least one pharmaceutically acceptable additive.

In a third aspect, the present invention is directed to a method of preparing a dual-acting compound, in particular a supramolecular complex, comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation selected from the group consisting of Na, K and NH_4;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to a method of making a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

comprising adding a linking moiety and a solvent to a mixture of an angiotensin receptor antagonist and a NEPi; and

(d) isolating the linked pro-drug.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic), congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned dual-acting compound or combination , in particular the supramolecular complex, or the afore-mentioned linked pro-drug, preferably, the complex, to a subject in need of such treatment.

Figure 1 shows a pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units. The following color code is used: grey = carbon atom; blue = nitrogen atom; red = oxygen atom; violet = sodium atom

Detailed Description

The present invention relates to a dual-acting compound or combination, in particular a supramolecular complex, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor, which can form a unique molecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

One embodiment of the invention is directed to a physical combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

Specifically, it is preferred that the two active agents are combined with each other so as to form a single dual-acting compound, in particular a supramolecular complex. By doing so, a new molecular or supramolecular entity is formed having distinct properties different to the above physical combination.

Thus, the present invention is directed to a dual-acting compound, in particular a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and

(c) a pharmaceutically acceptable cation preferably selected from the group consisting of Na, K and NH_4.

The present invention is also directed to a dual-acting compound, in particular a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat such as (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$ in a suitable solvent, wherein Cat is a cation preferably selected from the group consisting of Na, K and NH_4;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatvely

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is further directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The two components are each linked to a linking moiety thereby creating a linked pro-drug. Preferably, the linked pro-drug is substantially pure; as used herein, "substantially pure" refers to at least 90%, more preferably at least 95% and most preferably at least 98% purity.

As one preferred embodiment of the present invention, the linked pro-drug has a structure such that by linking the two components with the linking moiety, a supramolecular complex is formed.

For the purpose of the present invention, the term “dual-acting compound” is intended to describe that these compounds have two different modes of action in one compound, one is

the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound.

For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Typically, hydrogen bonding can be observed between the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Ionic bonds can be present between the cation and one or both of the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Other types of bonds may also be present within the compound such as van der Waals forces. For illustrative purposes, the dual-acting compound of the present invention could be represented as follows:

$$(ARB)\text{-}(L)_m\text{-}(NEPi)$$

wherein L is a linking moiety, such as a cation or is a noncovalent bond and m is an integer from 1 or more. In other words the ARB and NEPi moiety can be connected via non-covalent bonds such as hydrogen bonding. Alternatively or additionally they may be connected via a linking moiety such as a cation.

In one embodiment, the dual-acting compound may be considered to be a linked pro-drug, whereby the linking moiety, such as the cation, linking the two pharmaceutically active agents, the ARB and the NEPi, forms the pro-drug of these agents which are released once the linked pro-drug is ingested and absorbed.

In a preferred embodiment, the dual-acting compound is a complex, in particular a supramolecular complex.

For the purpose of the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species

present in the supramolecular complex distinguishing this complex over a physical mixture of the species.

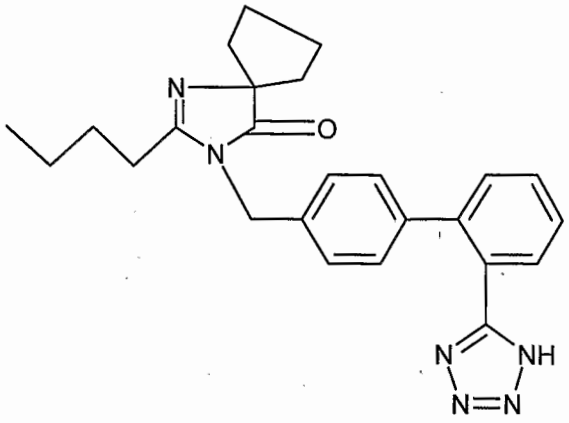
The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π–π stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. As a preferred embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.

Typically, the dual-acting compound, in particular the supramolecular complex shows properties such as melting point, IR spectrum etc. that are different from a physical mixture of the species.

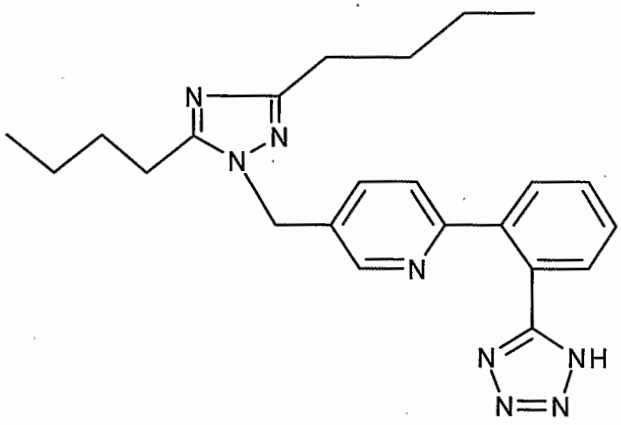
Preferably, the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular hydrogen bonds, between the two pharmaceutically active agents and any solvent, if present, preferably water. Moreover, it is preferred that the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular ionic and hydrogen bonds, between the two pharmaceutically active agents, the cation and any solvent, if present, preferably water. The cation is preferably coordinated to several oxygen ligands, thus, providing a linkage between these oxygen ligands. The oxygen ligands come from the carbonyl and carboxylate groups present in the two pharmaceutically active agents and preferably also from any solvent, if present, preferably water.

The dual acting compound comprises a molecular moiety of an angiotensin receptor antagonist. This means that a molecular moiety derived from an angiotensin receptor antagonist is participating in the build-up of the dual-acting compound. The angiotensin receptor antagonist is part of the compound and connected to the NEP inhibitor directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term “angiotensin receptor antagonist” will be used when describing this part of the compound. Angiotensin receptor antagonists (ARBs) suitable for use in the present invention

include, without limitation, valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan saprisartan, tasosartan, elisartan, the compound with the designation E-1477 of the following formula

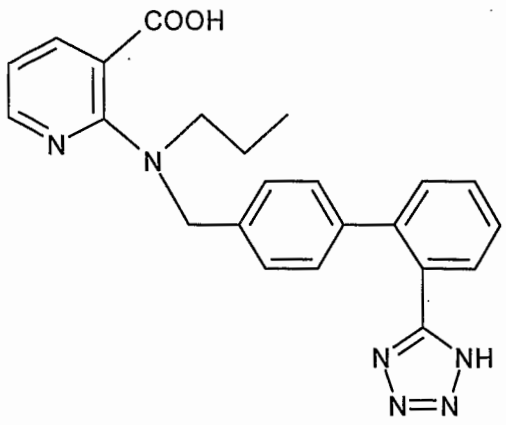


the compound with the designation SC-52458 of the following formula



and

the compound with the designation the compound ZD-8731 of the following formula



Suitable angiotensin II receptor antagonist also includes, but is not limited to, saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-3l5995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Also included within the scope of this aspect of the invention are combinations of the above-identified ARBs.

ARBs to be used for preparing the combination or complex in accordance with the present invention can be purchased from commercial sources or can be prepared according to known methods. ARBs may be used for purposes of this invention in their free form, as well as in any suitable salt or ester form.

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.

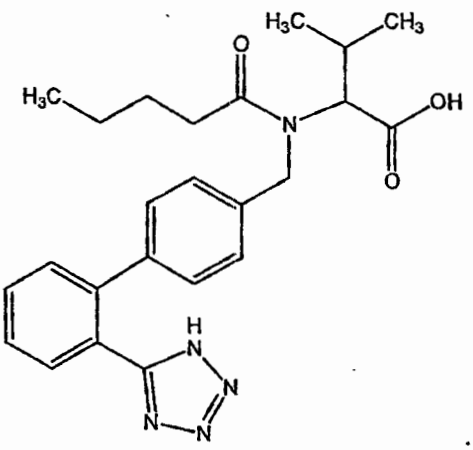
Mono-potassium salt of valsartan in amorphous form; di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

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.

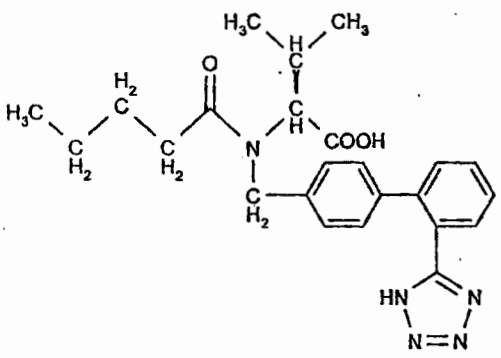
Preferably when preparing the dual-acting compound, in particular the complex according to the present invention, the free form of the ARB is used.

In a preferred embodiment of this invention, the angiotensin receptor blocker used in the combination or complex of the present invention is Valsartan the molecular structure of which is shown below

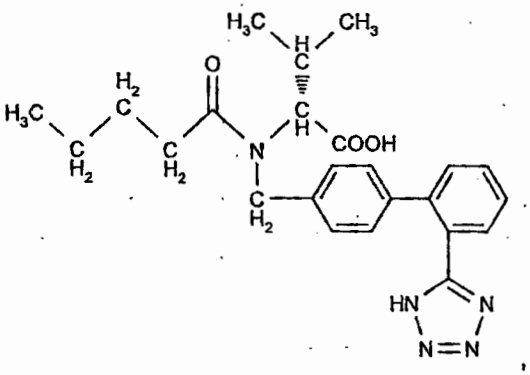
21489-10714

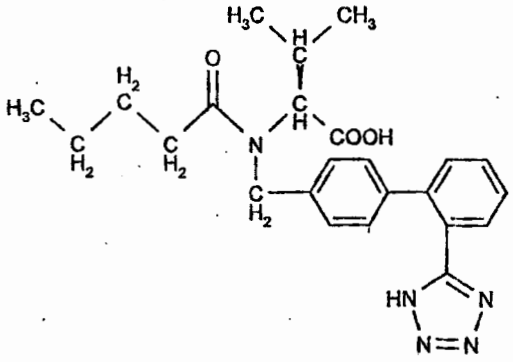


Valsartan may be in the racemic form or as one of the two isomers shown below



or





preferably

Valsartan ((*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) used according to the present invention can be purchased from commercial sources or can be prepared according to known methods. For example, the preparation of valsartan is described in U.S. Patent No. 5,399,578 and EP 0 443 983.

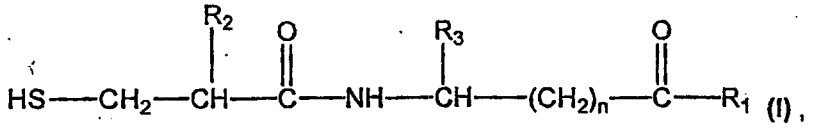
Valsartan may be used for purposes of this invention in its free acid form, as well as in any suitable salt form. Additionally, esters or other derivatives of the carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of the tetrazole grouping. Reference to ARBs includes reference to pharmaceutically acceptable salts thereof.

Preferably, the ARB is a diprotic acid. Thus, the angiotensin receptor blocker has a charge of 0, 1 or 2 depending on the pH of the solution.

In the combination of the present invention, the ARB is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na. This includes both the mono- and di-salt of these cations, preferably the di-salt. In particular in the case of valsartan this means that both the carboxylic acid moiety and the tetrazole moiety form the salt.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the ARB is employed in the preparation and the cationic species present in the complex is introduced by using a base, e.g. (Cat)OH.

The dual acting compound comprises a molecular moiety of a neutral endopeptidase inhibitor. This means that a molecular moiety derived from a neutral endopeptidase inhibitor is participating in the build-up of the dual-acting compound. The neutral endopeptidase inhibitor is part of the compound and connected to the ARB directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "neutral endopeptidase inhibitor" will be used when describing this part of the compound. Neutral endopeptidase inhibitors suitable for use in the present invention include those of formula (I)



(I),

wherein

R_2 is alkyl of 1-7 carbons, trifluoromethyl, phenyl, substituted phenyl, -(CH_2)1 to 4-phenyl, or -(CH_2)1 to 4-substituted phenyl;

R_3 is hydrogen, alkyl of 1-7 carbons, phenyl, substituted phenyl, -(CH_2)1 to 4-phenyl or -(CH_2)1 to 4-substituted phenyl;

R_1 is hydroxy, alkoxy of 1-7 carbons or NH_2;

n is an integer from 1-15;

and the term substituted phenyl refers to a substituent selected from lower alkyl of 1-4 carbons, lower alkoxy of 1-4 carbons, lower alkylthio of 1-4 carbons, hydroxy, Cl, Br or F.

Preferred neutral endopeptidase inhibitors of formula (I) include compounds,

wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1-9; and

R_1 is hydroxy.

Another preferred neutral endopeptidase inhibitor is (3S,2'R)-3-{1-[2'-(ethoxycarbonyl)-4'-phenyl-butyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid or a pharmaceutically acceptable salt thereof.

Preferred neutral endopeptidase inhibitors suitable for use in the present invention include, without limitation, SQ 28,603; *N*-[*N*-[1(*S*)-carboxyl-3-phenylpropyl]-(*S*)-phenylalanyl]-(*S*)-isoserine; *N*-[*N*-[((1*S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine; *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester; *N*-(3-carboxy-1-oxopropyl)-(4*S*)-*p*-phenylphenylmethyl)-4-amino-2*R*-methylbutanoic acid; (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-*oxo*-3-phenylpropyl]amino]benzoic acid; 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2*S*-(2-methoxyethoxymethyl)propanoic acid; *N*-((2*S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; *N*-(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine; (*S*)-(2-biphenyl-4-yl)-1-(1*H*-tetrazol-5-yl)ethylamino) methylphosphonic acid; (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl; *N*-(2-carboxy-4-

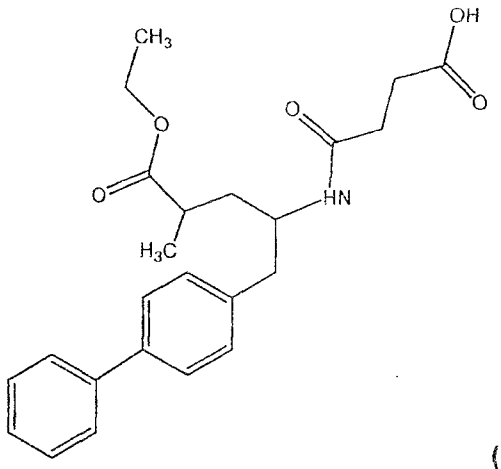
thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine; *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; *N*-[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine; *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; *N*-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine; *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine; *N*-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine; *N*-[1-[[1(*S*)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-isoserine; 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-*oxo*-3,1-propanediyl]]-*bis*-(*S*)-methionine; *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine; *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; *N*-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(*S*)-isoserine; *N*-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester; 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof.

Neutral endopeptidase inhibitors can be purchased from commercial sources or can be prepared according to known methods, such as those set forth in any of U.S. Patent No. 4,722,810, U.S. Patent No. 5,223,516, U.S. Patent No. 4,610,816, U.S. Patent No. 4,929,641, South African Patent Application 84/0670, UK 69578, U.S. Patent No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP 00343911, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S. Patent No. 5,273,990, U.S. Patent No. 5,294,632, U.S. Patent No. 5,250,522, EP 00636621, WO 93/09101, EP 00590442, WO 93/10773, U.S. Patent No. 5,217,996.

Neutral endopeptidase inhibitors may be used for purposes of this invention in their free form, as well as in any suitable salt form. Reference to neutral endopeptidase inhibitors includes reference to pharmaceutically acceptable salts thereof.

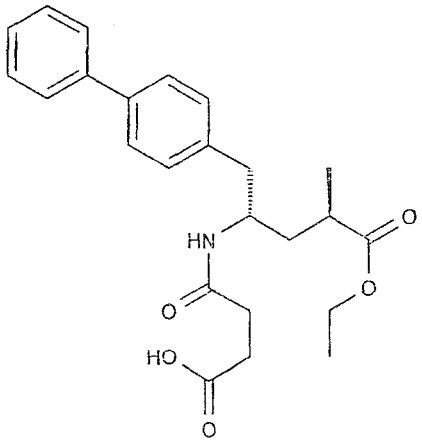
Additionally esters or other derivatives of any carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of any other acidic grouping. In a preferred embodiment of this invention, the NEPi is 5-biphenyl-4-yl-4-(3-carboxy-

propionylamino)-2-methyl-pentanoic acid ethyl ester of formula (II) or the respective hydrolysed form 5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid.



(II) .

The compound of formula (II) can exist as the (2*R*,4*S*), (2*R*,4*S*), (2*R*,4*S*) or (2*R*,4*S*) isomer. Preferred is (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester as shown below:



The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. Patent No. 5,217,996. It can be purchased from commercial sources or can be prepared according to known methods. The compound of formula (II) may be used for purposes of this invention in its free form, as well as in any suitable salt or ester form.

Preferably the NEPi is a monoprotic acid. Thus, the NEPi has a charge of 0 or 1 depending on the pH of the solution.

In the combination of the present invention, the NEPi is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the NEPi is employed in the preparation and the cationic species present in the complex is introduced by using a base, (Cat)OH.

The dual acting compound preferably comprises non-covalent bonds between the ARB and the NEPi. Alternatively or in addition, it optionally comprises a linking moiety such as a pharmaceutically acceptable cation.

The linking moiety includes, but is not limited to, generally regarded as safe (GRAS) compounds or other pharmacologically acceptable compounds. The linking moiety may be an ion or a neutral molecule. In the case wherein the linking moiety is an ion the linked pro-drug is a salt and when the linking moiety is a neutral molecule the linked pro-drug is a co-crystal. Without being bound by any particular theory, the acidic portion of the ARB and NEPi donate a proton to the basic linking moiety such that all three components then become united to form one molecule. When the linked pro-drug is ingested by the subject intended to be treated the more acidic nature of the ingestion environment causes the linked pro-drug to separate into individual components concomitant with ingestion and absorption and therefore be converted into active agents to provide their beneficial biological action to treat the intended diseases.

In the case of a linked pro-drug salt or the dual-acting compound, the linking moiety or the cation, respectively, is preferably a positively charged mono-, di- or tri-valent cation, an organic base or an amino acid. Preferred cations (Cat) both for the linked pro-drug in general and the dual-acting compound, in particular the complex are basic cations, even more preferably metallic cations. Preferred metallic cations include, but are not limited to Na, K, Ca, Mg, Zn, Fe or NH_4. Amine bases and salt forming agents may also be employed, such as benzathine, hydrabamine, ethylenediamine, n-n-dibenzyl-ethylenediamine, L-arginine, choline hydroxide, N-methyl-glucamine, (Meglumine), L-Lysine, dimethylaminoethanol (Deanol), t-butylamine, diethylamine, 2-(diethylamino)-ethanol, 4-(2-

hydroxyethyl)-morpholine, Thromethanine (TRIS), 4-acetamidophenol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol, benzylamine, cyclohexylamine, diethanolamine, ethanolamine, imidazole, piperazine and triethanolamine.

Most preferably, the cation is Na, K or NH_4, such as Na. In one embodiment Ca is preferred.

In the case of a linked pro-drug co-crystal, the linking moiety is may also be a neutral molecule which provides hydrogen-bonding functionality.

In one embodiment, the linked pro-drugs of this invention are represented as set forth below, wherein scheme (1) and (2) represent a salt and scheme (3) represents a co-crystal:

NEPi • Xa• ARB scheme (1)

NEPi • XaYb• ARB scheme (2)

NEPi • Zc• ARB scheme (3),

wherein

X is Ca, Mg, Zn or Fe;

Y is Na, K or NH4;

Z is a neutral molecule; and

a, b and c reflect the stoichiometry of the linked pro-drug, preferably, a, b and c are a valence of 1^+, 2^+ or 3^+.

For the linked pro-drugs of schemes (1) and (2), above, preferably the NEPi is a monoprotic acid and ARB is a diprotic acid. The angiotensin receptor blocker has a charge of 0, 1 or 2 and the NEPi has a charge of 0 or 1 depending on the pH of the solution, while the overall molecule will be neutral. Ratios of ARB to NEPi will be 1:1, 1:2, 1:3, 3:1, 2:1, 1:1, preferably 1:1, 1:2 or 1:3, most preferably 1:1.

Multi-component salts, particularly with zinc and calcium have been reported in the literature, e.g., *Chem Pharm Bull*, Vol. 53, p. 654 (2005). These ions require a coordination geometry that facilitates the crystallization of multi-component systems. The metal ions have coordinating geometries governed by the atomic orbitals for each species

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of linked pro-drugs of valsartan and a NEPi comprise a linkage between the carboxylic acid and the linking moiety or a linkage between the tetrazole grouping and the linking moiety. In yet another embodiment, the linked pro-drug comprises a trivalent linking moiety linked to the valsartan carboxylic acid grouping, the tetrazole grouping and the NEPi grouping.

In an embodiment of this aspect of the invention, valsartan is linked to (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester by a calcium salt ion.

In a preferred embodiment of the present application, the angiotensin receptor antagonist and the neutral endopeptidase inhibitor are present in a molar ratio of 1:1, 1:2, 1:3, 3:1, 2:1, more preferably 1:1 in the combination as well as in the supramolecular complex. This is also true for the linked pro-drug. Moreover, in the complex, angiotensin receptor antagonist, the neutral endopeptidase inhibitor and the cation are present in a molar ratio of 1:1:1, 1:1:2, 1:1:3, more preferably 1:1:3. This applies equally to the linked pro-drug.

The combination or the dual-acting compound, in particular the complex of the present invention may contain a solvent. This is particularly preferred in the case of the dual-acting compound, in particular the complex, where the solvent may contribute to the intermolecular structure, e.g. the supramolecular interactions. Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride, preferably water. If a solvent is present, one or more molecules per molecule of the active agent can be present. In this case, namely if a stoichiometric amount of the solvent is present, preferably 1, 2, 3, 4 or 5, more preferably 3, molecules of solvent, such as water, can be present per molecule of active agent. Alternatively, the solvent may be present in non-stoichiometric amounts. This means preferably any stoichiometric fraction of the solvent, such as 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3.25, 3.5, 3.75, 4.25, 4.5 and 4.75, preferably 2.5, molecules of solvent, such as water, can be present per molecule of active agent. If the dual-acting compound, in particular the complex is in the crystalline form, the solvent may be part of the molecular packing and be trapped in the crystal lattice.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3} \bullet xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, preferably

[ARB(NEPi)]$Na_3 \bullet xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, more preferably

[valsartan ((2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3 \bullet x\ H_2O$, wherein x is 0, 1, 2 or 3, such as 3.

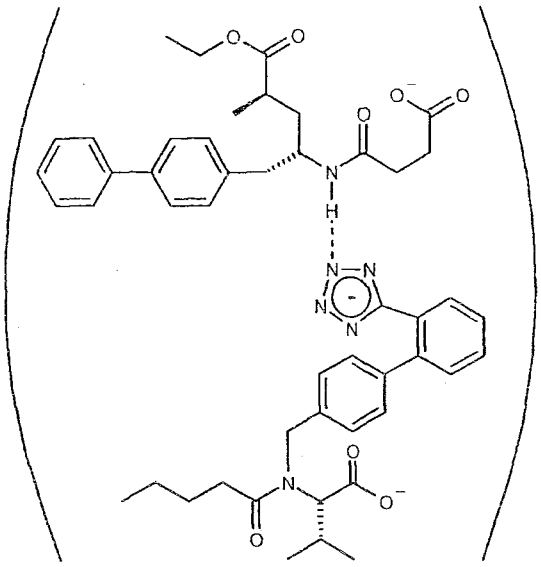
Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3} \bullet xH_2O$, wherein x is 0 to 3, such as 2.5, preferably

[ARB(NEPi)]$Na_3 \bullet xH_2O$, wherein x is 0 to 3, such as 2.5, more preferably

[(*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) (5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3 \bullet x\ H_2O$, in particular [((*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3 \bullet x\ H_2O$, wherein x is 0 to 3, such as 2.5. In this most preferred example, the complex is termed trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

A simplified structure of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate used to formally calculate the relative molecular mass, is shown below.



. 3 Na^+ . 2.5 H_2O

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of the dual-acting compound, in particular, the complex, of valsartan and a NEPi comprises an interaction between the carboxylic acid and the cation, such as Na, or the solvent, such as water, or a linkage between the tetrazole grouping and the cation, such as Na, or the solvent, such as water. In yet another embodiment, the dual-acting compound, in particular, the complex, comprises an interaction between the valsartan carboxylic acid grouping, the tetrazole grouping or the NEPi grouping and the cation, such as Na, or the solvent, such as water.

The combination or dual-acting compound, in particular, the complex, of the present invention is preferably in the solid form. In the solid state it can be in the crystalline, partially crystalline, amorphous, or polymorphous form, preferably in the crystalline form.

The dual-acting compound, in particular, the complex, of the present invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents. Thus, it can have different properties that make it particularly useful for manufacturing and therapeutic applications. The difference of the dual-acting compound, in particular, the complex, and the combination can be exemplified by the dual-acting compound of (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester

which is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture.

Specifically, such a dual-acting compound is preferably characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer using Cu-Ka radiation (lamda=1.54056 A) with a Peltier-cooled Silicon detector at room temperature (25degree C). Scan range was from 1.5degree to 40degree in 2 theta with a scan rate of 3degree/minute. The most important reflections in the X-ray diffraction diagram comprise the following interlattice plane intervals:

The preferred characterization of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values 2Θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

or with an error limit of ±0.1:

4.45, 5.52, 5.57, 9.94, 12.82, 15.66, 17.01, 17.12, 17.2, 18.32, 18.46, 19.76, 21.53, 21.72, 23.17, 23.27, 24.88, 25.3, 27.4, 27.88, 28.04, 30.2.

The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals:

2Θ in [°] : .4.5, 5.6, 12.8, 17.0, 17.2, 19.8, 21.5, 27.4, in particular 4.45, 5.57, 17.01, 17.2, 19.76, 21, 27.4.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields cell constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods. The program used is Powder Pattern within the application software Materials Studio (Accelrys). A

comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, obtained from measurements and from calculating the single crystal data, is illustrated in the table below.

Table

measured		calculated		measured		calculated	
2Θ in [°]	Intensity	2Θ in [°]	Intensity	2Θ in [°]	Intensity	2Θ in [°]	Intensity
4.45	very strong	4.15	very strong	19.76	strong	19.6	very weak
5.52	Strong	5	strong	21.53	weak	19.8	very weak
5.57	strong	6.5	strong	21.72	very weak	21.4	very weak
9.94	very weak	9.75	weak	23.17	weak	23.1	very weak
12.82	very strong	12.6	weak	23.27	weak	23.15	very weak
15.66	very weak	15.05	strong	24.88	very weak		very weak
17.01	weak	16.9	very strong	25.3	weak	25.3	very weak
17.12	strong	17.1	strong	27.4	weak	27.3	very weak
17.2	weak	17.15	weak	27.88	very weak	27.9	very weak
18.32	weak	18.25	very	28.04	weak		

			weak				
18.46	weak	18.3	weak	30.2	weak		

Relative intensity between 100% to 50% is referred to as very strong, 50% to 10% as strong, 10% to 5% as weak, and below 5% as very weak.

The invention relates to trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, a crystalline solid which is characterized by the data and parameters obtained from single crystal X-ray analysis and X-ray powder patterns. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

Crystal data

sum formula	$C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$
molecular mass	957.99
crystal colour	colourless
crystal shape	tabular: hexagonal
crystal system	monoclinic
space group	$P2_1$
Cell parameters	a=20.344 Å
	b=42.018 Å
	c=20.374 Å
	$\alpha = 90^0$
	β=119.29°

	$\gamma = 90°$
volume of unit cell	15190.03 $Å^3$
Z (the number of asymmetric units in the unit cell)	2
calculated density	1.26845 g/cm3

Single crystal X-ray measurement data

diffractometer	Nonius KappaCCD
X-ray generator	Nonius FR571 X-ray generator with a copper rotating anode
temperature	270 K and 150 K

Notes:
Two data sets on two suitable single crystals were collected at two different temperatures to assure no phase change during cooling.
None of the hydrogen atoms on the water or amine nitrogen atoms were observed in the Fourier maps so they were not included in the refinement.

Computer program used to solve the structure
SHELXD (Sheldrick, Göttingen)

In three dimensions, the unit cell is defined by three edge lengths a, b, and c, and three interaxial angles α, β, und γ. In this way, the volume of the unit cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above). The details for trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic unit cell exists, its cell content of twelve formula units of $C_{48}H_{55}N_6O_8Na_3 \bullet 2.5\ H_2O$ occurring as a result of two asymmetric units on two-fold positions.

The acentric space group $P2_1$ determined from the single crystal X-ray structure is a common space group for enantiomorphically pure molecules. In this space group there are two general positions which means that for twelve formula units in the unit cell there must be 18 sodium ions and 15 waters in the asymmetric unit.

A pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units is shown in Figure 1.

Based on the single crystal structure solution, the asymmetric unit of the trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate supramolecule comprises six each of ARB and NEPi moieties, 18 sodium atoms, and 15 water molecules. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-utylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate may be considered a sodium supramolecular complex, coordinated by oxygen ligands. These oxygens come from twelve carboxylate groups and eighteen carbonyl groups of the above moieties, and from 13 of the 15 water molecules. The crystal is an infinite 3-dimensional network of these sodium complexes.

Such a compound may also be characterized by an infrared absorption spectrum obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) showing the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st). Characteristic to the complex are in particular the following peaks 1711(st), 1637(st), 1597(st) and 1401(st). The error margin for all absorption bands of ATR-IR is $\pm$ 2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Such a compound may also be characterized by a Raman spectrum measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) showing the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ± 2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Such a compound may also be characterized by distinct melting properties measured by differential scanning calorimetry (DSC). Using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for such a complex are observed at 139°C and 145°C, respectively. The heating rate is 10 K/min.

The second embodiment of the present invention is directed to pharmaceutical compositions comprising a combination, a linked pro-drug or a dual-acting compound, in particular the complex as described herein and at least one pharmaceutically acceptable additive. The details regarding the combination and the complex, including the ARB and the NEPi, are as described above with regard to the first embodiment of the invention.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the combination or dual-acting compound, in particular the complex, alone or in combination with at least one pharmaceutically acceptable carrier, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

Pharmaceutically acceptable additives suitable for use in the present invention include, without limitation and provided they are chemically inert so that they do not adversely affect the combination or the dual-acting compound, in particular the complex of the present invention, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and

combinations thereof. The amount of each additive in a solid dosage formulation may vary within ranges conventional in the art. Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; β-cyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known *per se*, e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the linked pro-drug, combination or dual-acting compound, in particular the complex with solid excipients, if desired, granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compounds in the combination or dual-acting compound, in particular the complex can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. The projected efficacy in animal disease models ranges from about 0.1 mg/kg/day to about 1000 mg/kg/day given orally, and the projected dose for human treatment ranges from about 0.1 mg/day to about 2000 mg/day. Preferred ranges are from about 40 mg/day to about 960 mg/day of the linked pro-drug, preferably about 80 mg/day to about 640 mg/day. The ARB component is administered in a dosage of from about 40 mg/day to about 320 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosages of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80 mg, 160 mg/160 mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are "therapeutically effective amounts". Preferred dosages for the linked pro-drug, combination or dual-acting compound, in particular the complex of the pharmaceutical composition according to the present invention are therapeutically effective dosages.

The pharmaceutical compositions may contain in addition another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl™; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY™ R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene

synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors. Most preferred combination partners are diuretics, such as hydrochlorothiazide, and/or calcium channel blockers, such as amlodipine or a salt thereof.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the figures 1 to 7.
A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications).

Accordingly, the present invention provides pharmaceutical compositions in addition a therapeutically effective amount of another therapeutic agent, preferably selected from antidiabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypolipidemic agents as described above.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, e.g. applying the following methodology:

The antihypertensive and neutral endopeptidase 24.11 (NEP)-inhibitory activities of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is assessed in conscious rats. The blood pressure-lowering effect is evaluated in double-transgenic rats (dTGRs) that overexpress both human renin and its substrate, human angiotensinogen (Bohlender, et al, High human renin hypertension in transgenic rats. Hypertension; 29(1 Pt 2):428-34, 1997). Consequently, these animals exhibit an angiotensin II-dependent hypertension. The NEP-inhibitory effect of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is determined in conscious Sprague-Dawley rats infused with exogenous atrial natriuretic peptide (ANP). Potentiation of plasma ANP levels is used as an index of NEP inhibition in vivo. In both models, trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is administered orally as a powder in gelatin mini capsules. The results are summarized below.

- Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate exhibits a dose-dependent and long-lasting antihypertensive effect after oral administration in conscious dTGRs, a rat model of fulminant hypertension.

- Oral administration of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly and dose-dependently inhibits NEP with a long duration of action, as reflected by its potentiation of plasma ANP

immunoreactivity (ANPir) in conscious Sprague-Dawley rats infused with exogenous ANP.

Antihypertensive effect in vivo

The dTGRs are instrumented with radiotelemetry transmitters for continuous measurement of arterial blood pressure and heart rate. Animals are randomly assigned to vehicle (empty capsule) or treatment (at 2, 6, 20 or 60 mg/kg, p.o.) groups. Baseline 24-hr mean arterial pressure (MAP) is approximately 170-180 mmHg in all groups. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate dose-dependently reduces MAP. The values obtained from the treatment groups are dose-dependent, and the results from the three highest doses are significantly different from the vehicle controls

Inhibition of NEP in vivo

The extent and duration of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate for NEP inhibition in vivo is assessed with methodologies as described previously (Trapani, et al, CGS 35601 and its orally active prodrug CGS 37808 as triple inhibitors of endothelin-converting enzyme-1, neutral endopeptidase 24.11, and angiotensin-converting enzyme. J Cardiovasc Pharmacol; 44(Suppl 1):S211-5, 2004). Rat ANP(1-28) is infused intravenously at a rate of 450 ng/kg/min in conscious, chronically cannulated, male Sprague-Dawley rats. After one hour of infusion, rats are randomly assigned to one of six groups: untreated control, vehicle (empty capsule) control, or one of four doses of drug (2, 6, 20, or 60 mg/kg, p.o.). ANP infusion is continued for an additional eight hours. Blood samples are collected for measuring plasma ANPir by a commercial enzyme immunoassay kit at -60 min (i.e., before initiating ANP infusion), -30 min (after 30 min of ANP infusion), 0 min ("baseline"; after 60 min of ANP infusion but before dosing with drug or its vehicle), and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr post-dosing.

Before ANP infusion, ANPir is low (0.9-1.4 ng/ml) and similar in all six groups. ANP infusion rapidly (by 30 min) elevates ANPir to ~10 ng/ml. This ANPir level is sustained for the duration of the experiment in the untreated and vehicle control groups. In contrast, trisodium

[3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly (within 15 min) and dose-dependently augments ANPir. In summary, orally administered LCZ696 rapidly and dose-dependently inhibited NEP with a long duration of action as reflected by the potentiation of plasma ANPir.

The available results indicate an unexpected therapeutic effect of a compound according to the invention.

In a third aspect, the present invention is directed to a method of making a linked pro-drug of an ARB or a pharmaceutically acceptable salt thereof and a NEPi or a pharmaceutically acceptable salt thereof comprising the steps of:

(a) adding an inorganic salt forming agent to a solvent to form a linked pro-drug salt forming solution;

(b) adding the salt forming solution to a mixture of an ARB and a NEPi such that the ARB and NEPi form a linked pro-drug; and

(c) isolating the linked pro-drug.

Preferably, the components are added in an equivalent amount.

The inorganic salt forming agent includes, but is not limited to, calcium hydroxide, zinc hydroxide, calcium methoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate and magnesium hydrogen carbonate, sodium hydroxide, sodium methoxide, sodium acetate, sodium formate. The inorganic salt forming agent releases the linking moiety into the solvent such that when an ARB and a NEPi are present a linked pro-drug is formed.

Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethylacetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents.

The inorganic salt forming agent and the solvent when combined should have a pH which promotes linked pro-drug formation. The pH may be between about 2 and about 6, preferably between about 3 and about 5, most preferably between 3.9 and 4.7.

The linked pro-drug is isolated by crystallization and chromatography. Specific types of chromatography include, e.g., ligand specific resin chromatography, reverse phase resin chromatography and ion-exchange resin chromatography.

A specific example comprises contacting a divalent salt of one component with a mono-valent salt of the other component of the linked pro-drug. Specifically the mixed salt of valsartan and a mono-basic NEPi are synthesized by contacting the calcium salt of valsartan with the sodium salt of the NEPi component. Isolation of the desired mixed salt is carried out by selective crystallization or chromatography using ligand specific resins, reverse phase resins or ion-exchange resins. Similarly this process can be conducted with a monovalent salt of both components, such as the sodium salt of both components.

In another embodiment of this aspect of the invention, a co-crystal of the linked pro-drug is obtained. In a method of making a linked pro-drug co-crystal the inorganic salt forming agent is replaced with a neutral molecule which provides hydrogen binding properties. The solvent may be part of the molecular packing and be trapped in the crystal lattice.

In a preferred embodiment of the third aspect, the present invention is directed to a method of preparing a dual-acting compound comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The details regarding the complex, including the ARB, the NEPi and the cation, are as described above with regard to the first embodiment of the invention.

Preferably, in step (i) the ARB and the NEPi are added in an equivalent molar amount. Both the ARB and the NEPi are preferably used in the free form. The solvent used in step (i) may be any solvent that allows dissolution of both the ARB and the NEPi. Preferred solvents include those mentioned above, namely water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, DMF, NMF and methylene chloride and mixtures of such solvents, such as ethanol-water, methanol-water, 2-propanol-water, acetonitrile-water, acetone-water, 2-propanol-toluene, ethyl acetate-heptane, isopropyl acetate-acetone, methyl-t-butyl ether-heptane, methyl-t-butyl ether-ethanol, ethanol-heptane, acetone-ethyl acetate, actetone-cyclohexane, toluene-heptane, more preferably acetone.

Preferably, in step (ii) the basic compound of Cat is a compound capable of forming a salt with the acidic functionalities of the ARB and the NEPi. Examples include those mentioned above, such as calcium hydroxide, zinc hydroxide, calcium methoxide, calcium ethoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate, magnesium hydrogen carbonate, sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium ethoxide, sodium acetate, sodium formate, potassium hydroxide, potassium carbonate, potassium hydrogen carbonate, potassium methoxide, potassium ethoxide, potassium acetate, potassium formate, ammonium hydroxide, ammonium methoxide, ammonium ethoxide, and ammonium carbonate. Perchlorates may also be used. Amine bases or salt forming agents such a those mentioned above may also be used, in particular benzathine, L-arginine, cholin, ethylene diamine, L-lysine or piperazine. Typically an inorganic base is

employed with Cat as specified herein. More preferably, the basic compound is (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$, still more preferably Cat(OH), such as NaOH. The basic compound is employed in an amount of at least 3 equivalents relative to either the ARB or the NEPi, preferably it is employed in stoichiometric amount to obtain the dual-acting compound, in particular the complex with three cations. The solvent used in step (ii) may be any solvent or mixtures of solvents that allow dissolution of Cat(OH). Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably water.

In step (iii) the solutions obtained in steps (i) and (ii) are combined. This can take place by adding the solution obtained in step (i) to the solution obtained in step (ii) or vice versa, preferably, the solution obtained in step (ii) to the solution obtained in step (i).

According to the first alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex precipitates in step (iv). This mixing and precipitation is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 2 h, at room temperature. It is advantageous to add seeds of the dual acting compound. This method facilitates precipitation.

In step (iv) according to this first alternative, a co-solvent is typically added. The co-solvent employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the compound to precipitate. Distillation, either continuous or stepwise, with replacement by this co-solvent results in a mixture predominantly of the co-solvent. Preferred solvents include ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent is employed to facilitate precipitation. The solid is collected, e.g. by filtration, and is dried to obtain the dual-acting compound, in particular the complex in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60 °C, preferably 30 to 40 °C. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure or reduced pressure of e.g. 10 to 30 bar, such as 20 bar.

According to a second alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex the mixture preferably forms a clear solution. This mixing is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 1 h, at room temperature. If necessary, the temperature may be raised so as to ensure a clear solution.

The obtained mixture is then further treated by solvent exchange to obtain the dual-acting compound, in particular the complex.

In step (iva) according to this second alternative, the solution is preferably evaporated to dryness at elevated temperatures such as > room temperature to 50 °C, more preferably 30 to 40 °C.

Preferably, in step (va) the solvent or solvent mixture employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the dual-acting compound, in particular the complex to precipitate. Preferred solvents include the ones mentioned above for step (i), such as water, ethanol, 2-propanol, acetone ethylacetate, isopropyl acetate, methyl-*t*-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent or solvent mixture is employed to facilitate precipitation.

In step (via) precipitation can take place at room temperature. It can be effected by leaving the mixture standing or by agitating the mixture, preferably by agitating it. This is preferably effected by stirring and/or sonication. After precipitation, the solid is collected, e.g. by filtration, and is dried to obtain the compound in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60 °C, preferably room temperature. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina

pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned combination, linked pro-drug or he dual-acting compound, in particular the complex to a subject in need of such treatment.

The combination, linked pro-drug or he dual-acting compound, in particular the complex of the first embodiment may be administered alone or in the form of a pharmaceutical composition according to the second embodiment. Information regarding dosing, i.e., the therapeutically effective amount, etc., is the same regardless of how the combination, linked pro-drug or he dual-acting compound, in particular the complex is administered.

The combination, linked pro-drug or he dual-acting compound, in particular the complex is beneficial over a combination of ARBs or neutral endopeptidase inhibitors alone or other ARB/NEPi combinations with regard to use as first line therapy, ease of formulation and ease of manufacture.

Specific embodiments of the invention will now be demonstrated by reference to the following examples. It should be understood that these examples are disclosed solely by way of illustrating the invention and should not be taken in any way to limit the scope of the present invention.

Example 1

Preparation of [valsartan ((2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O

The dual-acting compound of valsartan and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 0.42g of (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and 0.41g of valsartan free acid in 40ml acetone. Separately, 0.111g of NaOH are dissolved in 7ml H_2O. The two solutions are combined and stirred at room temperature for 1 hour and a clear solution was obtained. The solution is evaporated at 35°C

to yield a glassy solid. The glassy solid residue is then charged with 40ml acetone and the resulting mixture is stirred and sonicated until precipitation occurred (~ 5 minutes). The precipitate was filtered and the solid is dried at room temperature in open air for 2 days until a constant mass of the crystalline solid is obtained.

Characterization by various methods could confirm the presence of both valsartan and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and complex formation in contrast to a simple physical mixture. Significant spectral peaks for the complex are observed e.g. in the XRPD, IR, and Raman spectroscopy which are not present for the physical mixture. See below for details on the characterization.

Example 2

Alternative Preparation of [valsartan ((2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O

The dual acting compound of valsartan and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 22.96 mmol of (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and valsartan (10.00 g; 22.96 mmol) in acetone (300 mL). The suspension is stirred at room temperature for 15 min to obtain a clear solution. A solution of NaOH (2.76 g; 68.90 mmol) in water (8 mL) water is then added to this solution over a period of 10 min. Solids start to precipitate in 10 min. Alternatively, precipitation can be induced by seeding. The suspension is stirred at 20-25 °C for 2 h. This suspension is concentrated at 15-30 °C under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. Isopropyl acetate (150 mL) is then added to the batch and the suspension is concentrated again at 15-30 °C under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. This operation (addition of 150 mL of isopropyl acetate to the batch and concentration) is repeated once again. The suspension is stirred at 20-25 °C for 1 h. The solids are collected by filtration under nitrogen over a Büchner funnel, washed with isopropyl acetate (20 mL), and dried at 35 °C under reduced pressure (20 mbar) to afford the compound.

Characterization revealed the same product as in Example 1.

Example 3

Alternative Preparation of [valsartan ((2*R*,4*S*)-5-bipheny-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O using seeding

A reactor is charged with 2.00 kg (2,323 mmol) of AHU377 calcium salt and 20 L of isopropyl acetate. The suspension is stirred at 23 ± 3 °C, and 4.56 L of 2 *N* HCl was added. The mixture is stirred at 23 ± 3 °C for 15 min to obtain a clear two-phase solution. The organic layer is separated and washed with 3 x 4.00 L of water. The organic layer is concentrated at 30-100 mbar and 22 ± 5 °C to ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution as a colorless solution.

To the above reactor containing ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution is added 1.984 kg (4,556 mmol) of Valsartan and 40 L of acetone. The reaction mixture is stirred at 23 ± 3 °C to obtain a clear solution which is filtered into a reactor. To the reaction mixture is added a solution of 547.6 g (13,690 mmol) of NaOH in 1.0 L of water at 23 ± 3 °C (which was pre-cooled to 20 ± 5 °C and in-line filtered) over a period of 15-30 min while maintaining the internal temperature at 20-28 °C (slightly exothermic). The flask is rinsed with 190 mL of water and added into the reaction mixture. The reaction mixture is stirred at 23 ± 3 °C for 15 min and a slurry of 4.0 g of [valsartan ((2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na_3 • 2.5 H_2O seeds in 50 mL of isopropyl acetate is added. The mixture is stirred at 23 ± 3 °C for 2 h to obtain a suspension. The suspension is heated to an internal temperature at 40 ± 3 °C over a period of 20 min and 20 L of isopropyl acetate is added over a period of 20 min while maintaining the internal temperature at 40 ± 3 °C . The suspension is stirred at this temperature for an additional 30 min. The mixture is concentrated at an internal temperature at 35 ± 5 °C (T_j 45 ± 5 °C) under reduced pressure (200-350 mbar) to ~35 L of a white slurry (solvent collected: ~25 L). Then 30 L of isopropyl acetate is added the mixture is concentrated at an internal temperature at 35 ± 5 °C (T_j 45 ± 5 °C) under reduced pressure (100-250 mbar) to ~30 L of a white slurry (solvent collected: ~40 L). Again 40 L of isopropyl acetate is added and the mixture is concentrated at an internal temperature at 35 ± 5 °C (T_j 45 ± 5 °C) under reduced pressure (100-200 mbar) to ~30 L of a white slurry (solvent collected: ~30 L). The reaction

mixture is cooled to 23 ± 3 °C over ~20 min and stirred at this temperature for an additional 3 h. The solid is collected by filtration under nitrogen over a polypropylene pad on Büchner funnel. The solid is washed with 2 X 5 L of isopropyl acetate and dried at 35 °C under reduced pressure (20 mbar) until isopropyl acetate content <0.5% to afford the above product as a white solid.

Characterization revealed the same product as in Example 1.

X-ray powder diffraction

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Scintag XDS2000 powder diffractometer for the most important lines for the sample give the following results:

d in [Å] : 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w)

The error margin for all interlattice plane intervals is ± 0.1 Å. The intensities of the peaks are indicated as follows: (w) = weak; (m) = medium; and (st) = strong.

Average values 2Θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

Elemental analysis

Elemental analysis gives the following measured values of the elements present in the sample. The findings of the elemental analysis, within the error limits, correspond to the overall formula of $(C_{48}H_{55}N_6O_8Na_3)\cdot 2.5H_2O$

Found	C: 60.05%	H: 6.24%	N: 8.80%
Calculated*	C: 60.18%	H: 6.31%	N: 8.77%

Infrared spectroscopy

The infrared absorption spectrum for the sample obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

The error margin for all absorption bands of ATR-IR is ± 2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

Raman spectroscopy

Raman spectrum of the sample measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) shows the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ± 2 cm^{-1}

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

High Resolution CP-MAS ^{13}C NMR Spectroscopy

The samples are investigated by high resolution CP-MAS (Cross Polarization Magic Angle Spinning) ^{13}C NMR spectroscopy using a Bruker-BioSpin AVANCE 500 NMR spectrometer equipped with a 300 Watt high power ^{1}H, two 500 Watt high power X-amplifiers, necessary high power pre-amplifiers, a "MAS" controller and a 4 mm BioSolids high resolution Bruker probe.

Each sample is packed in a 4mm ZrO_2 rotor. Critical experimental parameters are 3 msec ^{13}C contact times, 12 KHz spinning speed at the magic angle,. a "ramped" contact time, using a "SPINAL64" ^{1}H decoupling scheme, a recycle delay of 10 secs and 1024 scans at 293 deg K. The chemical shifts are referenced with respect to an external Glycine carbonyl at 176.04 ppm.

High resolution CP-MAS ^{13}C NMR shows the following significant peaks (ppm):

179.0, 177.9 177.0, 176.7, 162.0, 141.0, 137.2, 129.6, 129.1, 126.7, 125.3, 64.0, 61.5, 60.4, 50.2, 46.4, 40.6, 38.6, 33.5, 32.4, 29.8, 28.7, 22.3, 20.2, 19.1, 17.8, 16.8, 13.1, 12.1, 11.1.

A physical mixture of individual Na salts of Valsartan and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester revealed a simple inert mixture of the two salts. However, the sample of the complex prepared in Example 1 exhibited distinctly different spectral features in comparison to a 1:1 mixture of the sodium salts.

DSC and TGA

As measured by differential scanning calorimetry (DSC) using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for the sample is observed at 139°C and 145°C, respectively.

As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100°C and the second step above 120°C.

Both DSC and TGA instruments are operated at a heating rate of 10 K/min.

Example 4

Preparation of Linked Pro-Drug of Scheme (1)

Linked pro-drug of valsartan calcium salt and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared at room temperature by dissolving 114 mg of the calcium salt of valsartan and 86 mg of (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring.

Approximately 120 mg of white solids are collected by filtration. Liquid chromatography (LC) and elemental analysis indicate 1:1 ratio between (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

Preparation of Linked Pro-Drug of Scheme (2)

Linked pro-drug of valsartan calcium salt and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and Tris is prepared at room temperature by dissolving 57 mg of the calcium salt of valsartan, 43 mg of (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid, and 12.6 mg of *tris*(hydroxymethyl)aminomethane (Tris) in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring. Approximately 83 mg of white solids are collected by filtration. LC and elemental analysis indicate 1:1 ratio between (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

CLAIMS:

1. Trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate in the solid form.

2. The compound of claim 1 in the crystalline form.

3. The compound of claim 1 or 2, which is an asymmetric unit comprising six each of $C_{48}H_{55}N_6O_8Na_3 \bullet 2.5\ H_2O$, wherein the molecular mass of each $C_{48}H_{55}N_6O_8Na_3 \bullet 2.5\ H_2O$ is 957.99 and wherein each of $C_{48}H_{55}N_6O_8Na_3 \bullet 2.5\ H_2O$ comprises an ARB moiety and a NEPi moiety, 3 sodium atoms, and 2.5 water molecules, wherein said ARB moiety is a (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine molecular moiety and said NEPi moiety is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester molecular moiety.

4. The compound of claim 1, 2 or 3, characterized by

an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm^{-1})(± 2 cm^{-1}): 2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

5. The compound of any one of claims 1 to 4 characterized by

an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals:

d in [Å] (± 0.1 Å): 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w).

6. A dual-acting compound obtained by:

(i) dissolving (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a suitable solvent;

(ii) dissolving a basic compound of Na in a suitable solvent;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) – (iii), as the first method, followed by steps (iva) – (via) by:

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

7. The compound of claim 6 wherein the suitable solvent in steps (i), and/or (va) is acetone.

8. The compound of claim 6 or 7 wherein the basic compound of Na is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

9. The compound of any one of claims 6 to 8 in the crystalline form.

10. The compound of any one of claims 6 to 9 in the form of a hydrate.

11. A pharmaceutical composition comprising

(a) the compound according to any one of claims 1 to 10; and

(b) at least one pharmaceutically acceptable additive.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable additive is a diluent or filler, a disintegrant, a glidant, a lubricant, a binder, or a colorant, or any combination thereof.

13. A method of preparing the compound according to any one of claims 1 to 5, said method comprising the steps of:

(i) dissolving (*S*)-*N*-valeryl-*N*-{[2'-(1*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2*R*,4*S*)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a suitable solvent;

(ii) dissolving a basic compound of Na in a suitable solvent;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the compound; or alternatively

obtaining the compound by exchanging the solvent(s) employed in steps (i) – (iii), as the first method, followed by steps (iva) – (via) by:

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the compound.

14. The method of claim 13 wherein the suitable solvent in steps (i) and/or (va) is acetone.

15. The method of claim 13 or 14, wherein the basic compound of Na is NaOH, Na_2CO_3, $NaHCO_3$, NaOMe, NaOAc or NaOCHO.

16. Use of a compound according to any one of claims 1 to 10 for the preparation of a medicament for the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart

failure, left ventricular dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

17. The use according to claim 16 for the treatment of hypertension.

18. A pharmaceutical composition comprising

(a) the compound according to any one of claims 1 to 10;

(b) a therapeutic agent being an anti-diabetic, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent; and

(c) at least one pharmaceutically acceptable additive.

19. The pharmaceutical composition according to claim 18 wherein the therapeutic agent is amlodipine besylate.

20. The pharmaceutical composition according to claim 18, wherein the therapeutic agent is hydrochlorothiazide.

21. The use according to claim 16 for the treatment of acute heart failure.

22. The use according to claim 16 for the treatment of chronic heart failure.

23. Use of a compound according to any one of claims 1 to 10 for the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart failure, left ventricular dysfunction,

hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

24. The use according to claim 23 for the treatment of hypertension.

25. The use according to claim 23 for the treatment of acute heart failure.

26. The use according to claim 23 for the treatment of chronic heart failure.

27. The pharmaceutical composition according to claim 11 or 12 for use in the treatment or prevention of a condition or disease, which is hypertension, acute heart failure, chronic heart failure, congestive heart failure, left ventricular dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, glaucoma or stroke.

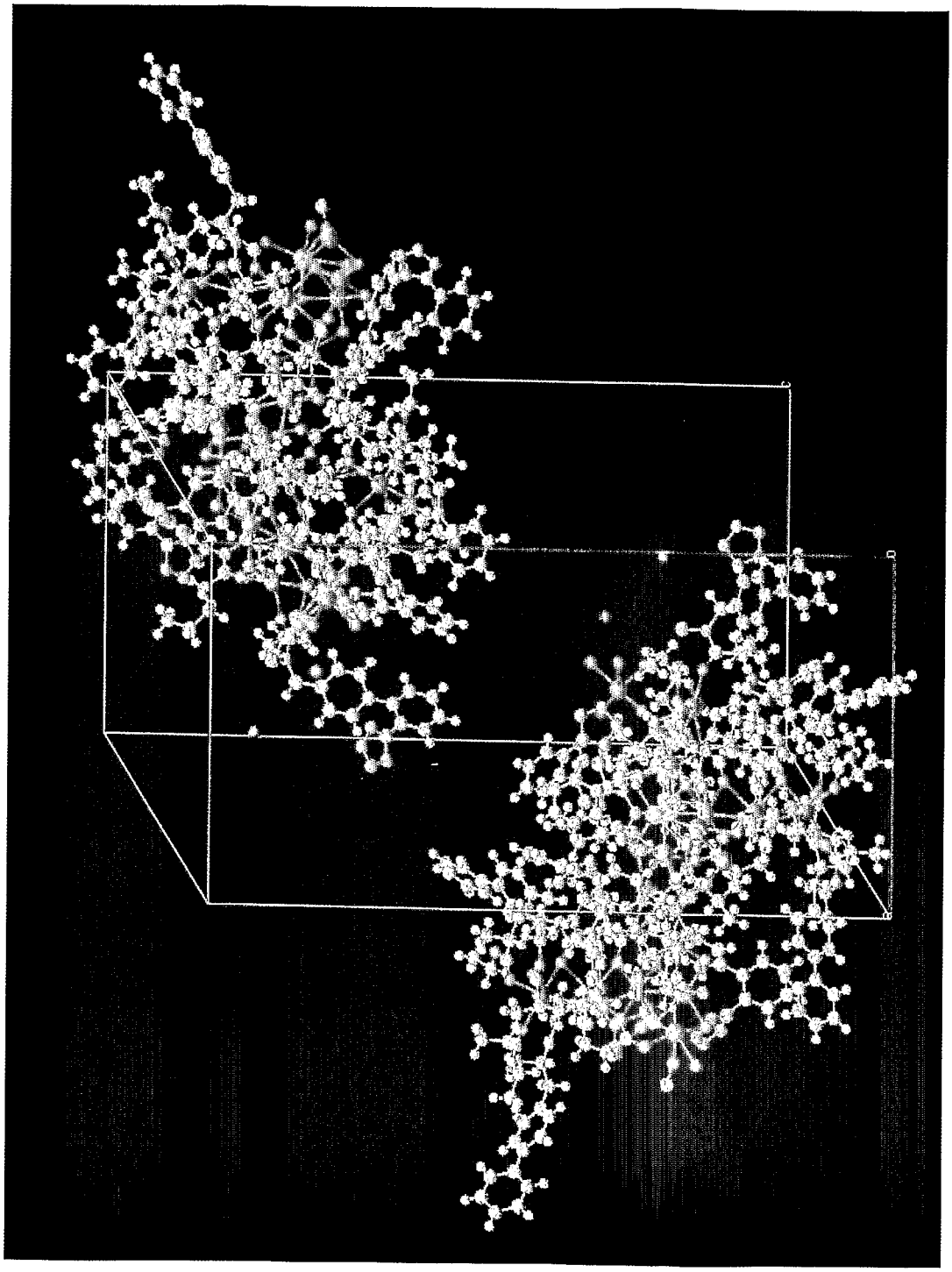
28. The pharmaceutical composition according to claim 11 or 12 for use in the treatment of hypertension.

29. The pharmaceutical composition according to claim 11 or 12 for use in the treatment of acute heart failure.

30. The pharmaceutical composition according to claim 11 or 12 for use in the treatment of chronic heart failure.

Figure 1: unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units

grey = carbon atom; blue = nitrogen atom; red = oxygen atom; violet = sodium atom



Appendix “ B ”

Canadian Patent No. 2,703,598

Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2703598 C 2016/08/09

(11)(21) 2 703 598

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2008/11/04
(87) Date publication PCT/PCT Publication Date: 2009/05/14
(45) Date de délivrance/Issue Date: 2016/08/09
(85) Entrée phase nationale/National Entry: 2010/04/22
(86) N° demande PCT/PCT Application No.: US 2008/082324
(87) N° publication PCT/PCT Publication No.: 2009/061713
(30) Priorité/Priority: 2007/11/06 (US60/985,668)

(51) Cl.Int./Int.Cl. *A61K 9/00* (2006.01), *A61K 31/216* (2006.01), *A61K 9/20* (2006.01)

(72) Inventeurs/Inventors:
AL-FAYOUMI, SULIMAN, US;
HU, JIAHUI, US;
KUMARAPERUMAL, NATRAJAN, US;
ROYCE, ALAN EDWARD, US;
RUEGGER, COLLEEN, US;
ZANNOU, ERIKA AINA, US

(73) Propriétaire/Owner:
NOVARTIS AG, CH

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : COMPOSITIONS PHARMACEUTIQUES A DOUBLE ACTION FONDEES SUR DES SUPERSTRUCTURES DE RECEPTEUR ANTAGONISTE/BLOQUEUR D'ANGIOTENSINE ET D'INHIBITEUR D'ENDOPEPTIDASE NEUTRE

(54) Title: DUAL-ACTING PHARMACEUTICAL COMPOSITIONS BASED ON SUPERSTRUCTURES OF ANGIOTENSIN RECEPTOR ANTAGONIST/BLOCKER (ARB) AND NEUTRAL ENDOPEPTIDASE (NEP) INHIBITOR

(57) Abrégé/Abstract:
Solid oral dosage forms, especially tablets, of a pharmaceutical composition comprising a supramolecular complex can be formed from a direct compression process or a compaction process such as roller compaction. Such solid oral dosage forms feature an immediate release profile that allows for fast release of the therapeutic agent. A particularly useful supramolecular complex is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3- ethoxycarbonyl-l-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl {2''-(tetrazol-5-ylate)biphenyl-4'- ylmethyl } amino)butyrate]hemipentahydrate.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/061713 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 9/20* (2006.01)
A61K 31/216 (2006.01)

(21) International Application Number:
PCT/US2008/082324

(22) International Filing Date:
4 November 2008 (04.11.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/985,668 6 November 2007 (06.11.2007) 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)*: **AL-FAYOUMI, Suliman** [JO/US]; 31 Knollwood Drive, Morristown, NJ 07960 (US). **HU, Jiahui** [CN/US]; 92 Bradley Lane, Bridgewater, NJ 08807 (US). **KUMARAPERUMAL, Natrajan** [IN/US]; 40-B, Byrne Court, Wayne, NJ 07470 (US). **ROYCE, Alan, Edward** [US/US]; RR 4 Box 9LE, Saylorsburg, PA 18353 (US). **RUEGGER, Colleen** [US/US]; 89 Poplar Drive, Morris Plains, NJ 07950 (US). **ZANNOU, Erika, Aina** [FR/US]; 12 Mary Ellen Drive, Edison, NJ 08820 (US).

(74) Agent: **MAJKA, Joseph, T.**; Novartis, Patent Department, One Health Plaza, Bldg. 101 - 2nd Floor, East Hanover, NJ 07936-1080 (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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

WO 2009/061713 A1

(54) Title: DUAL-ACTING PHARMACEUTICAL COMPOSITIONS BASED ON SUPERSTRUCTURES OF ANGIOTENSIN RECEPTOR ANTAGONIST/BLOCKER (ARB) AND NEUTRAL ENDOPEPTIDASE (NEP) INHIBITOR

(57) Abstract: Solid oral dosage forms, especially tablets, of a pharmaceutical composition comprising a supramolecular complex can be formed from a direct compression process or a compaction process such as roller compaction. Such solid oral dosage forms feature an immediate release profile that allows for fast release of the therapeutic agent. A particularly useful supramolecular complex is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate.

DUAL-ACTING PHARMACEUTICAL COMPOSITIONS BASED ON SUPERSTRUCTURES OF ANGIOTENSIN RECEPTOR ANTAGONIST/BLOCKER (ARB) AND NEUTRAL ENDOPEPTIDASE (NEP) INHIBITOR

Field of the Invention

The present invention relates to a solid oral dosage form comprising a therapeutic agent, for example LCZ696. Such a pharmaceutical composition may be prepared by a dry formulation process such as direct compression or compaction process to form a solid oral dosage form.

Background of the Invention

Angiotensin II is a hormone that causes blood vessels to constrict which can result in hypertension and strain on the heart. This hormone interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, e.g., AT1 and AT2, have been identified thus far. In recent times, great effort have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) prevent angiotensin II from binding to its receptors in the walls of blood vessels thereby reducing 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.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see *Pharmacol Rev*, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see *J Hypertens*, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see *J Clin Pharmacol*, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see *Peptides*, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral

endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see *Lancet*, Vol. 365, p. 217 (2005); and *Hypertension*, Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke.

A dual-acting compound or combination, in particular a supramolecular complex of two active agents with different mechanisms of action, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor has been disclosed in U.S. Patent Applications Nos. 60/735,093 filed November 9, 2005; 60/735,541 filed November 10, 2005; 60/789,332 filed April 4, 2006; and 60/822,086 filed August 11, 2006 and in International publication no. WO2007/056546.
Such supramolecular complexes may be used for the treatment
of patients with various cardiovascular and/or renal diseases.

A particularly useful therapeutic agent is the supramolecular complex, trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate also referred to as LCZ696.

There is a need to formulate such a supramolecular complex into pharmaceutical compositions, especially solid oral dosage forms, such that the therapeutic benefits of the compounds may be delivered to a patient in need thereof. An object of the present invention is to provide an exemplary solid oral dosage form that may be ingested by a patient.

There has been widespread use of tablets since the latter part of the nineteenth century, and the majority of solid oral dosage forms are marketed as tablets. Major reasons

of tablet popularity as a dosage form are simplicity, low cost, and the speed of production. Other reasons include stability of the drug product, convenience in packaging, shipping and dispensing. To the patient, tablets offer ease of administration, ease of accurate dosage, compactness, portability, and blandness of taste. Thus, it is another object of the present invention to provide a tablet formulation of the therapeutic agent.

The formulation of dual acting compounds such as supramolecular complexes is not trivial since typical formulation techniques may have a negative effect on the drug substance leading to e.g. increased amorphism and/or dissociation of the components of the dual acting compound. In general, one should avoid to expose the therapeutic agent during the formulation to moisture, excessive heat and/or high shear forces. This may pose a number of formulation issues and difficulties which need to be addressed.

Summary of the Invention

The present invention features solid oral dosage forms for pharmaceutical compounds containing a therapeutic agent, especially a supramolecular complex. In one of aspect of the present invention, the featured supramolecular complex is a dual acting compound. A dual-acting compound or combination features a supramolecular complex of two active agents with different mechanisms of action, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor. In another aspect of the present invention the featured supramolecular complex is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate. It was found that with such a formulation, a very different release profile was found than with the two components valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester alone. In particular, the formulation offers a better exposure and thus bioavailability than valsartan. These unexpected advantages offer the possibility to prepare pharmaceutical compositions with new and lower doses of the therapeutic agent. The pharmaceutical formulations containing a therapeutic agent, especially a supramolecular complex may be manufactured by a dry formulation process such as a direct compression or roller compaction process. Thus, another aspect of the

present invention is a solid oral dosage form manufactured by mixing the therapeutic agent with at least one pharmaceutically acceptable excipient, and subsequently directly compressing the mixture with suitable equipment, such as a tablet press, or compacting the mixture with a suitable equipment, such as a roller compactor.

According to one aspect of the present invention, there is provided a solid oral dosage form comprising: (a) the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate in a concentration from about 4% to about 90% by weight of the composition; and (b) at least one pharmaceutically acceptable excipient, wherein the compound is present in a dose strength of 40, 50, 100, 200 or 400 mg corresponding to the respective combined amount of valsartan free acid and (2R,4S)-5-biphenyl-4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a 1:1 ratio per unit dosage form.

According to another aspect of the present invention, there is provided a process for making the solid oral dosage form as described herein comprising the steps of: (a) mixing the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate with at least one pharmaceutically acceptable excipient to form a blend; (b) directly compressing said blend into a solid oral dosage form.

Brief Description of the Drawings

The accompanying drawing, which is incorporated in and constitute a part of the specification, illustrates an exemplary embodiment of the present invention.

FIG. 1 shows a chart depicting the in vitro dissolution profiles of 5 mg and 50 mg directly compressed tablets of a supramolecular complex trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate.

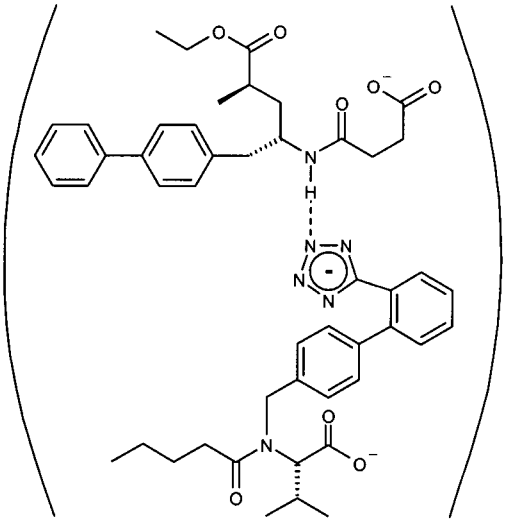
FIG. 2 shows a chart depicting the in vitro dissolution profiles of 100, 200 and 400 mg roller compacted coated tablets of a supramolecular complex trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate at pH 6.8.

FIG. 3 shows a chart depicting the in vitro dissolution profile of 400 mg roller compacted coated tablets of a supramolecular complex trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate at pH 4.5.

Detailed Description of the Invention

The present invention relates to pharmaceutical compositions comprising a therapeutic agent. The pharmaceutical compositions of the present invention can be manufactured by a direct compression or preferably a roller compaction process resulting in pharmaceutically acceptable tablets.

As used herein, the term "therapeutic agent" refers to the supramolecular complex, trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate as shown in the following simplified representation:



The above therapeutic agent comprises an angiotensin receptor antagonist, a neutral endopeptidase inhibitor (NEPi) and a cation, i.e., Na. This therapeutic agent is fully described with regard to its preparation and its characteristics in WO2007/056546. This therapeutic agent is a "dual-acting compound" which is intended to describe a compound having two different modes of action simultaneously, i.e., one is the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound, and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound. The therapeutic agent may be present in the pharmaceutical composition in a range from about 4% to about 90%, such as 4% to 60%, by weight of the composition.

As used herein the term, "supramolecular complex" is meant to describe an interaction between two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular

bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing this complex over a physical mixture of species.

As used herein the term "pharmaceutical composition" means, for example, a mixture containing a therapeutically effective amount of a therapeutic compound in a pharmaceutically acceptable carrier to be administered to a mammal, e.g., a human in order to treat kinase dependent diseases. A particularly useful pharmaceutical composition resulting from the present invention is a pharmaceutically acceptable tablet.

As used herein the term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are, within the scope of sound medical judgment, suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio. With respect to a pharmaceutically acceptable tablet, the term also encompasses an acceptable *in vitro* dissolution profile.

The concentration of therapeutic agent in the pharmaceutical composition is present in a therapeutically effective amount which will depend on absorption, inactivation and excretion rates of the therapeutic agent as well as other factors known to one of ordinary skill in the art. Furthermore, it is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular recipient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the pharmaceutical compositions. The therapeutic compound may be administered once, or may be divided into a number of smaller doses to be administered at varying intervals of time. Thus, an appropriate therapeutically effective amount is known to one of ordinary skill in the art.

For example, the unit dose of the therapeutic agent will be in the range from about 1 to about 1000, such as 40 to 400 mg (e.g., 100 mg, 200 mg, 400) mg per day. Alternatively lower doses may be given, for example doses of 0.5 to 100 mg; 0.5 to 50 mg; or 0.5 to 20 mg per day. In the present case, it was unexpectantly found that the valsartan component when delivered in the form of the dual acting compound such as the supramolecular complex has a greater exposure and thus higher bioavailability than valsartan on its own.

Therefore it is possible to lower the dose with regard to the valsartan component. Specifically, typical doses of valsartan of the Diovan® formulation are 80 mg, 160 mg, and 320 mg. Given that the dual acting compound such as the supramolecular complex comprises the components valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, both having very similar molecular weight, in a 1:1 ratio, one would have not foreseen that a 100 mg, 200 mg and 400 mg dose of the dual acting compound would correspond to a 80 mg, 160 mg and 320 mg of valsartan single dose of the Diovan® formulation, respectively, based on the exposure.

As used herein the term "immediate-release" refers to the rapid release of the majority of the therapeutic compound, e.g., greater than about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, or about 90% within a relatively short time, e.g., within 1 hour, 40 minutes, 30 minutes or 20 minutes after oral ingestion. Particularly useful conditions for immediate-release are release of at least or equal to about 80% of the therapeutic compound within thirty minutes after oral ingestion. The particular immediate-release conditions for a specific therapeutic compound will be recognized or known by one of ordinary skill in the art. The immediate release profile can be determined from an *in vitro* dissolution test.

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 6.8 using a paddle stirring element at 50 rpm (rotations per minute) or alternatively at pH 4.5 using a paddle stirring element at 75 rpm as specified. The dissolution medium is preferably a buffer, typically a phosphate buffer, especially one as described in the example “Dissolution Test”.

Accordingly, the present invention provides preferably solid oral dosage forms delivering a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, wherein the oral dosage form exhibits an *in vitro* dissolution profile, when measured by the USP paddle method at about 50 rpm in 900 mL of 0.05M at pH 6.8 phosphate buffer and at 37±0.5°C, such that after 10 min, from a mean of about 10% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released, after 20 min, from a mean of about 30% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released, after 30 min, from a mean of about 40% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

Moreover, the present invention provides preferably solid oral dosage forms delivering a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, wherein the oral dosage form exhibits an *in vitro* dissolution profile, when measured by the USP paddle method at about 75 rpm in 1000 mL of pH 4.5 phosphate buffer and at 37±0.5°C, such that after 10 min, from a mean of about 20% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released, after 20 min, from a mean of about 30% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released, after 30 min, from a mean of about 40% to a mean of about 100% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

In one embodiment of the present invention, the therapeutic agent is present in an amount of about 100 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released. In another embodiment, a the therapeutic agent is present in an amount of about 200 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released. Yet in another embodiment, a the therapeutic agent is present in an amount of about 400 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution

profile such that after 10 min, a mean of about 40% of valsartan free acid, is released, after 20 min, a mean of about 70% of valsartan free acid, is released, after 30 min, a mean of about 90% of valsartan free acid, is released.

The exact dose of the therapeutic 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.

Surprisingly, the it was found that the PK/PD profile as obtained with the solid oral dosage form in accordance with the present invention concerning valsartan free acid is very distinct from the single formulation containing only valsartan, in particular the Diovan® formulation. This very distinct and unique pharmacokinetic and pharmacodynamic profile of valsartan free acid following administration of the therapeutic showed a substantially enhanced oral bioavailability (~1.4 to1.6 fold, in particular 1.6 fold) and a trend towards a faster onset (t_{max} 1.8±0.3 h) than that following valsartan administration in the form of the Diovan® formulation (approx. t_{max} 2.6 h). Together, this pharmacokinetic and pharmacodynamic profile of the present dosage form of the therapeutic agent support the further development for the improved treatment of cardiovascular diseases.

Accordingly, the present invention provides solid oral dosage forms delivering a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, and a carrier medium, wherein the oral dosage form provides a rapid rate of absorption of valsartan free acid with a t_{max} of 1 to 2.2 h following administration of a single dose of said dosage form. More specifically, a t_{max} of 1.4 to 2.0 h can be observed. This is in stark contrast to the rate of absorption of valsartan following administration of Diovan® where a t_{max} of 2.5 to 4.0 h, more specifically, 2.8 to 3.0 h, is observed. For example, the present invention provides a solid oral dosage form comprising about 200 mg trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate, or a

respective amount of valsartan free acid, and a carrier medium, said dosage form providing a t_{max} valsartan free acid of 1.5 to 1.9 h following administration of a single dose of said dosage form.

Furthermore, the present invention provides a solid oral dosage form delivering a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, and a carrier medium, wherein the oral dosage form provides a dose-normalized mean plasma exposure (AUC_{0-24}) of 230 to 400 ng•h/mL/mg-equivalent following administration of a single dose of said dosage form. More specifically, a dose-normalized geometric mean exposure AUC_{0-24} of 270 to 320 ng•h/mL/mg-equivalent can be observed. The corresponding exposure observed with valsartan administration in the form of Diovan® is much lower. Consequently, the present invention provides a solid oral dosage form delivering a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, and a carrier medium, with a mean relative bioavailability of 140 to 185%, such as 150 to 165%, as compared to valsartan following administration of Diovan®. For example, the present invention provides a solid oral dosage form comprising about 200 mg trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate, or a respective amount of valsartan free acid, and a carrier medium, said dosage form providing mean plasma exposure (AUC_{0-24}) of 16,000 to 18,000, such as 16,970, ng•h/mL following administration of a single dose of said dosage form.

Thus, with the solid oral dosage form of the present invention, one can achieve not only a faster rate of absorption but also a greater extent of absorption than with Diovan®. These pharmacokinetic properties are expected to lead to therapeutic advantages over valsartan administration on its own.

The solid oral dosage form mentioned above comprises moieties of

valsartan or a salt thereof and

(2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid or (2*R*,4*S*)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester ethyl ester or a salt thereof.

The term "moieties" means that the component is present as such or preferably in the form of a supramolecular complex. Most preferably, the solid oral dosage form comprises trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate which means that both moieties are present in one dual acting molecule or supramolecular complex.

As used herein the term "excipient" refers to a pharmaceutically acceptable inert ingredient that is used in the manufacture of solid oral dosage forms. Examples of categories of excipients include, but are not limited to, binders, disintegrants, lubricants, glidants, stabilizers, fillers and diluents. Excipients can enhance the processing characteristics of the pharmaceutical formulation, i.e., render the formulation more suitable for direct compression by increasing flowability and/or cohesiveness.

As used herein, the term "direct compression" refers to the general process of directly compressing the ingredients in the pharmaceutical formulation (i.e., therapeutic agent and excipients) without changing the physical and chemical properties of the therapeutic agent. The therapeutic agent, along with pharmaceutically acceptable excipients, in the form of powders, are blended in a low shear apparatus, for example a twin shell blender. The blended composition is then filled into a die and directly compressed into a by a punch. A tablet press, for example, can accomplish this compression step. Useful excipients in a direct compression process include, but are not limited to fillers, binders, lubricants and glidants. Direct compression is particularly suitable for a solid oral dosage form having a strength of from 0.5 mg to 200 mg of the therapeutic agent.

As used herein, the term "compaction" refers to the general process of dry granulating to form a tablet (e.g., by slugging or roller compaction). The therapeutic agents and pharmaceutically acceptable excipients are made into slugs (as in slugging) or ribbons (as in roller compaction). The roller compaction process densifies the powder by removing any air. The densified material is then reduced to a uniform granule size and subsequently compressed. Useful excipients in a roller compaction process include, but are not limited to

fillers, binders, lubricants, disintegrants and glidants. Roller compaction is particularly suitable for a solid oral dosage form having a strength of from 50 to 800 mg of the therapeutic agent.

It has been found that roller compaction offers particular advantages for higher doses to provide the therapeutic agent in a suitable tablet size without compromising on the quality of the drug substance. Especially, excessive amorphism as well as separation of the components of the dual acting compound can be minimized or prevented.

A solid oral dosage form according to the invention comprises additives conventional in the dosage form in question. Tabletting aids, commonly used in tablet formulation can be used and reference is made to the extensive literature on the subject, see in particular Fiedler's "Lexicon der Hilfstoffe", 4th Edition, ECV Aulendorf 1996.
These include but are not limited to disintegrants, binders, lubricants, glidants, stabilising agents, fillers or diluents, surfactants and the like.

Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches; clays; celluloses; alginates; gums; cross-linked polymers, e.g., cross-linked polyvinyl pyrrolidone or crospovidone, e.g., POLYPLASDONE XL from International Specialty Products (Wayne, NJ); cross-linked sodium carboxymethylcellulose or croscarmellose sodium, e.g., AC-DI-SOL from FMC; and cross-linked calcium carboxymethylcellulose; soy polysaccharides; and guar gum, most preferably cross-linked polyvinyl pyrrolidone or crospovidone. The disintegrant may be present in a concentration from about 0% to about 65%; e.g., from about 1% to about 40%; (e.g., from about 0.05% to about 10%) by weight of the composition (prior to optional coating).

Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and derivatives thereof, for example, microcrystalline cellulose, e.g., AVICEL PH from FMC (Philadelphia, PA), hydroxypropyl cellulose, in particular low substituted hydroxypropyl cellulose, e.g. hydroxypropyl cellulose having a hydroxypropyl content of 5 to 16 % by weight and a Mw of from 80 000 to 1 150 000, more particularly 140 000 to 850 000, such as LH21, hydroxylethyl cellulose and hydroxylpropylmethyl cellulose METHOCEL from Dow Chemical Corp. (Midland, MI); sucrose; dextrose; corn syrup;

polysaccharides; and gelatin, most preferably celluloses such as hydroxypropyl cellulose, in particular low substituted hydroxypropyl cellulose. The binder may be present in a concentration from about 1 to about 60%; e.g., from 5% to about 40% by weight of the composition, in particular from 10% to about 40% by weight of the composition (prior to optional coating), if direct compression methods are employed, or from 5% to about 30% by weight of the composition (prior to optional coating) if roller compaction is employed. Although some of the excipients could also be considered as disintgrants, for the purposes of the present invention they are solely regarded as binders.

Examples of pharmaceutically acceptable fillers and pharmaceutically acceptable diluents include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose, in particular Cellulose MK GR, powdered cellulose, sorbitol, and sucrose, in particular microcrystalline cellulose. The filler may be present in a concentration from about 4% to about 60%; e.g. from about 20% to about 40% by weight of the composition (prior to optional coating).

Examples of pharmaceutically acceptable lubricants and pharmaceutically acceptable glidants include, but are not limited to, colloidal silica, magnesium trisilicate, starches, talc, tribasic calcium phosphate, magnesium stearate, aluminum stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, powdered cellulose, glyceryl behenate, stearic acid, hydrogenated castor oil, glyceryl monostearate, and sodium stearyl fumarate. The glidant may be present in a concentration from 0% to 10%, such as up to 2%, for example approximately 0.1% (prior to optional coating). The lubricant may be present in an amount from 0% to 5%; e.g., from about 0.5% to about 5% (prior to optional coating).

It is a characteristic of the preferred present solid oral dosage forms that they contain only a relatively small amount of additives given the high content of active agent. This enables the production of physically small unit dosage forms. The total amount of additives in a given unit dosage may be about 65 % or less by weight based on the total weight of the solid oral dosage form (prior to optional coating), more particularly about 55 % or less.

Preferably the additive content is in the range of about 35 to 55 % by weight, more particularly 40 to 45 % by weight.

The absolute amounts of each additive and the amounts relative to other additives is similarly dependent on the desired properties of the solid oral dosage form and may also be chosen by the skilled artisan by routine experimentation without undue burden. For example, the solid oral dosage form may be chosen to exhibit accelerated and/or delayed release of the active agent with or without quantitative control of the release of active agent.

Thus, where accelerated release is desired, e.g. about 90% release within a ten minute, more particularly a five minute period, a disintegrant such as crosslinked polyvinyl pyrrolidone, for example those products known under the registered trade marks Polyplasdone®XL or Kollidon®CL, in particular having a molecular weight in excess of 1 000 000, more particularly having a particle size distribution of less than 400 microns or less than 74 microns, or reactive additives (effervescent mixtures) that effect rapid disintegration of the tablet in the presence of water, for example so-called effervescent tablets that contain an acid in solid form, typically citric acid, which acts in water on a base containing chemically combined carbon dioxide, for example sodium hydrogencarbonate or sodium carbonate, and releases carbon dioxide.

Whereas if delayed release is desired one can employ pellet coating technology, wax matrix systems, polymer matrix tablets or polymer coatings conventional in the art.

Quantitative control of the release of the active agent can be achieved by conventional techniques known in the art. Such dosage forms are known as oral osmotic systems (OROS), coated tablets, matrix tablets, press-coated tablets, multilayer tablets and the like.

In a solid oral dosage form wherein the active agent consist entirely of the dual acting compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate, preferred additives are microcrystalline cellulose, hydroxypropylcellulose, Crospovidone, Mg, Ca or Al stearate, anhydrous colloidal silica and talc. The amounts of additive employed will depend upon how much active agent

is to be used. The stearate, e.g. Mg stearate is preferably employed in amounts of 1.0 to 6.0% by weight, e.g. 1.5% to 4.0 % by weight (prior to optional coating). Whereas the silica is preferably employed in an amount of from 0.1 to 2% by weight. The microcrystalline cellulose is preferably present in an amount of 10 to 30%, e.g. 20-21%. The crosspovidone is preferably present in an amount of 1 to 20 %, more preferably 5 to 15%, e.g. 8-10%

The solid oral dosage forms according to the present invention may be in the form of dragées in which case the solid oral dosage form is provided with a coating typically a sugar, shellac or other film coating entirely conventional in the art. Attention is drawn to the numerous known methods of coating employed in the art, e.g. spray coating in a fluidized bed, e.g. by the known methods using apparatus available from Aeromatic, Glatt, Wurster or Hüttlin, in a perforated pan by the Accela Cota method, or to the submerged sword coating method. The additives commonly used in confectioning are employed in such methods.

The invention provides in another of its aspects a process of making a solid oral dosage form as hereinabove described. Such solid oral dosage form may be produced by working up the final composition defined hereinabove in appropriate amounts, to form unit dosage forms.

In one embodiment there is provided a process of making the solid oral dosage forms as hereinabove described comprising the steps of

(a) mixing a dual acting compound with at least one pharmaceutically acceptable excipient to form a blend;

(b) directly compressing said blend into a solid oral dosage form.

A further preferred embodiment of the present invention is a process for the manufacture of a solid oral dosage form according to the present invention for higher doses of the dual acting compound. Such a solid oral dosage form can be prepared by the following method, comprising the steps of mixing a dual acting compound with at least one pharmaceutically acceptable excipient to form a blend; compacting, such as roller compacting, said blend; optionally mixing with further pharmaceutically acceptable excipients, and optionally compressing the final blend into a solid oral dosage form.

More particularly, said method comprises the steps of

(a) sieving the dual acting compound and pharmaceutically acceptable excipients to form a sieved material;
(b) blending the sieved material to form a blended material;
(c) compacting, such as roller compacting, the blended material to form a compacted material;
(d) milling the compacted material to form a milled material referred to as the granulate;
(e) optionally blending the milled material with outer phase, i.e., with pharmaceutically acceptable excipients to form a final mixture;
(f) optionally compressing the final blend to form a tablet and
(g) optionally applying a film coat in order to obtain the film coated tablets.

The process is carried out in the absence of water, i.e. it is a dry compression method. The relative humidity is preferably < 55%. The temperature is preferably ambient temperature (20 – 25°C) but can be increased up to 65 °C, such as up to 40 °C. These conditions are preferred to avoid decomposition into the individual components or amorphism of the therapeutic agent.

Compaction to form a coprimate requires the compaction of the dry ground components. Compaction may be carried out using a slugging technique or preferably, roller compaction. Roller compaction apparatus is conventional and essentially utilises two rollers which roll towards each other. A hydraulic ram forces one of the rollers against the other to exert a compacting force against the ground particles fed into the roller compactor via a screw conveyor system. A compaction force of 20 to 60 kN, more preferably 20 to 40 KN, is preferably used. Within this range of compaction forces it has surprisingly been found that the therapeutic agent can be formulated appropriately without decomposition into the individual components or amorphism of the therapeutic agent. The particular optimum compaction force is dependent on the active agent content in any given formulation and therefore also depends on the amount and nature of the additives present.

It was surprising that despite the relatively weak non-covalent forces holding the components of the therapeutic agent together, the above formulation techniques leave the therapeutic agent intact and allow for reliable preparation methods of suitable solid oral dosage forms.

The following examples are illustrative, but do not serve to limit the scope of the invention described herein. The examples are meant only to suggest a method of practicing the present invention.

Quantities of ingredients, represented by percentage by weight of the pharmaceutical composition, used in each example are set forth in the respective tables located after the respective descriptions.

Examples 1 and 2

The therapeutic agent in this example is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate. Table 1 shows the formulation for Examples 1 and 2 having 5 mg and 50 mg of therapeutic agent respectively.

Ingredients	Function	Example 1 Percentage (w%/w%)	Example 2 Percentage (w%/w%)
therapeutic agent		**4.7**	**9.4**
microcrystalline cellulose	filler	**46.2**	**41.5**
Talc	glidant	**4.3**	**4.3**
low substituted hydroxypropylcellulose	binder/disintegrant	**34.8**	**34.8**
colloidal silicon dioxide	glidant	**0.4**	**0.4**
Crospovidone	disintegrant	**8.7**	**8.7**
magnesium stearate	lubricant	**0.9**	**0.9**
Total		**100%**	**100%**

The therapeutic agent is first sieved through a 40 mesh screen. Added to the therapeutic agent Is microcrystalline cellulose and crospovidone, the mixture is sieved through a 20 mesh screen. The mixture is then blended for about a hundred rotations in a bin blender. The low substituted hydroxypropylcellulose and colloidal silicon dioxide is then added to the bin blender which is then rotated for another hundred rotations. Talc is then added to the mixture and bin blended. The final addition is magnesium stearate. The powdered mixture is then compressed into a tablet weighing about 115 mg for Example 1

and about 575 mg for Example 2. The dissolution profiles of these examples at pH 6.8 are shown in Fig. 1.

Examples 3 to 6

The therapeutic agent in this example is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate. Tables 2 and 3 show the formulation for Examples 3 to 6 having 40mg, 100 mg, 200 mg and 400 mg of therapeutic agent respectively.

Ingredients	mg/tab
INTRAGRANULAR	
Therapeutic agent	45.4
Microcrystalline Cellulose	14
L-HPC (low substituted)	10
Crospovidone	4
Colloidal silicon dioxide	0.4
Talc	0.8
Magnesium Stearate	1.4
EXTRAGRANULAR	
Crospovidone	3.2
Magnesium Stearate	0.8
Total tablet weight (mg)	80

Ingredients	100mg mg/Tablet	200mg mg/Tablet	400mg mg/Tablet
INTRAGRANULAR			
LCZ696-ABA.001	107.8	215.6	431.2
Microcrystalline Cellulose (Cellulose MK GR)	40.2	80.4	160.8
L-HPC (low sub)	25.0	50.0	100.0
Crospovidone	10.0	20.0	40.0
Colloidal silicon dioxide	1.0	2.0	4.0
Talc	1.5	3.0	6.0
Magnesium Stearate	3.0	6.0	12.0
EXTRAGRANULAR			
Talc	0.5	1.0	2.0
Crospovidone	8.0	16.0	32.0
Magnesium Stearate	3.0	6.0	12.0
Opadry White	4.43	6.63	9.95
Opadry Yellow	2.86	4.30	6.44
Opadry Red	0.65	0.98	1.47

Opadry Black	0.06	0.09	0.14
Weight gain per tablet (mg)	8	12	18
Total Tablet weight (mg)	208	412	818

Magnesium stearate, talc, colloidal silicon dioxide and microcrystalline cellulose are first sieved through a 30 mesh screen. The above mixture, the therapeutic agent, crospovidone and low substituted hydroxypropylcellulose are then blended for about 120 rotations in a bin blender. Afterwards, the obtained blend is sieved through a 30 mesh screen. The sieved mixture is then blended for about 120 rotations in a bin blender. The blend is compacted using a roller compactor BEPEX 50 with a compaction force of 30 kN. After compaction, the mixture is milled using a Frewitt Oscillator and sieved through an 18 mesh screen to obtain the final internal phase or granulate. The granulate is blended with crospovidone and talc (external excipients), sieved through a 30 mesh screen, for about 50 rotations in a bin blender. Thereafter, the obtained mixture is blended with magnesium stearate (external excipient), sieved through a 30 mesh screen, for about 50 rotations in a bin blender. The obtained final mixture is then compressed into a tablet using a Fette 3090 apparatus. The coating was applied using Opadry coating polymer to obtain coated tablets. The dissolution profiles of Examples 3 to 5 at pH 6.8 are shown in Fig. 2 and the dissolution profile of Example 6 at pH 4.5 is shown in Fig. 3.

Example : DISSOLUTION TESTING

The tablets of the Examples are tested for their dissolution in 900 ml of pH 6.8 phosphate buffer with paddles at 50 rpm.

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.

1L of a buffered aqueous solution, adjusted to pH 6.8 ± 0.05 (0.05 M Phosphate buffer solution obtained by dissolving 6.805g of potassium dihydrogen phosphate and 0.896g of sodium hydroxide in and diluting to 1000 ml with water, and adjusting the pH to 6.80±0.05 using 0.2M sodium hydroxide or 1M phosphoric acid; 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 50+2 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.

Their dissolution profiles are shown in FIG. 1 and in FIG. 2. Greater than 90% of the therapeutic agent is released from both Example 1 and Example 2 tablets in less than ten minutes and Greater than 70% of the therapeutic agent is released from both Examples 3 to 5 tablets in less than 20 minutes.

The tablets of the Examples can also be tested using the above method at pH 4.5 by carrying out the method as described above and applying the following modifications:

Preparation of pH 4.5 phosphate buffer solution is achieved by dissolving 13.61 g of potassium dihydrogen phosphate in 750 ml of water, adjusting the pH if necessary with 0.1M sodium hydroxide or with 0.1M hydrochoric acid and diluting to 1000.0 ml with water.

Dissolution testing condition at pH 4.5:

Conditions	
Speed of rotation	75 ± 3 rpm
Test medium	Phosphate buffer solution pH 4.5
Volume of test medium	1000 ml

The dissolution profile for Example 6 at pH 4.5 is shown in FIG. 3. Greater than 80% of the therapeutic agent is released from Examples 6 tablets in less than 20 minutes.

Examples : Measurement of pharmacokinetic parameters

1) 5 to 80 mg doses:

The study employs a two-period, parallel group, ascending single dose (5, 20, 80 mg of LCZ696 and 40 mg Diovan® (marketed formulation of valsartan), placebo controlled design with dose selection based on FDA exploratory-IND guidance. The dosages of

LCZ696 are obtained by using the 5mg and 50mg tablets as manufactured above and employing for the 20mg and 80mg dose multiple tablets of 5mg and/or 50mg strength.

To enable comparison of the exposure to valsartan between LCZ696 and Diovan® at different dose levels, valsartan's exposure (AUC) and C_{max} values are normalized to the actual amount of anhydrous salt-free- valsartan administered (normalized by mg-equivalent). The AUC_{0-24} values are calculated as ng·h/ml/mg-equivalent of valsartan, and the geometric means are compared. The mean relative bioavailability of valsartan with LCZ696 administration is substantially higher than with Diovan® with the ratio of geometric means for the three LCZ696 cohorts ranging from 107% to 249%. Valsartan exposures following administration of LCZ696 are dose linear and since there is no statistically significant deviations in the dose normalized valsartan exposure between the 3 cohorts, the data from all 3 cohorts is combined (n = 24) to get a pooled estimate of the relative bioavailability of valsartan for LCZ696 compared to 40 mg Diovan®. Exposure (AUC) and C_{max} values normalized to mg-equivalent of anhydrous salt-free- valsartan are summarized in Table 4.

The rate and extent of absorption of valsartan with LCZ696 is greater than with Diovan®. The dose-equivalent normalized C_{max} of valsartan is higher following LCZ696 administration than following Diovan® administration (ratio of geometric means for AUC is 161%, 90% CI: 140-185%). Also, a trend towards a shorter t_{max} (mean 1.3-1.8 h) for valsartan is observed following LCZ696 administration than that (mean 2.4-3.0 h) following Diovan® administration.

Table 4 Summary of dose-normalized pharmacokinetic parameters on valsartan for each cohort, and for pooled data

	Dose-normalized PK parameters	Geometric means		Ratio LCZ696 / Diovan	90% CI of ratio
		LCZ696	40 mg Diovan®		
Cohort A (5 mg LCZ696)	AUC_{0-inf}, ng*h/ml/mg-equivalent	372	205	1.81	1.32 - 2.49
	AUC_{0-24}, ng*h/ml/mg-equivalent	364	201	1.81	1.31 - 2.50
	Cmax, ng/ml/mg-equivalent	56	27	2.09	1.29 - 3.38
Cohort B (20 mg LCZ696)	AUC_{0-inf}, ng*h/ml/mg-equivalent	284	206	1.38	1.08 - 1.77
	AUC_{0-24}, ng*h/ml/mg-equivalent	280	203	1.38	1.07 - 1.77
	Cmax, ng/ml/mg-equivalent	44	26	1.69	1.26 - 2.27
Cohort C (80 mg LCZ696)	AUC_{0-inf}, ng*h/ml/mg-equivalent	245	149	1.64	1.31 - 2.06
	AUC_{0-24}, ng*h/ml/mg-equivalent	244	146	1.67	1.33 - 2.08
	Cmax, ng/ml/mg-equivalent	43	20	2.1	1.55 - 2.86
*Combined Cohorts A-B-C	AUC_{0-inf}, ng*h/ml/mg-equivalent	296	185	1.6	1.39 - 1.84
	AUC_{0-24}, ng*h/ml/mg-equivalent	292	182	1.61	1.40 - 1.85
	Cmax, ng/ml/mg-equivalent	47	24	1.95	1.62 - 2.36

* Based on the dose-normalized exposures to valsartan, there was no statistically significant difference between cohorts therefore therefore the data from three cohorts were pooled

2) 50 to 1200 mg doses:

This study uses an interwoven single- and multiple-ascending dose design (randomized, double-blind, placebo controlled, time-lagged, parallel group) to assess safety, tolerability, and pharmacokinetics of LCZ696 in healthy volunteers. The doses for this study are as follows: 200, 600, 900, and 1200 mg for the single dose cohorts; 50, 200, 600, and 900 mg for the multiple dose cohorts lasting 14 days.

Mean t_{max} and $t_{1/2}$ estimates for all analytes are consistent with earlier findings obtained from the above single dose study of lower doses (i.e., Study above).

Minimal accumulation was evident for all analytes following administration of 50-900 mg LCZ696 once daily for 14 days.

Table 5 Summary of LCZ696 pharmacokinetic parameters for valsartan following single dose administration.

	t_{max} (h)	C_{max} ng/ml	AUC_{0-24} (ng.h/ml)	$t_{1/2}$ (h)
200 mg:	1.7	3309	16970	11.7
600 mg :	1.9	7269	40645	16.6
900 mg :	2.2	8374	53568	14.9
1200 mg :	2.2	7448	60118	8.9

Table 6 Summary of LCZ696 pharmacokinetic parameters for valsartan following daily administration for 14 days.

	t_{max} (h)	C_{max} ng/ml	AUC_{0-24} (ng.h/ml)	$t_{1/2}$ (h)
50 mg:	1.6	1233	6935	15.2
200 mg :	1.8	3990	21079	22.1
600 mg :	2.2	8563	58876	22.6
900 mg :	4.9	8960	54920	15.0

It is understood that while the present invention has been described in conjunction with the detailed description thereof that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the following claims. Other aspects, advantages and modifications are within the scope of the claims.

CLAIMS:

1. A solid oral dosage form comprising:

(a) the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate in a concentration from about 4% to about 90% by weight of the composition; and

(b) at least one pharmaceutically acceptable excipient,

wherein the compound is present in a dose strength of 40, 50, 100, 200 or 400 mg corresponding to the respective combined amount of valsartan free acid and (2*R*,4*S*)-5-biphenyl-4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester in a 1:1 ratio per unit dosage form.

2. The solid oral dosage form of claim 1, wherein said solid oral dosage form comprises trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)-propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate in a concentration from 4% to 60% by weight of the composition.

3. The solid oral dosage form of claim 1, wherein said solid oral dosage form is a tablet.

4. The solid oral dosage form of claim 3, wherein said tablet is an immediate-release formulation.

5. The solid oral dosage form of claim 3, wherein the compound is present in a dose strength of 40, 50, 100, 200 or 400 mg and the tablet is a roller compacted tablet.

6. The solid oral dosage form of claim 1, wherein the pharmaceutically acceptable excipients comprise (i) microcrystalline cellulose, (ii)

hydroxypropylcellulose, (iii) Crospovidone, (iv) Mg, Ca or Al stearate, (v) anhydrous colloidal silica and (v) talc.

7. The solid oral dosage form according to claim 6, wherein Mg stearate is employed in amounts of 1.0 to 6.0% by weight, anhydrous colloidal silica is employed in an amount of from 0.1 to 2% by weight, microcrystalline cellulose is present in an amount of 10 to 30% by weight, and crospovidone is present in an amount of 1 to 20% by weight.

8. A process for making a solid oral dosage form according to claim 1 comprising the steps of:

(a) mixing the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate with at least one pharmaceutically acceptable excipient to form a blend;

(b) directly compressing said blend into a solid oral dosage form.

9. A process for making a solid oral dosage form according to claim 5 comprising the steps of

(a) mixing the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate with at least one pharmaceutically acceptable excipient to form a blend;

(b) compacting said blend; and

(c) compressing the final blend into a solid oral dosage form.

10. A process according to claim 9 comprising the additional step of mixing the compacted blend as obtained in step b) with further pharmaceutically acceptable excipients.

11. A process for making a solid oral dosage form according to claim 5 comprising the steps of

(a) sieving the compound trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate and pharmaceutically acceptable excipients to form a sieved material;

(b) blending the sieved material to form a blended material;

(c) compacting the blended material to form a compacted material;

(d) milling the compacted material to form a milled material; and

(e) compressing the final mixture to form a tablet.

12. A process according to claim 11 comprising the additional step of blending the milled material obtained in step d) with further pharmaceutically acceptable excipients to form a final mixture.

13. A process according to claim 11 or 12 comprising the additional step of applying a film coat to the tablet obtain in step e) in order to obtain film coated tablets.

14. The solid oral dosage form according to claim 1, wherein the solid oral dosage form exhibits an *in vitro* dissolution profile, such that after 30 min, a mean of about 10% to a mean of about 100 % (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

15. The solid oral dosage form according to claim 1, wherein the solid oral dosage form exhibits an *in vitro* dissolution profile, such that after 30 min, a mean of at least 40% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

16. The solid oral dosage form according to claim 1, wherein the solid oral dosage exhibits an in vitro dissolution profile, such that after 10 min, a mean of at least 40% (by weight) of valsartan free acid, or a pharmaceutically acceptable salt thereof, is released.

17. The solid oral dosage form according to claim 1, wherein

(i) the compound is present in an amount of about 100 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released, or

(ii) the compound is present in an amount of about 200 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 50% of valsartan free acid, is released, after 20 min, a mean of about 85% of valsartan free acid, is released, after 30 min, a mean of about 95% of valsartan free acid, is released; or

(iii) the compound is present in an amount of about 400 mg per unit dosage form, and the oral dosage form exhibits an *in vitro* dissolution profile such that after 10 min, a mean of about 40% of valsartan free acid, is released, after 20 min, a mean of about 70% of valsartan free acid, is released, after 30 min, a mean of about 90% of valsartan free acid, is released.

18. The solid oral dosage form according to claim 1 that delivers a therapeutically effective amount of valsartan free acid, or a pharmaceutically acceptable salt thereof, and a carrier medium, wherein the oral dosage form provides a rate of absorption of valsartan free acid with a t_{max} of 1 to 2.2 h following administration of a single dose of said dosage form and / or provides a dose-normalized mean plasma exposure (AUC_{0-24}) of 230 to 400 ng•h/mL/mg-equivalent following administration of a single dose of said dosage form.

19. The solid oral dosage form according to claim 1 for the preparation of a medicament for increasing the rate of absorption and / or exposure of valsartan free acid.

20. The process according to claim 9, wherein the compacting in step (b) is roller compacting.

21. The process according to claim 11, wherein the compacting in step (c) is roller compacting.

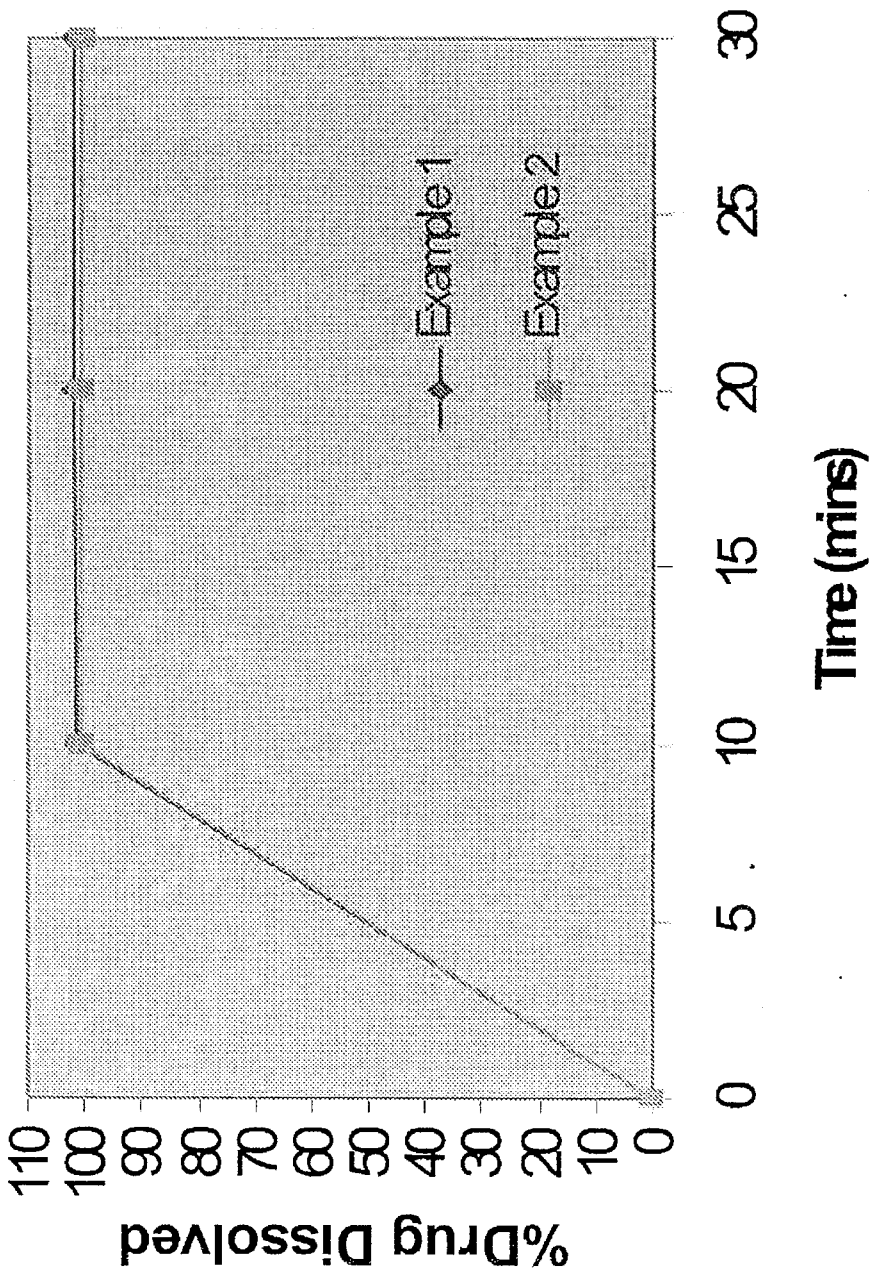

%Drug Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (mins)
Example 1
Example 2

Figure 1

Figure 2

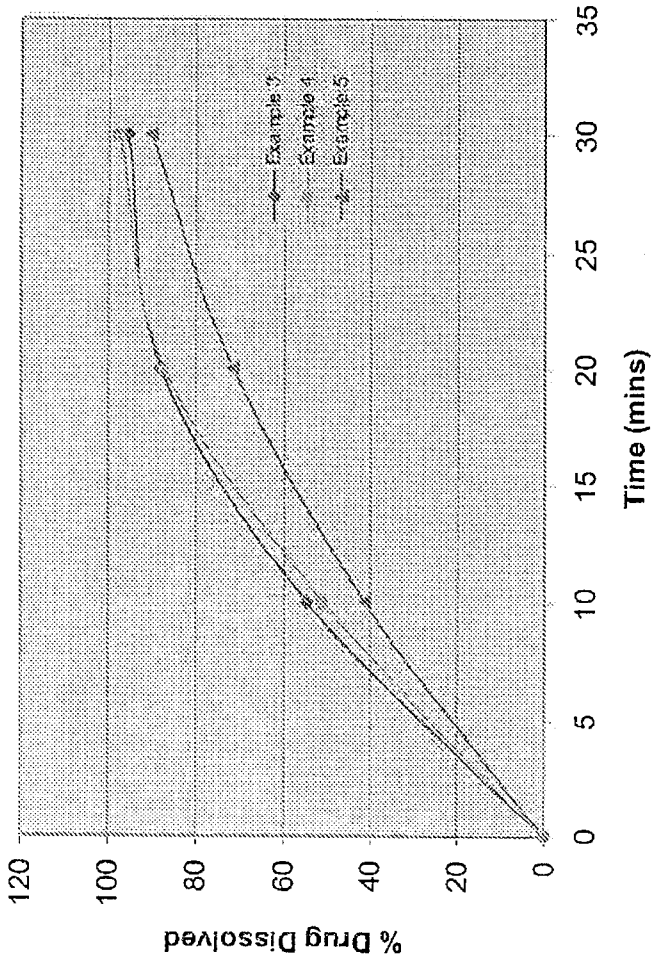
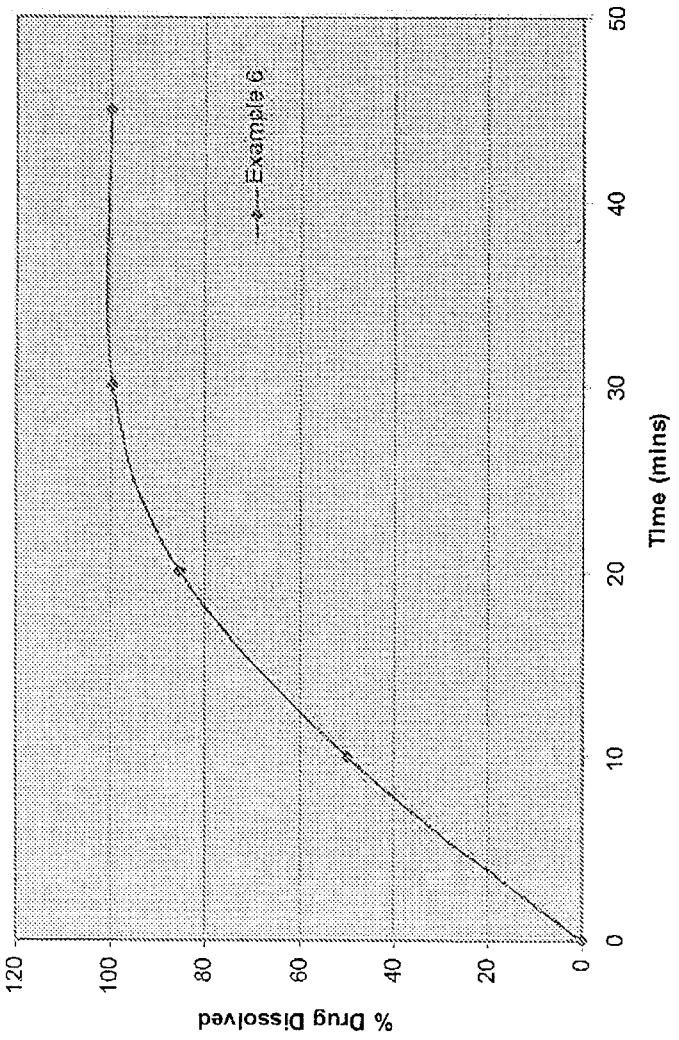

% Drug Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Time (mins)
Example 1
Example 4
Example 5

Figure 3


Example 6
% Drug Dissolved
120
100
80
60
40
20
0
0
10
20
30
40
50
Time (mins)