

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-081364-00004-0000

Fecha: 2008-12-30 15:55:49 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Evt. 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 70

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Número del expediente: 07-81.364

Solicitante: NOVARTIS AG

SOLICITUD PUBLICADA

Apoderado: CARLOS REYNALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: "COMBINACIONES FARMACÉUTICAS QUE COMPRENDEN UN INHIBIDOR DE LA RENINA, UNA ENDOPEPTIDASA NEUTRAL Y OPCIONALMENTE UN DIURÉTICO Y UN BLOQUEADOR DEL RECEPTOR DE LA ANGIOTENSINA II".

Gaceta:

596

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual _____	
	Teléfono: (571)3719900 Fax: (571)3730818	Número 802.006.279-4	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO	IDENTIFICACIÓN	
	Dirección: BOHORQUEZ	C.C. ☒	NIT ☐
	CARRERA 13 No. 119-95 104	C.E. ☐	Otro ☐
	Teléfono: (571) 2131215 Fax: (571) 6121979	Cual _____	
	E-mail: negocios@optimum-co.com	Número 51'975.664 P 83823	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Signo opositor: No cumple con los requisitos de patentabilidad.

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

5 Comprobante de pago No. _____

Fecha _____

6 ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredite la existencia y representación legal de las partes, cuando sean personas jurídicas.

7

NOMBRE: ELIANA ISaura MORENO B.

FIRMA: 

C.C. 51975664

TP. 83823 CSJ

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201

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISaura MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No 07 081.364, titulada "**COMBINACIONES FARMACÉUTICAS QUE COMPRENDEN UN INHIBIDOR DE LA RENINA, UNA ENDOPEPTIDASA NEUTRAL Y OPCIONALMENTE UN DIURÉTICO Y UN BLOQUEADOR DEL RECEPTOR DE LA ANGIOTENSINA II**", cuyo titular es **NOVARTIS AG**, publicada en la gaceta No. 596 del 30 de septiembre de 2008.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 29 días del mes de diciembre de 2008.

GYNOPHARM S.A.

Cédula de Extranjería No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:



ELIANA ISaura MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

RECONOCIMIENTO DE DOCUMENTO PRIVADO
 Ante mí, LILIANA CONSTANZA BARBOSA PLATA,
 Notaria Veinticinco del Circuito de Bogotá (E),
 comparece Andrés Pabón
 identificado con cédula de ciudadanía DE 819 728 111
 y declara que la firma puesta en el presente
 instrumento privado es suya y que el contenido
 del mismo es cierto. **29 DIC. 2008**
 Bogotá D.C.
 FIRMA: [Firma]
 LILIANA CONSTANZA BARBOSA PLATA
 NOTARIA VEINTICINCO

**NOTARIA PRIMERA DE CHIA
 PRESENTACION PERSONAL**

Este memorial dirigido a Superintendencia Cio.
 fué presentado personalmente ante el suscrito notario por Eliana
Tabarra Moreno Bohaguer
 Identificado C.C. 51.975.664 Bta
 T.P. de Abogado No. 83.823. Bta.
 Chía **30 DIC 2008**



Eliana Tabarra Moreno Bohaguer



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20081223

Hora Certificado 10:53:07

Operacion : 02NJK1223017

PAGINA No. 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura P?blica No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta C?mara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A.-----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

Correo electr?nico:

C E R T I F I C A

DURACION: El t?rmino de duraci?n de la sociedad se fij? hasta el 16 de Dic/bre de 2047. ✓

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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PAGINA No. 2

uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal.

c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci?n
Autorizado		
\$*****4,000,000,000 *****	4,000,000 *****	1,000 *****
Suscrito		
\$*****2,672,646,000 *****	2,672,646 *****	1,000 *****
Pagado		
\$*****2,672,646,000 *****	2,672,646 *****	1,000 *****

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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PAGINA No. 3

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le correspondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.

C E R T I F I C A

Que segun Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.

cuya parte pertinente se inscribi? en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Llobet Poal Manuel
2. Zanatta Reheman Leonardo Andres
3. Munoz Marroquin Diego

CC.*****14,670,196

CC.*****2,760,271

CC.*****7,688,292

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20081223 Hora Certificado 10:53:07

Operacion : 02NJK1223017 PAGINA No. 4

4. Montealegre Gonzalez Andres Leonardo CC.*****79,950,262

Suplentes

1. Agudelo Pelaez Luis Hernando	CC.*****14,238,997
2. Aroca Almanza Arleth Ayelina	CC.*****36,718,415
3. Penaranda Urbina Adriana Paola	CC.*****53,120,683
4. tovar Vasquez Ruth	CC.*****52,175,756

C E R T I F I C A

Que segun Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre
Gerente General.

Palacios Aragon Luis Alberto

Identificaci?n

CE.*****319,788

C E R T I F I C A

Que segun Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Suplente del Gerente.

Mollajoli Centurion Andres Fernando

Identificaci?n

CE.*****351,283

C E R T I F I C A

Que segun Acta No. 16 del 08 de Mayo de 2008 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Revisor Fiscal

Marroquin Sepulveda Edgar

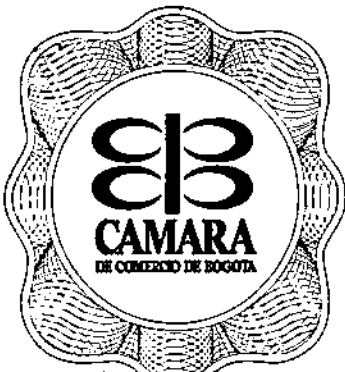
Identificaci?n

CC.*****17,147,542

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro respectivo, consta que el senor RUBEN MINSKI GONTOWNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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PAGINA No. 5

Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los (que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su ?ltima Renovacion fue el: 23 de Abril de 2008.

La informacion sobre embargos de establecimiento se suministra en Certificados de Matr?cula, la de contratos sujetos a registro, en Certificados Especiales.

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Referencia : Expediente N° 07 081364

Asunto : Oposición a la solicitud de patente de Invención titulada "COMBINACIONES FARMACÉUTICAS QUE COMPRENDEN UN INHIBIDOR DE LA RENINA, UNA ENDOPEPTIDASA NEUTRAL Y OPCIONALMENTE UN DIURÉTICO Y UN BLOQUEADOR DEL RECEPTOR DE LA ANGIOTENSINA II"

Solicitante : NOVARTIS AG

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 596 del 30 de Septiembre de 2008

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMBINACIONES FARMACÉUTICAS QUE COMPRENDEN UN INHIBIDOR

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 19 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79

E-mail: negocios@optimum.co - www.optimum-co.com

Bogotá Colombia



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DE LA RENINA, UNA ENDOPEPTIDASA NEUTRAL Y OPCIONALMENTE UN
DIURÉTICO Y UN BLOQUEADOR DEL RECEPTOR DE LA ANGIOTENSINA
II", cuyo titular es *NOVARTIS AG*, y pido a Usted declarar fundada esta oposición y
en consecuencia negar el registro de la patente solicitada.

Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la
CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés
de nuestra representada para oponerse al registro de la patente de la referencia,
atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la
ley como se analizará más adelante y de ser concedida afectaría directamente la
comercialización de algunos productos de mi representada, que contienen, en
particular compuestos relacionados con bloqueadores del receptor de angiotensina II.
Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la
presente oposición dentro del trámite administrativo que se surte en esta
Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 9 de agosto de 2007
reivindicando prioridad bajo la solicitud US20050652325P del 2005-02-11; y fue
publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 596 del 30 de
Septiembre de 2008, cuya publicación internacional corresponde a la
WO2006086456 del 2006-08-17.



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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

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2.2. La solicitud colombiana 07 081364 objeto de la presente oposición, se refiere a una

combinación que comprende: (i) un inhibidor de renina, o una sal farmacéuticamente aceptable del mismo; (ii) un inhibidor de endopeptidasa neutra (NEP), o una sal farmacéuticamente aceptable del mismo; y opcionalmente por lo menos un agente terapéutico seleccionado del grupo que consiste de: (a) un diurético, o una sal farmacéuticamente aceptable del mismo; y (b) un bloqueador del receptor de angiotensina II (ARB), o una sal farmacéuticamente aceptable del mismo; para la prevención, demora de establecimiento, y/o tratamiento de una enfermedad o condición mediada por la actividad de la angiotensina II y/o de la endopeptidasa neutra, cuyo método comprende administrar a un animal de sangre caliente que lo necesite, una cantidad terapéuticamente efectiva de una combinación de la presente invención; en donde se selecciona un inhibidor de renina a partir del grupo que consiste en RO 66-1132, RO 66-1168, y un compuesto de la Fórmula: en donde R1 es halógeno, haloalquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono-alquilo de 1 a 6 átomos de carbono, o alcoxi de 1 a 6 átomos de carbono-alquilo de 1 a 6 átomos de carbono; R2 es halógeno, alquilo de 1 a 4 átomos de carbono, o alcoxi de 1 a 4 átomos de carbono; R3 y R4 son independientemente alquilo de 3 a 6 átomos de carbono ramificado; y R5 es cicloalquilo, alquilo de 1 a 6 átomos de carbono, hidroxi-alquilo de 1 a 6 átomos de carbono, alcoxi de 1 a 6 átomos de carbono-alquilo de 1 a 6 átomos de carbono.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*", los usos no están contemplados como patentables; y, Artículo



Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

20.- No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: EP0498361 publicada el 12 de agosto de 1992.
- D2: WO0240007 publicada el 23 de mayo de 2002.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela métodos de tratamiento de hipertensión o paro cardíaco congestivo que incluye una dosificación que incluye una combinación de un antagonista de angiotensin II o un inhibidor renina con un inhibidor neutro endopeptidasa. Igualmente se refiere a composiciones farmacéuticas que comprenden dichas combinaciones y medios para administrar dichas composiciones farmacéuticas en combinación. Particularmente, en los ejemplos y reivindicaciones dicha anterioridad D1 revela composiciones farmacéuticas para tratar la hipertensión y el infarto congestivo que comprenden un inhibidor NEP y un inhibidor de renina o una antagonista de angiotensina II. Por lo tanto además que la presente solicitud comprende un



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método terapéutico no patentable a luz de la norma colombiana, también revela una combinación que no es novedosa como lo indica esta solicitud anterior D1 de 1992 que revela con anterioridad tal combinación usualmente usada para el tratamiento de una enfermedad o condición mediada por la actividad de la angiotensina II. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Ahora bien, el documento D2 revela una combinación que comprende el inhibidor renina de fórmula (I) o una sal farmacéuticamente aceptable de eso. En particular dicha anterioridad D2 define en los ejemplos 1 a 11 y en las reivindicaciones se refiere a composiciones que comprenden un inhibidor de renina tal como aliskiren y un dual conversor de angiotensina enzima neutral endopetidasa tal como ACE/NEP y un diurético tal como hidroclorotiazida. Por lo tanto, visto dicho documento D2 la presente solicitud carece evidentemente de NOVEDAD.

2.7. En conclusión, este documento objeto de oposición a la luz del documento D1 y D2 carece evidentemente de NOVEDAD.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 081364 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.9. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

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comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud

de patente o, en su caso, de la prioridad reconocida." A la fecha de prioridad, 11 de febrero de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1 y D2, un compuesto farmacéutico que combine: (i) un inhibidor de renina, o una sal farmacéuticamente aceptable del mismo; (ii) un inhibidor de endopeptidasa neutra (NEP), o una sal farmacéuticamente aceptable del mismo; y opcionalmente por lo menos un agente terapéutico seleccionado del grupo que consiste de: (a) un diurético, o una sal farmacéuticamente aceptable del mismo; y (b) un bloqueador del receptor de angiotensina II (ARB), sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.10. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la



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tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación

industrial." La solicitud pretendida no cumple con dos los tres requisitos de patentabilidad.

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2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada "COMBINACIONES FARMACÉUTICAS QUE COMPRENDEN UN INHIBIDOR DE LA RENINA, UNA ENDOPEPTIDASA NEUTRAL Y OPCIONALMENTE UN DIURÉTICO Y UN BLOQUEADOR DEL RECEPTOR DE LA ANGIOTENSINA II", cuyo titular es NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 596 del 30 de Septiembre de 2008.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: EP0498361 publicada el 12 de agosto de 1992.
- D2: WO0240007 publicada el 23 de mayo de 2002.

4. FUNDAMENTO DE DERECHO

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax (571) 6 12 19 79

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Bogotá Colombia

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

D1: EP0498361 publicada el 12 de agosto de 1992.

- D2: WO0240007 publicada el 23 de mayo de 2002.



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6. NOTIFICACIONES

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Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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(1)



Europäisches Patentamt
European Patent Office
Office européen des brevets



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(57) Combination of an angiotensin II antagonist or renin inhibitor with a neutral endopeptidase inhibitor.

(57) Treatment of hypertension or congestive heart failure with a combination of an angiotensin II antagonist or a renin inhibitor with a neutral endopeptidase inhibitor, pharmaceutical compositions comprising said combinations and kits for administering separate pharmaceutical compositions in combination are disclosed, wherein the angiotensin II antagonists include saralasin, sar 1, ile 8 angiotensin II, Dup 753, EXP 6155, EXP 6803 and PD 123319, the renin inhibitors include enalapril, RO 42-5892, A 65317, CP 80794, ES 1005, ES 8881, SQ 34017, CGP 29287, CGP 38580, SR 43845, U-71038, A 62196, and A 64662, and the neutral endopeptidase inhibitors include N-[N-[(1S)-carboxyl-3-phenylpropyl]- (S)-phenylalanyl]- (S)-isoserine, N-[N-[(1S)-carboxyl-2-phenylethyl]- (S)-phenylalanyl]-β-alanine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]-methionine, SQ 28603, UK 69578, SQ 29072, thiorphan, retro-thiorphan and phosphoramidon.

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BACKGROUND OF THE INVENTION

The present invention relates to the treatment of hypertension and congestive heart failure with a combination of an angiotensin II antagonist or a renin inhibitor with a neutral endopeptidase inhibitor.

In a second aspect, this invention relates to a pharmaceutical composition comprising an A II antagonist or a renin inhibitor in combination with an NEP inhibitor and to kits comprising an A II antagonist and an NEP inhibitor or a renin inhibitor and an NEP inhibitor.

The renin angiotensin system is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and a vasoactive mediator, A II. See J. Cardiovasc. Pharmacol., 15(Supp B) (1990) p. S1-S5. The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide A II by ACE. A II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, antinatriuresis, stimulation of vascular growth and stimulation of cardiac growth. A II functions as a pressor hormone and is involved the pathophysiology of several forms of hypertension.

Inhibitors of the renin angiotensin system are well known; such drugs lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described, for example, in N. Eng. J. Med., 316, 23 (1987) p. 1429-1435. A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which class includes the drugs captopril, enalapril, lisinopril and spiropril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide A II, it has been reported in Hypertension, 16, 4 (1990) p. 383-370 that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in Circ. Res., 66, 1 (1990) p. 242-248 to be mediated by elevation of bradykinin levels rather than inhibition of A II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease which cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See Biochem. J., 241, (1987) p. 237-247. Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANF), brain natriuretic peptide, met and leu enkephalin, bradykinin, neurokinin A, and substance P.

ANF are a family of vasodilator, diuretic and antihypertensive peptides which have been the subject of many recent reports in the literature, for example Annu. Rev. Pharm. Tox., 29, (1989) p. 23-54. One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to maintain salt and water homeostasis as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in Am. J. Physiol., 256 (1989) p. R469-R475 and an enzymatic inactivation via NEP reported in Biochem. J., 243 (1987) p. 183-187. It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al in J. Pharmacol. Exp. Ther., 250, 2 (1989) p. 624-631 and in Hypertension, 15, 2 (1990) p. 152-161, while the potentiation of ANF by NEP in general was disclosed in U.S. patent 4,749,688. In U.S. 4,740,499, Oline disclosed the use of thiorphan and ketorphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The antihypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

U.S. 4,749,688 also established the antihypertensive action of NEP inhibitors and that co-administration of an ACE inhibitor and a NEP inhibitor results in a greater reduction of blood pressure than observed with either agent alone. The antihypertensive effect is best manifested under conditions in which the renin angiotensin system is suppressed, as reported by Sybertz et al in the references cited above. For example, NEP inhibitors reduce blood pressure effectively in the Desoxycorticosterone sodium acetate (DOCA NA) hypertensive rat, a volume-dependent, renin-suppressed model of hypertension, but are less effective under conditions in which the renin angiotensin system is activated, such as in the spontaneously hypertensive rat (SHR) and in the two kidney Goldblatt hypertension model. Studies in the SHR and in the two-kidney Goldblatt hypertension model using a prodrug of the NEP inhibitor N-[2(S)-mercaptomethyl-3-(2-methyl-

phenyl)propionyl]methionine in combination with the ACE inhibitor spirapril demonstrated the greater efficacy of the combination compared to either drug alone. However, this interaction was inhibited in SHR which had been nephrectomized, a manipulation which markedly suppresses renin levels.

An explanation of this interactive effect of ACE inhibitors and NEP inhibitors on blood pressure is that suppression of the renin angiotensin system allows for full expression of the ANF-like antihypertensive effect of the NEP inhibitor. A II and ANF exert opposite effects on the cardiovascular system and it has been proposed by Johnston et al in Am. J. Med., 87, (Supp 6) (1990) p. 6B-24S-6B-26S that these two hormonal systems act to counterbalance one another.

An enhanced effect from a combination of an A II receptor antagonist or a renin inhibitor with an NEP inhibitor is, however, unexpected for several reasons. First, as discussed above, ACE inhibitors exert pharmacological effects other than inhibition of formation of A II. ACE degrades numerous substrates, including bradykinin, neurotensin, and substance P. In some instances, e.g. with bradykinin and substance P, both ACE and NEP will degrade the peptide. Since substance P and bradykinin are vasodilators, an alteration of the metabolism of either of these, or more efficient protection from degradation by inhibiting the two enzymes could account for an enhanced effect. Moreover, although nephrectomy, a maneuver which strikingly reduces plasma renin levels, eliminated the enhanced interaction of the ACE inhibitor and NEP inhibitor, the NEP inhibitor alone did not lower blood pressure in this state. Thus, the interactions of ACE inhibitors and NEP inhibitors are complex and the effect of an A II receptor antagonist or a renin inhibitor in combination with an NEP inhibitor cannot be predicted solely from data obtained from the combination of an ACE inhibitor and NEP inhibitor.

SUMMARY OF THE INVENTION

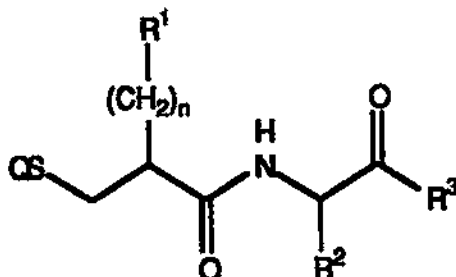
The present invention relates to a method of treating hypertension or congestive heart failure comprising administering an effective amount of a combination of an A II antagonist and a NEP inhibitor to a mammal in need of such treatment. The invention also relates to a method of treating hypertension or congestive heart failure comprising administering an effective amount of a combination of a renin inhibitor and a NEP inhibitor to a mammal in need of such treatment.

Another aspect of the invention relates to pharmaceutical compositions comprising an effective amount of a combination of an A II antagonist and a NEP inhibitor in a pharmaceutically acceptable carrier and to pharmaceutical compositions comprising an effective amount of a combination of a renin inhibitor and a NEP inhibitor in a pharmaceutically acceptable carrier.

Since the present invention relates to a method of treatment comprising a combination of actives wherein the actives may be administered separately, the invention in a third aspect relates to combining separate pharmaceutical compositions in kit form.

DETAILED DESCRIPTION

The NEP inhibitors suitable for use in this invention include, but are not limited to compounds disclosed in U.S. 4,610,816, herein incorporated by reference, including in particular N-[N-[(1S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine and N-[N-[(1S)-carboxyl-2-phenylethyl]-(S)-phenylalanyl]-β-alanine; compounds disclosed in U.S. 4,801,609 and 4,829,641, each herein incorporated by reference, including compounds of the formula



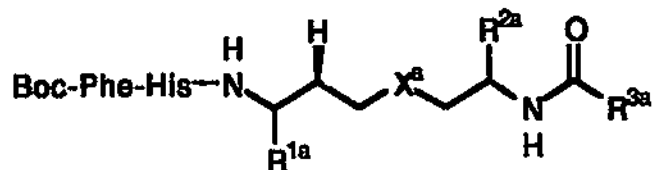
wherein R¹ is phenyl substituted by alkyl, R² is alkyl-S(O)₀₋₂(CH₂)_q, R³ is OR⁷ wherein R⁷ is hydrogen or lower alkyl, Q is hydrogen or R¹⁰CO- wherein R¹⁰ is alkyl, n is 0-2 and q is 1-4, and in particular N-[2(S)-

mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; SQ 28803 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application 84/0870; UK 69578 (cis-4-[[1-(2-carboxy-3-(2-methoxyethoxy)propyl)-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

The A II antagonists suitable for use in this invention include, but are not limited to saralasin; sar 1 (1-(N-methylglycine-angiotensin II); Ile 8 angiotensin II (1-de-L-aspartic acid -8-L-isoleucine-angiotensin II); Dup 753 (2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, monopotassium salt) and active metabolites thereof; EXP 6155 (2-butyl-1-[[4-(4-carboxyphenyl)methyl]-4-chloro-1H-imidazole-5-acetic acid, disodium salt); EXP 6803 (2-butyl-1-[[4-[(2-carboxybenzoyl)amino]phenyl]-methyl]-4-chloro-1H-imidazole-5-acetic acid α-methyl ester, monosodium salt); and PD 123319 (1-(4-dimethylamino-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid). Dup 753, EXP 6155 and EXP 6803 are disclosed in European Patent Applications 253,310 and 324,377; PD 123319 is disclosed in European Patent Application 245,637.

The renin inhibitors suitable for use in the present invention include, but are not limited to, enalapril, RO 42-5892, A 65317 [(2R)-2-benzyl-3-[(2-methoxyethoxymethoxyethyl)methylaminocarbonyl]-propionyl-L-His(2'S,1'R,5S)-3-ethyl-5[(1'-hydroxy-2'-amino-3'-cyclohexylpropyl)oxazolidin-2-one amide]; CP 60784; ES 1005 (N-[4-[[1-[(5-amino-6-hydroxyhexyl)-amino]carbonyl]-3-methyl-butyl]amino]-2-hydroxy-1-(2-methylpropyl)-4-oxobutyl]-α-[[3-(1-naphthalenyl)-2-(1-naphthalenylmethyl)-1-oxopropyl]-amino]-1H-imidazole-4-propanamide dihydrochloride); ES 8891 (5-cyclohexyl-2,4,6-trideoxy-N-hexyl-4-[[N-[3-(1-naphthalenyl)-N-(4-morpholinyl)-acetyl]-L-alanyl]-3-(4-thiazolyl)-L-alanyl]amino]-L-threo-pentonamide); SQ 34017; CGP 29287 (carbobenzoyloxy-Arg-Arg-Pro-Phe-His-Sar-Ile-His-Lys(BOC)OMe); CGP 38580 (N-[4-[(butylamino)-carbonyl]-1-(cyclohexylmethyl)-2-hydroxy-5-methylhexyl]-α-[[2-[[1,1-dimethylethyl]-sulfonyl]methyl]-1-oxo-3-phenylpropyl]amino]-1H-imidazole-4-propanamide), disclosed in U.S. 4,758,584; SR 43845 (3-Pyr-(CH₂)-CO-Phe-His-ACHPA-Ile-NH-C(CH₃)-(CH₂OH)₂); U-71039 (BOC-Pro-Phe-N-MeHis-Leu α -(CHOHCH₂)Val-Ile-Amp); A 62188 (N-(2-methyl-1-oxopropyl)-L-phenylalanyl]-N-[1S,2R,3S]-4-azido-1-(cyclohexylmethyl)-2,3-dihydroxybutyl-L-histidinamide); A 64682 (N-(3-amino-3-methyl-1-oxobutyl)-4-methoxy-L-phenylalanyl]-N-[1S,2R,3S]-1-(cyclohexyl-methyl)-2,3-dihydroxy-5-methylhexyl-L-histidinamide) and those disclosed by Watkins et al in U.S. 4,908,613, including those disclosed in the following publications, cited therein:

Compounds of the formula



wherein R^{1a} is selected from cyclohexylmethyl, benzyl or butyl; X^a is S or O; R^{2a} is selected from isobutyl, cyclohexylmethyl or benzyl; and R^{3a} is phenethyl. A preferred compound within this class is one wherein R^{1a} is cyclohexylmethyl, R^{2a} is isobutyl, R^{3a} is phenethyl and X^a is S. These compounds are described by Luly et al., *Pharmacologist*, 27 (3), (1985) p. 260, and can be prepared by known techniques from known materials.

Other renin inhibitors are disclosed, for example Szeleke et al., U.S. Pat. No. 4,424,207 discloses as having the formula



where

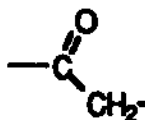
Pro, Phe and His may be in substituted form;

X^b = H; or an acyl or other N-protecting group e.g. acetyl, pivaloyl, t-butyloxycarbonyl (Boc), benzoyl or lower alkyl (primarily C₁-C₅); or an L- or D-amino-acyl residue, which may itself be N-protected similarly;

Y^b = D- or L-His or other D- or L-basic or aromatic amino-acetyl residue, or is absent;

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- (e) L- or D-Lys
 (f) L- or D-Arg unprotected or as the ester or amide
 (g) L- or D-Ser and
 (h) amino alcohol derived from (e)-(g) as such or protected in ester or ether form
 5 $Z^b + W^b =$ alcohol derived from
 (i) L-Tyr
 (ii) L-Phe
 (iii) D-Tyr or D-Phe
 (iv) His
 10 such peptide being in the above form or modified by isosteric replacement of one or more remaining peptide bonds by reduced, $-CH_2-NH-$, keto,



hydroxy, $-CH(OH)-CH_2-$, or hydrocarbon, $-CH_2-CH_2-$ isosteric links and further being in free form or in
 20 protected or salt form at one or more remaining peptide, carboxyl, amino, hydroxy or other reactive groups, in particular as their physiologically acceptable acid addition salts at basic centers.

Veber et al., U.S. 4,479,941, discloses renin inhibitor compounds such as

- IBU-His-Pro-Phe-His-Sta-Leu-benzylamide;
 IBU-His-Pro-Phe-His-Sta-Leu-2-phenylethylamide;
 25 IBU-His-Pro-Phe-His-Sta-Leu-3-phenylpropylamide;
 IBU-His-Pro-Phe-His-Sta-Leu-1,2-diphenylethylamide;
 BOC-Phe-His-Sta-Leu-(+)-1,2-diphenylethylamide;
 BOC-Phe-His-Sta-Leu-(-)-1,2-diphenylethylamide;
 BOC-Phe-His-Sta-Leu-benzylamide;
 30 BOC-Phe-His-Sta-Leu-(+)- α -phenylethylamide;
 BOC-Phe-His-Sta-Leu-(-)- α -phenylethylamide;
 BOC-Phe-His-Sta-Leu-(+)- α -naphthylethylamide;
 BOC-Phe-His-Sta-Leu-(-)- α -naphthylethylamide;
 BOC-Phe-His-Sta-Leu-p-chlorobenzylamide;
 35 BOC-Phe-His-Sta-Leu-p-methoxybenzylamide;
 BOC-Phe-His-Sta-Leu-10,11-dihydro-5H-dibenzo[a,d]-cyclohepteneamide;
 BOC-Phe-His-Sta-Leu-D,L-threo-1,2-diphenyl-2-hydroxyethylamide;
 BOC-Phe-His-Sta-Leu-Sta;
 BOC-Phe-His-AHPPA-Leu-benzylamide;
 40 Acetyl-Phe-His-AHPPA-Leu-benzylamide;
 BOC-Phe-His-Sta-Leu-(2-amidomethylpyridine);
 BOC-Phe-His-Sta-Leu-(4-amidomethylpyridine);
 BOC-Phe-His-Sta-Leu-(4-amido-1-benzylpiperidine);
 BOC-Phe-His-Sta-Leu-[N-(3-amidopropyl)diethanolamine];
 45 BOC-Phe-His-AHPPA-Leu-(2-amidomethylpyridine);
 BOC-Phe-His-ACHPA-Ile-(2-amidomethylpyridine);
 IVA-His-D-Pro-Phe-His-ACHPA-Ile-(2-amidomethylpyridine);
 ' (+) refers to the optical rotation of the amine.

A preferred compound within this class is BOC-Phe-His-Sta-Leu-(4-amido-1-benzyl-piperidine).

- 50 Veber et al., U.S. 4,478,826, discloses renin inhibitor compounds such as
 tert-Butyloxycarbonyl-His-Pro-Phe-His-Sta-Leu-Leu-Leu-OCH₃,
 tert-Butyloxycarbonyl-His-Pro-Phe-His-Sta-Leu-Tyr-NH₂,
 iso-Butyryl-His-Pro-Phe-His-Sta-Leu-Phe-Lys-NH₂,
 tert-Butyloxycarbonyl-His-Pro-Phe-p-I-Phe-Sta-Leu-Phe-NH₂,
 55 iso-Valeryl-His-Pro-Phe-His-Sta-Leu-Val-Phe-NH₂,
 His-Pro-Phe-His-Sta-Leu-Phe-NH₂,
 iso-Valeryl-His-Pro-Phe-His-Sta-Leu-Phe-NH₂,
 Acetyl-Pro-Phe-His-Sta-Leu-Phe-NH₂.

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Acetyl-Phe-His-Sta-Leu-Phe-NH₂,
 tert-Butyloxycarbonyl-Phe-His-Sta-Leu-Phe-NH₂,
 tert-Butyloxycarbonyl-His-Pro-Phe-Phe-Sta-Leu-Phe-NH₂,
 iso-Butyryl-His-Pro-Phe-His-Sta-Ala-Phe-NH₂.

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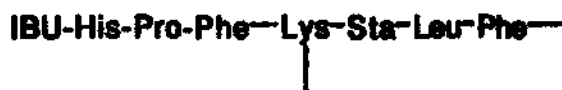


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A preferred compound within this class is IVA-His-Pro-Phe-His-Sta-Leu-Phe-NH₂.
 Veber et al., U.S. 4,384,994 discloses renin inhibitor compounds such as
 N-phenoxyacetyl-L-leucyl-(3S,4S)-statyl-L-valyl-L-phenylalanine;
 N-phenoxyacetyl-L-leucyl-(3S,4S)-statyl-L-leucyl-L-phenylalanine
 N-phenoxyacetyl-L-leucyl-(4S)-amino-(3S)-hydroxy-5-phenylpentanoyl-L-leucyl-L-phenylalanine;
 L-leucyl-(3S,4S)-statyl-L-valyl-L-phenylalanine;
 L-leucyl-(3S,4S)-statyl-L-leucyl-L-phenylalanine;
 L-leucyl-(4S)-amino-(3S)-hydroxy-5-phenylpentanoyl-L-leucyl-L-phenylalanine;
 and the amide and C₁₋₄ alkyl ester forms of the above peptides.
 Boger et al., U.S. 4,485,089, discloses renin inhibitor compounds such as

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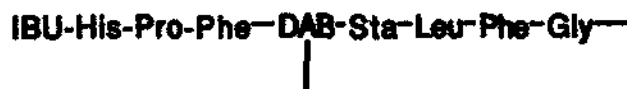
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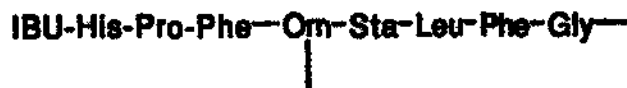
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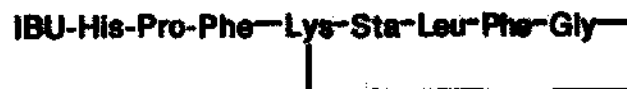
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(a) hydrogen; or
(b) alkyl of 1 to 3 carbon atoms;

(a) $\text{CH}_2\text{C}_6\text{H}_5$; or
(b) alkyl of 1 to 3 carbon atoms:

(a) hydrogen; or
(b) alkyl of 1 to 6 carbon atoms;

wherein p^m is 0, 1 or 2;

15 be D, L or DL; and the pharmacologically acceptable salts thereof.

15 be D, L or DL; and the pharmacologically acceptable salts thereof.



as having renin inhibitory activity.

In the general formula (I)^a each of the symbols X^{aa}, Y^{aa} and Z^{aa} which are identical or different, 30 represent an amino-acid residue selected from arginine, glutamic acid, aspartic acid, lysine, histidine or valine, forming with the free carboxyl group of the pepstatin or of the adjacent amino-acid a peptide bond -CONH-; the carboxyl function of the terminal amino-acid may exist in free form or in the form of an ester of an aliphatic alcohol containing 1 to 4 carbon atoms, and the indices aa, ba, and ca are each equal to zero or 1, the sum aa + ba + ca being equal to 1, 2 or 3.

Hayashi et al., U.S. 3,995,875, discloses renin inhibitors of the formula



46 wherein F' is an octadeca-9,12-dienoyl, octadeca-9,12,15-trienoyl, 4-(4'-chlorophenoxy)phenoxyacetyl or α -[4-(4'-chlorophenoxy)phenoxy]propionyl group, and m' is 2 or 3, or their pharmaceutically acceptable acid addition salts.

The following definitions apply throughout the specification: IBU = iso-butyryl; BOC = Tert-butoxycarbonyl; AHPPA = (3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid; ACHPA = (3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid; IVA = iso-valeryl; DAB = 2S-amino-4-aminobutyric acid; Hlys = homolysine, 2S-amino-6-aminoheptanoic acid; POA = phenoxyacetyl; Hcys = L-homocysteine.

The above descriptions of classes of renin inhibitors for use in the present invention were taken from the noted patents and publications or abstracts thereof. Reference should be made to such patents and publications themselves for their full disclosures of such classes and specific compounds within such classes, and as to any typographical errors or the like which may have occurred in transcription. Also, in describing such renin inhibitors, the superscript letters a,b,l,m,q and r were included to distinguish among the various classes of compounds and the variable substituent groups thereof.

The antihypertensive effects of NEP inhibitors, A II antagonists and renin inhibitors, and of combinations

of NEP inhibitors with A II antagonists or renin inhibitors are determined according to the following procedures.

For the DOCA salt hypertension model, male Sprague Dawley rats weighing 100-150 g are anesthetized with ether and the right kidney is removed. Three pellets containing Doc acetate (desoxycorticosterone acetate, DOCA, 25 mg/pellet) are implanted subcutaneously. Animals recover from surgery, are maintained on normal rat chow and are allowed free access to a fluid of 1% NaCl and 0.2% KCl instead of tap water for a period of 25-30 days. This procedure results in a sustained elevation in blood pressure and is a slight modification of published procedures (e.g. Brock et al. 1982) that have been used to produce DOCA salt hypertension in the rat.

On the day of the study, animals are again anesthetized with ether and the caudal artery is cannulated for blood pressure measurement. Patency of the caudal artery cannula is maintained with a continuous infusion of dextrose in water at a rate of 0.2 ml/hr. Animals are placed into restraining cages where they recover consciousness. Blood pressure is measured from caudal artery catheter using a Statham pressure transducer attached to a Beckman oscillographic recorder. In addition, a cardiovascular monitoring device (Buxco Electronics, Inc.) and a digital computer are used to calculate average blood pressures.

After an equilibration period of at least 1.5 hr., animals are dosed subcutaneously (1 ml/kg) with vehicle (methylcellulose, hereinafter MC), NEP inhibitor, A II antagonist, renin inhibitor, a combination of NEP inhibitor and A II antagonist, or a combination of NEP inhibitor and renin inhibitor and blood pressure is monitored for the next 4 hours. The doses of drug are chosen based on amounts previously determined to be effective for inhibition of the respective enzymes.

Two kidney, 1-clip (2K,1C) Goldblatt hypertension is produced in male Sprague Dawley rats as described by DeForrest et al (1984). Rats weighing 180-200 g are anesthetized with ether or Brevital (60 mg/kg, ip) and the left kidney is exposed through a flank incision. A silver clip with an internal diameter of 0.15 mm is placed around the left renal artery. The contralateral kidney remains untouched. The animal is used 3-4 weeks after surgery when sustained hypertension greater than 150 mm Hg is established.

On the day of the experiment, fasted rats are anesthetized with ether and the abdominal aorta is cannulated via the caudal artery with polyethylene tubing. The rats are placed in plastic restrainers and allowed to regain consciousness for at least 90 min. The rats are dosed by oral gavage with a single drug or with a combination of drugs as suspensions in 0.4% methylcellulose vehicle. Blood pressure is recorded continuously from the caudal artery on an oscillographic recorder.

The antihypertensive effect in SHR is determined as follows. Animals are prepared for blood pressure measurement as described above. After stabilization, animals are dosed subcutaneously with test drugs, combinations thereof or placebo and blood pressure is monitored for the next 4 hours.

ANF has been shown to exert beneficial hemodynamic and renal actions in congestive heart failure (CHF) with the exception of the most severe states, in which its actions may be blunted. ANF and the renin angiotensin system also act as physiological antagonists of one another in CHF. Therefore, it is contemplated that the combination of an ANF-potentiating NEP inhibitor and an inhibitor of the renin angiotensin system will be useful in the treatment of CHF. Measurements of the degree of diuresis and natriuresis, as well as hemodynamics, are used to determine the efficacy of the present combination in the treatment of CHF.

The combinations of this invention comprise an NEP inhibitor and an A II antagonist, and an NEP inhibitor and a renin inhibitor. The components of each combination can be administered in the same pharmaceutical composition or by co-administration of separate pharmaceutical compositions. A variety of pharmaceutical dosage forms are suitable, preferably for oral or parenteral administration, although mechanical delivery systems such as transdermal dosage forms are also contemplated.

The daily dosages of the combinations of this invention for treatment of hypertension or congestive heart failure are as follows: for NEP inhibitors, the typical dosage is about 0.3 mg/kg to about 100 mg/kg of mammalian weight per day administered in single or divided doses; for A II antagonists, the typical dosage is about 0.1 mg/kg to about 50 mg/kg of mammalian weight per day administered in single or divided doses; and for renin inhibitors, the typical daily dosage is about 0.1 mg/kg to about 100 mg/kg mammalian weight, administered in single or divided doses. The exact dose of any component or combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Generally, in treating humans having hypertension or congestive heart failure, the combinations of this invention can be administered in dosage ranges as follows: for the combination of NEP inhibitor and A II antagonist, about 10 to about 500 mg NEP inhibitor per dose given 1 to 4 times a day, and about 5 to about 100 mg A II antagonist given 1 to 3 times a day; and for the combination of NEP inhibitor and renin inhibitor, about 10 to about 500 mg NEP inhibitor given 1 to 4 times a day, and about 5 to about 600 mg

renin inhibitor given 1 to 3 times a day. Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g., where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The 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; betacyclodextrin; 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.

Since the present invention relates to treatment of hypertension and congestive heart failure with combinations of active ingredients wherein said active ingredients can be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, two kits are contemplated, each combining two separate units: an NEP inhibitor pharmaceutical composition and an A II antagonist pharmaceutical composition in one kit, and an NEP inhibitor pharmaceutical composition and a renin inhibitor pharmaceutical composition in a second kit. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral NEP formulation and parenteral A II antagonist formulation) or are administered at different dosage intervals.

Claims

1. A pharmaceutical composition for treating hypertension or congestive heart failure comprising an effective amount of a combination of a neutral endopeptidase inhibitor and either a renin inhibitor or an angiotensin II antagonist, in a pharmaceutically acceptable carrier.
2. A composition of claim 1 wherein:
 - the neutral endopeptidase inhibitor is selected from the group consisting of N-[N-[(1S)-carboxyl-3-phenylpropyl]-[S]-phenylalanyl]-[S]-isoserine; N-[N-[(1S)-carboxy-2-phenylethyl]-[S]-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propionyl]methionine; SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; and the pro-drugs thereof;
 - the angiotensin II antagonist is selected from the group consisting of saralasin; sar 1; Ile 8 angiotensin II; Dup 753; EXP 6155; EXP 6803; and PD 123319; and
 - the renin inhibitor is selected from the group consisting of enalapril; RO 42-5892; A 65317; CP 80784; ES 1005; ES 8891; SQ 34017; CGP 29287; CGP 38560; SR 43845; U-71038; A 62198; and A 64682.
3. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat hypertension or congestive heart failure in mammals which comprises in one container a pharmaceutical composition comprising a neutral endopeptidase inhibitor, and in a second container a pharmaceutical composition comprising a renin inhibitor or an angiotensin II antagonist.
4. The use of a neutral endopeptidase (NMEP) inhibitor, in combination with either a renin inhibitor or an angiotensin II antagonist, for the preparation of a pharmaceutical composition useful in the treatment of hypertension or congestive heart failure.
5. The use according to claim 4, wherein:
 - the neutral endopeptidase inhibitor is selected from the group consisting of N-[N-[(1S)-carboxyl-3-phenylpropyl]-[S]-phenylalanyl]-[S]-isoserine; N-[N-[(1S)-carboxy-2-phenylethyl]-[S]-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propionyl]methionine; SQ 28603; UK 69578; thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; and the pro-drugs thereof;
 - the angiotensin II antagonist is selected from the group consisting of saralasin; sar 1; Ile 8 angiotensin II; Dup 753; EXP 6155; EXP 6803; and PD 123319; and

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the renin inhibitor is selected from the group consisting of enalapril; RO 42-5882; A 85317; CP 80794; ES 1006; ES 8891; SQ 34017; CGP 28287; CGP 38580; SR 43845; U-71038; A 82186; and A 84862.

- 5 6. A composition according to any of claims 1 or 2, wherein:
the NMEP inhibitor is administered at a dosage level of 0.3 mg/kg mammalian weight per day;
the angiotensin II antagonist is administered at a dosage level of 0.1 mg/kg to 50 mg/kg
mammalian weight per day; and
the renin inhibitor is administered at a dosage level of 0.1 mg/kg to 100 mg/kg mammalian weight
10 per day.
7. A process for the preparation of a pharmaceutical composition according to any of claims 1, 2 or 6,
which comprises mixing a NMEP inhibitor, in combination with either a renin inhibitor or an angiotensin
II antagonist, with a pharmaceutically acceptable carrier.
- 15 8. A method of treating hypertension or congestive heart failure comprising administering an effective
amount of a combination of a neutral endopeptidase inhibitor and either a renin inhibitor or an
angiotensin II antagonist to a mammal in need of such treatment.
- 20 9. A method of claim 8 wherein:
the neutral endopeptidase inhibitor is selected from the group consisting of N-[N-(1(S)-carboxyl-3-
phenylpropyl)-(S)-phenylalanyl)-(S)-isoserine; N-[N-(((1S)-carboxy-2-phenylethyl)-(S)-phenylalanyl)-β-
alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propionyl]methionine; SQ 28603; UK 89578; thior-
phan; retro-thiorphan; phosphoramidon; SQ 28072; and pro-drugs thereof;
25 the angiotensin II antagonist is selected from the group consisting of saralasin; sar 1; Ile 8
angiotensin II; Dup 753; EXP 8155; EXP 6803; and PD 123319; and
the renin inhibitor is selected from the group consisting of enalapril; RO 42-5882; A 85317; CP
80794; ES 1006; ES 8891; SQ 34017; CGP 28287; CGP 38580; SR 43845; U-71038; A 82186; and A
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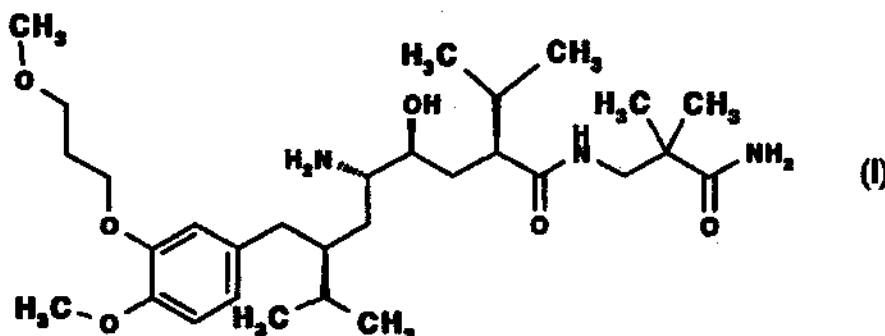
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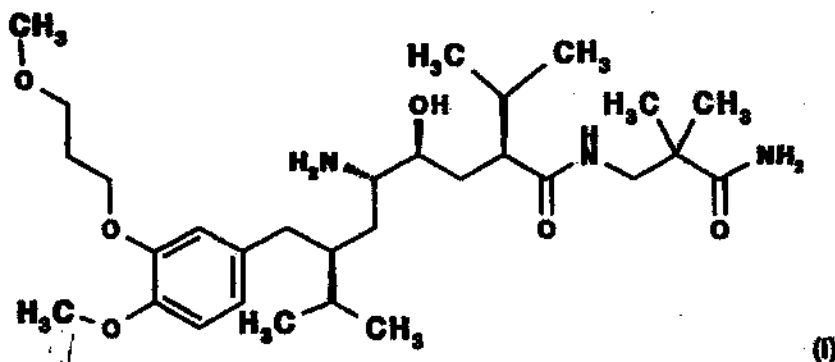
(57) Abstract: The invention relates to a combination comprising the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof.

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SYNERGISTIC COMBINATIONS COMPRISING A RENIN INHIBITOR FOR CARDIOVASCULAR DISEASES

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising the renin inhibitor of formula (I)



or a pharmaceutically acceptable salt thereof.

The invention especially relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof and at least one therapeutic agent selected from the group consisting of

- (i) an AT_1 -receptor antagonist or a pharmaceutically acceptable salt thereof,
- (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iv) a Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (ix) a diuretic or a pharmaceutically acceptable salt thereof.

The term "at least one therapeutic agent" shall mean that in addition to the compound of formula (I) one or more, for example two, furthermore three, active ingredients as specified according to the present invention can be combined.

Renin inhibit the action of the natural enzyme renin. The latter passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. That increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of e.g. the hypotensive effect of renin inhibitors.

The renin inhibitor of formula (I), chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide, is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

AT₁-receptor antagonists (also called angiotensin II receptor antagonists) are understood to be those active ingredients that bind to the AT₁-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT₁ receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

The class of AT₁ receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), tasosartan (cf. EP539088), telmisartan (cf. EP 522314), the compound with the designation E-1477 of the following formula

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HMG-Co-A reductase inhibitors (also called β -hydroxy- β -methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol in blood.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluvastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred HMG-Co-A reductase inhibitors are those agents which have been marketed, most preferred is fluvastatin and pitavastatin and also atorvastatin or, in each case, a pharmaceutically acceptable salt thereof.

The interruption of the enzymatic degradation of angiotensin I to angiotensin II with so-called ACE-inhibitors (also called angiotensin converting enzyme inhibitors) is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, movaltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

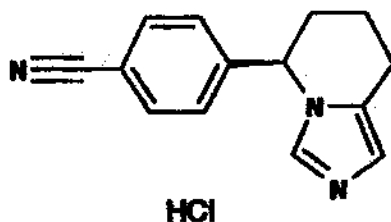
A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, nifedipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

Aldosterone synthase inhibitor is an enzyme that converts corticosterone to aldosterone by hydroxylating corticosterone to form 18-OH-corticosterone and 18-OH-corticosterone to aldosterone. The class of aldosterone synthase inhibitors is known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

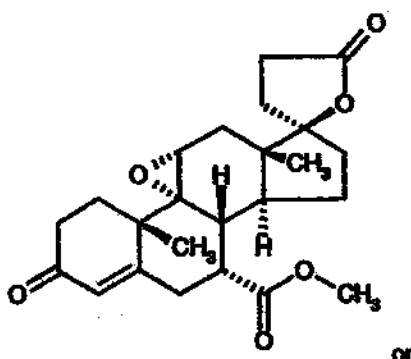
Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



A preferred steroidal aldosterone antagonist is eplerenone (cf. EP 122232 A) of the formula



spironolactone.

Compounds having an inhibitory effects on both angiotensin converting enzyme and neutral endopeptidase, so-called dual ACE/NEP inhibitors, can be used for the treatment of cardiovascular pathologies.

A preferred dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor is, for example, omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or Z 13752A (cf. WO 97/24342) or, if appropriate, a pharmaceutically acceptable salt thereof.

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists in three isoforms (ET-1, ET-2 and ET-3). (ET shall mean any or all the isoforms of ET). Elevated levels of ET have been reported in plasma from patients with e.g. essential hypertension. Endothelin receptor antagonist can be used to inhibit the vasoconstrictive effects induced by ET.

A preferred endothelin antagonist is, for example, bosentan (cf. EP 526708 A), enrasentan (cf. WO 94/25013), atrasentan (cf. WO 96/06095), especially atrasentan hydrochloride, derasentan (cf. EP 785928 A), BMS 193884 (cf. EP 702012 A), sitasentan (cf. US

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5594021), especially sitaxsentan sodium, YM 598 (cf. EP 882719 A), S 0139 (cf. WO 97/27314), J 104132 (cf. EP 714897 A or WO 97/37665), furthermore, tezosentan (cf. WO 96/19459), or in each case, a pharmaceutically acceptable salt thereof.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

Preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically accepted salt thereof and as second active agent an active agent selected from the group consisting of valsartan, fluvastatin, atorvastatin, pitavastatin, benazepril, enalapril, amlodipine, especially the besylate thereof, the (+) enantiomer of fadrozole, eplerenone, omapatrilate, Z 13752A, sitaxsentan, especially sitaxsentan sodium, darusentan and hydrochlorothiazide.

Furthermore preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically accepted salt thereof and one active agent selected from the group consisting of valsartan, fluvastatin, atorvastatin, pitavastatin, benazepril, enalapril, amlodipine, especially the besylate thereof, the (+) enantiomer of fadrozole, eplerenone, omapatrilate, Z 13752A, sitaxsentan, especially sitaxsentan sodium, and darusentan, furthermore comprising as third active agent hydrochlorothiazide.

The structure of the active agents identified by generic or tradenames 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). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

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The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

All the more surprising is the experimental finding that the combined administration of the renin inhibitor of formula (I) or a salt thereof with a therapeutic agent selected from the group consisting of (I) to (ix) results not only in a beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the combined treatment and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

In particular, all the more surprising is the experimental finding that the combination of the present invention results not only in a beneficial, especially a synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions as specified hereinafter.

It can be shown by established test models and especially those test models described herein that the combination of the renin inhibitor of formula (I) with a therapeutic agent selected from the group consisting of (I) to (ix) results in a more effective prevention or preferably treatment of diseases specified in the following. In particular, it can be shown by established test models and especially those test models described herein that the combination of the present invention results in a more effective prevention or preferably treatment of diseases specified hereinafter.

If taken simultaneously, this results not only in a further enhanced beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the simultaneous treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with diabetes mellitus, for a number of combinations as described herein. Moreover, for a human patient, especially for elderly people, it is more convenient and easier to remember to take two tablets at the same time, e.g. before a meal, than

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staggered in time, i.e. according to a more complicated treatment schedule. More preferably, both active ingredients are administered as a fixed combination, i.e. as a single tablet, in all cases described herein. Taking a single tablet is even easier to handle than taking two tablets at the same time. Furthermore, the packaging can be accomplished with less effort.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of the present invention is greater than the sum of the effects that result from methods and compositions comprising the active ingredients of this invention separately.

The person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the class of AT_1 -receptor antagonists or ACE inhibitors, respectively, or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The beneficial effects on blood pressure can, for example, be demonstrated in the test model as disclosed in R.L. Webb et al., in J. Hypertension, 16:843-852, 1998.

Methods:

The combination according to the present invention comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered by various routes of administration but are tested in this example using a continuous infusion via subcutaneously-implanted osmotic minipumps. Each agent can be tested over a wide-range of dosages to determine the optimal drug level for each agent in combination to elicit the maximal response. For these studies, it is preferred to use treatment groups consisting of at least 8 animals per group. Each study is best performed in which the effects of the combination treatment group are determined at the same time as the individual components are evaluated. Although drug effects may be observed with acute administration (such as 1 day), it is preferable to observe responses in a chronic setting as shown below in which experiments were done over a two to three week observation period. The long-term study is

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of sufficient duration to allow for the full development of compensatory responses to occur and therefore, the observed effect will most likely depict the actual responses of the test system representing sustained or persistent effects. The effects on blood pressure depicted below represent a synergistic antihypertensive effect when the two agents are used in combination.

Statistical Analysis:

The combination therapy can be compared to that of the monotherapy groups by determining the maximum change in blood pressure or the area under the curve (AUC) for change in blood pressure over time in each of the treatment groups. All values are represented as the group mean $\pm$ SEM. Statistical significance is obtained when $p < 0.05$. The AUC values for each of the treatment groups can be compared statistically using a one-way ANOVA followed by the appropriate post-hoc analysis, for example by performing a Tukey's test.

Results:

Blood pressure can be reduced to a similar degree using lower dosages of each of the components when given in combination than when the individual monotherapies are administered. An additional unexpected finding is that the blood pressure can be lowered to a greater extent with the combination than when the individual compound of formula (I) or a pharmaceutically acceptable salt thereof is given alone at a higher dosage.

These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardiovasc. Pharmacol. 27:347-354, 1996.

For example, the valuable potential of the combination of the present invention for the prevention and treatment of myocardial infarction (including the post-myocardial infarction indication to delay the progression to congestive heart failure) can be found using the following test model.

Study design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 6 treatment groups characterized by following features:

- sham-operated animals

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- CAO + vehicle
- CAO + compound of formula (I) or a pharmaceutically acceptable salt, especially the hemifumarate, thereof,
- CAO + aldosterone synthase inhibitor
- CAO + compound of formula (I) or a pharmaceutically acceptable salt, especially the hemifumarate, thereof, + aldosterone synthase inhibitor.

Following doses and routes of administration can be applied:

For the (+)-enantiomer of the hydrochloride of fadrozole

Alza osmotic minipumps 0.4 mg/kg/d.

During the study following variables are measured:

- infarct size
- LV chamber volume
- Interstitial and perivascular collagen density in spared LV myocardium
- COL-I and COL-III protein content in spared LV myocardium by Western blot
- cardiomyocytes cross-sectional area and length in sections of LV myocardium
- plasma concentrations of renin and aldosterone
- urine concentration of sodium, potassium and aldosterone
- blood pressure in conscious animals
- LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct size: Six μ m-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a software specifically developed (Porzio *et al.*, 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.*, 1995).

Histology: Hearts are fixed in situ, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and

the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.*, 1998).

Collagen content in LV spared myocardium: LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for collagen type I) or peroxidase (collagen type III).

Left ventricular chamber volume: LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.*, 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left ventricular hemodynamics: A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time ($+dP/dt$) and heart rate.

Non-invasive blood pressure: Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine electrolytes, hormones: Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C18 columns (Varian), separated by HPLC (Apex-II C18, 3 μ m, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulchem II, ESA) (Goldstein *et al.*, 1981). Plasma and urine aldosterone, and plasma angiotensin II are determined with specific radioimmunoassays

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(Aldock-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flame photometry.

Sample size

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial dysfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGF β , PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelial dysfunction can be demonstrated in the following pharmacological test:

Material and methods

Male 20-24 week-old SHR, purchased from RCC Ltd (Fullingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7).

The rats can be divided into 5 groups: group 1, control (n = 40); Group 2, the compound of formula (I) in form of the hemi-fumarate (ren1; n = 40); Group 3, enalapril (ena1; n = 30); Group 4, a combination (ena1ren1) of enalapril and the compound of formula (I) in form of the hemi-fumarate; (n = 30) and Group 5, the compound of formula (I) in form of the hemi-fumarate (ren2 - higher dose; n = 30). The drugs are administered in drinking fluid. The dose of enalapril is selected from the work of Sweet et al. (1987) indicating significantly increased survival in rats with healed myocardial infarction. The pressor effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reduced after treatment with the compound of formula (I) in form of the hemi-fumarate (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na⁺ and K⁺ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical analysis:

All data are expressed as mean $\pm$ SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

Results:

Even at non-blood pressure reducing doses, both the compound of formula (I) in form of the hemi-fumarate and enalapril treatment lead to significant improvements in survival rates.

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The surprising observation is that, in this model, blockade of the RAS with low doses of the renin inhibitor of formula (I) and, for example, and enalapril improved survival despite persistent kidney dysfunction and high blood pressure. There is no decrease in proteinuria and no reduction of kidney lesions. Kidney and heart sections show glomerulosclerosis, fibrinoid necrosis and fibrosis. These results clearly demonstrate that survival of SHR with endothelial dysfunction is independent of the blood-pressure lowering effect of the treatment and may be related to a direct effect on the endothelium.

An improvement of regression of atherosclerosis without effecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the compounds or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033-1037.

That the compounds or combinations according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87-95 (1998).

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

Accordingly, the invention furthermore relates to a method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

(i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (ix) a diuretic or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention relates to the use of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof,
- (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof, and
- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (ix) a diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;
- (e) glaucoma; furthermore
- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and

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(h) peripheral vascular disease.

The invention furthermore relates to a pharmaceutical composition for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;
- (e) glaucoma; furthermore
- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease;

comprising a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof,
- (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

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(ix) a diuretic or a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

A further aspect of the present invention is a kit for the prevention of, delay of progression of, treatment of a disease or condition according to the present invention comprising

- (a) an amount of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- (b) an amount of at least one therapeutic agent selected from the group consisting of components (I) to (ix), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
- (c) a container for containing said first, second etc. unit forms.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or

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condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound 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 compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

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The pharmaceutical preparation will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising an amount, being together with the further component(s) jointly effective, e.g.

The doses of renin inhibitor of formula (I) to be administered to warm-blooded animals, for example human beings, of, for example, approximately 70kg body weight, especially the doses effective in the inhibition of the enzyme renin, e.g. in lowering blood pressure and/or in improving the symptoms of glaucoma, are from approximately 3mg to approximately 3g, preferably from approximately 10mg to approximately 1 g, for example approximately from 20mg to 200mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Usually, children receive about half of the adult dose. The dose necessary for each individual can be monitored, for example by measuring the serum concentration of the active ingredient, and adjusted to an optimum level. Single doses comprise, for example, 10, 40 or 100 mg per adult patient.

Valsartan, as a representative of the class of AT₁-receptor antagonists, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

In case of HMG-Co-A reductase inhibitors, preferred dosage unit forms of HMG-Co-A reductase inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 120 mg, preferably, when using fluvastatin, for example, 20 mg, 40 mg or 80 mg (equivalent to the free acid) of fluvastatin, for example, administered once a day.

In case of ACE inhibitors, preferred dosage unit forms of ACE inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 20 mg, preferably 5 mg, 10 mg, 20 mg or 40 mg, of benazepril; from about 6.5 mg to 100 mg, preferably 6.25 mg, 12.5 mg, 25 mg, 50 mg, 75 mg or 100 mg, of captopril; from about 2.5 mg to about 20 mg, preferably 2.5 mg, 5 mg, 10 mg or 20 mg, of enalapril; from about 10 mg to about 20 mg,

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preferably 10 mg or 20 mg, of fosinopril; from about 2.5 mg to about 4 mg, preferably 2 mg or 4 mg, of perindopril; from about 5 mg to about 20 mg, preferably 5 mg, 10 mg or 20 mg, of quinapril; or from about 1.25 mg to about 5 mg, preferably 1.25 mg, 2.5 mg, or 5 mg, of ramipril. Preferred is t.i.d. administration.

Especially preferred are low dose combinations.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	64.00	NF, Ph. Eur
Croscopvidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water ⁷	-	
DIOLACK pale red 00F34899	7.00	
Total tablet mass	167.00	

⁷ Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tableting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan.

Formulation Example 2:

Film-coated tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry Light Brown 00F33172	10.00	
Total tablet mass	330.00	

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 3:

Film-Coated Tablets:

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Components	Composition Per Unit (mg)	Standards
Core: Internal phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
External phase		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [Lubricant]	2.00	USP/NF
Film coating		
Opadry [®] brown OOF 16711 ¹⁾	9.40	
Purified Water ²⁾	-	
Total tablet mass	199.44	

¹⁾ The composition of the Opadry[®] brown OOF16711 coloring agent is tabulated below.

²⁾ Removed during processing

Opadry[®] Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172)	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50

Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 4:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

Granulation/Drying

Valsartan and microcrystalline cellulose are spray-granulated in a fluidised bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidised bed dryer.

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Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical screw type mixer for approximately 10 minutes.

Encapsulation

Ten empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filled capsules are dedusted, visually inspected, weightchecked and quarantined until by Quality assurance department.

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	342.00

The formulation is manufactured e.g. as described in Formulation Example 4.

Formulation Example 6:

Hard Gelatine Capsule:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Croscopovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

Examples 7 to 11:

Example	7	8	9	10	11
Components	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)
Granulation					
Valsartan Drug Substance	80.000	160.000	40.000	320.000	320.000
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	54.000	108.000	27.000	216.000	216.000
Croscopovidone (NF, Ph.Eur.)	15.000	30.000	7.500	80.000	60.000
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.000	0.750	3.000	6.000
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	1.500	10.000	12.000
Blending					
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	—	—	—	3.000	-
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	0.750	8.000	6.000
Core Weight/mg	155.000	310.000	77.500	640.000	620.000
Coating	-	-	3.800	15.000	16.000

Example 12:

Hard gelatin capsule:

Component	Amount per unit (mg)
Capsule	
Fluvastatin Sodium ¹⁾	21.481 ²⁾
Calcium Carbonate	62.840
Sodium Bicarbonate	2.000
Microcrystalline Cellulose	57.220
Pregelatinized Starch	41.900
Purified Water ³⁾	Q.S.
Magnesium Stearate	1.050
Talc	9.430
Target Capsule Fill Weight	195.92
Capsule Shell	
Hard gelatin Capsule Shell	48.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	244.42

¹⁾ Includes a 2% overage for moisture²⁾ 20 mg of free acid is equivalent to 21.06 mg Na salt³⁾ partially removed during processing

Example 13:**Hard gelatin capsule**

Component	Amount per unit (mg)
Fluvastatin Sodium	42.962 ¹⁾
Calcium Carbonate	125.680
Sodium Bicarbonate	4.000
Microcrystalline Cellulose	114.440
Pregeatinized Starch	83.800
Purified Water ²⁾	Q.S.
Magnesium Stearate	2.100
Talc	18.860
Target Capsule Fill Weight	391.840
Capsule Shell	
Hard gelatin Capsule Shell	76.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	468.34

¹⁾ Includes a 2% overage for moisture

²⁾ 20 mg of free acid equivalent to 21.06 mg Na salt

³⁾ partially removed during processing

Example 14:**Round, slightly bi-convex, film-coated tablets with beveled edges:**

Component	Amount per unit [mg]
Table Core	
Fluvastatin Sodium ¹⁾	84.24 ²⁾
Cellulose Microcrystalline / Micro-crystalline cellulose fine powder	111.27
Hypromellose / Hydroxypropyl methyl cellulose (Methocel K100LVP CR; HPMC100 cps)	97.50
Hydroxypropyl cellulose (Klucel HXF)	16.25
Potassium hydrogen carbonate / Potassium bicarbonate	8.42
Povidone	4.88
Magnesium stearate	2.44
Core Tablet Weight	325.00
Coating	
Coating premix - Opadry Yellow (00F22737)	9.75
Total Weight	334.75
Water, purified ³⁾	Q.S.

¹⁾ 84.24 mg of the sodium salt of fluvastatin is equivalent to 80 mg of fluvastatin free acid²⁾ to be adjusted for moisture (LOD)³⁾ removed during processing

Example 15:

Round, biconvex, beveled-edged, film-coated tablets

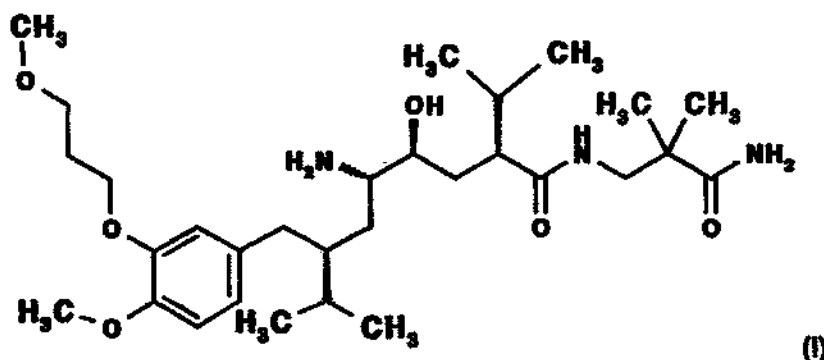
Ingredient	Unit wt/Vol. [mg]	Unit wt/Vol. [mg]	Unit wt/Vol. [mg]	Unit wt/Vol. [mg]
Benzapril Hydrochloride	5.00	10.00	20.00	40.00
Lactose Monohydrate, NF	142.00	132.00	117.00	97.00
Pregelatinized Starch, NF	8.00	8.00	8.00	8.00
Colloidal Silicon Dioxide, NF (Cab-O-Sil, M-5)	1.00	1.00	1.00	1.00
Croscollone, NF	3.00	3.00	3.00	3.00
Microcrystalline Cellulose, NF	18.00	18.00	18.00	24.25
Hydrogenated Castor Oil, NF	8.00	8.00		
Magnesium Stearate, NF			8.00	1.75
Color:	-			0.50
Yellow-Brown (suspension)		2.00		
Red-Brown (suspension)			0.50	
Purified Water, USP	trace	trace	trace	trace
Opadry Color:				
Yellow	8.38	8.38		
Pink			8.38	8.38
Total	183.38	180.38	183.88	183.88

Example 16:**Film-coated tablets**

The following constituents are processed for the preparation of 10 000 tablets each containing 100 mg of active ingredient:

What is claimed is

1. A pharmaceutical composition comprising the renin inhibitor of formula (I)



or a pharmaceutically acceptable salt thereof and at least one therapeutic agent selected from the group consisting of

- (i) an AT_1 -receptor antagonist or a pharmaceutically acceptable salt thereof,
 - (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
 - (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
 - (iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
 - (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
 - (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
 - (vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
 - (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
 - (ix) a diuretic or a pharmaceutically acceptable salt thereof;
- and a carrier.

2. A composition according to claim 1 wherein the renin inhibitor is present in form of the hemi-fumarate.

3. A composition according to claims 1 or 2 wherein, independent of one another,
- said AT_1 -receptor antagonist is valsartan or a pharmaceutically acceptable salt thereof;

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- said HMG-Co-A reductase inhibitor is fluvastatin and pitavastatin, or or a pharmaceutically acceptable salt thereof;
- said angiotensin converting enzyme (ACE) inhibitor is benazepril or enalapril, or a pharmaceutically acceptable salt thereof;
- said Calcium channel blocker is amlodipine or a pharmaceutically acceptable salt thereof;
- said an aldosterone synthase inhibitor is fadrozole (including the (+)-enantiomer thereof or a pharmaceutically acceptable salt thereof;
- said aldosterone antagonist is eplerenone;
- said dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor is omapatrilate or a pharmaceutically acceptable salt thereof;
- said endothelin antagonist is bosentan or a pharmaceutically acceptable salt thereof; and
- said diuretic is hydrochlorothiazide.

4. A composition according to any one of claims 1 to 3 for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of
- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
 - (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension; and
 - (c) endothelial dysfunction with or without hypertension,
 - (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia; and
 - (e) glaucoma.
5. A composition according to any one of claims 1 to 3 for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of
- (f) isolated systolic hypertension (ISH),
 - (g) diabetic retinopathy, and
 - (h) peripheral vascular disease.

6. A composition according to any one of claims 1 to 5 for simultaneous, separate or sequential use.

7. A kit for the prevention, delay of progression, or treatment according to claim 4 comprising

- (a) an amount of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- (b) an amount of at least one therapeutic agent selected from the group consisting of components (i) to (ix), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
- (c) a container for containing said first, second etc. unit forms.

8. Use of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

- (i) an AT_1 -receptor antagonist or a pharmaceutically acceptable salt thereof,
- (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vii) an dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (ix) a diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic

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hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention; and
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia; and
- (e) glaucoma.

9. Use of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof,
- (ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,
- (iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,
- (iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,
- (v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,
- (vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,
- (vii) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,
- (viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and
- (ix) a diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease.

10. A method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

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(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

(i) an AT_1 -receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutal endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

(ix) a diuretic or a pharmaceutically acceptable salt thereof.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-081364-00004-0000

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Tra. 11 PATENTEIYI Eva: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 70

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 101,500
FECHA : DICIEMBRE 30 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAD. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	14727985	18/12/2008	1,064,000.00
LAD. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	96103313	28/11/2008	1,064,000.00
GYNOFARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	105711141	26/12/2008	1,330,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LENAS COMERCIALES	266,000.00
	TOTAL :	\$ 266,000.00

SUN: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2020
Bogotá, D.C.,

Doctor:
Carlos Reinaldo Olarte García
Apoderado

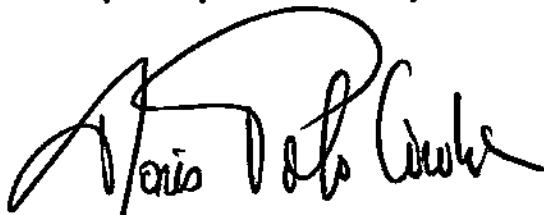
Oficio N°: 3418

ASUNTO:	Radicación PCT N°	07-81364
	Trámite	011
	Evento	378
	Actuación	440
	Folios	010

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



DORIS ELENA POLO CORDOBA
Jefe de la División de Nuevas Creaciones (E).

20 MAR. 2009

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021