

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: 08-0133459

Solicitante: **NOVARTIS AG**

**SOLICITUD
PUBLICADA**

Apoderado: **CARLOS REYNALDO OLARTE GARCIA**

Título de la nueva creación o denominación del signo **FORMAS DE DOSIFICACION**
SÓLIDAS DE VALSARTAN, AMLODIPINA, E HIDROCLOROTIAZIDA, Y METODOS PARA
ELABORARLAS. Gaceta: 604

Gaceta: 604

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A. Dirección: Carrera 14 N° 94-44 Piso 7 Torre b Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>802,006,279-4</u>
	Teléfono: 2 36 84 95 Fax: _____ E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: _____ Fax: _____ E-mail: (571)213 12 13 (571)612 19 79 negocios@optimum-co.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>51.940.252</u> TP <u>82701</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

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 acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA

FIRMA: _____

C.C. 51.940.252

TP. 82701



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 133459

Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMAS DE DOSIFICACIÓN SÓLIDAS DE
VALSARTAN, AMLODIPINA, E HIDROCLOROTIAZIDA,
Y MÉTODOS PARA ELABORARLAS"

Solicitante : NOVARTIS AG

Opositora : GYNOPHARM S.A.

Publicada en la ~~Gaceta~~ de la Propiedad Industrial

N° 604 del 29 de Mayo de 2009

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** 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 "FORMAS DE DOSIFICACIÓN SÓLIDAS DE VALSARTAN, AMLODIPINA, E HIDROCLOROTIAZIDA, Y MÉTODOS PARA ELABORARLAS", cuyo titular es NOVARTIS AG., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



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 VALSARTAN. 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 16 de diciembre de 2008 reivindicando prioridad bajo la solicitud US20060805883P 2006-06-27; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009, cuya publicación internacional corresponde a la WO2008002905 del 2008-01-03.

2.2. La solicitud colombiana 08 133459 objeto de la presente oposición, se refiere a formas de dosificación sólidas de una sola capa, de dos capas, y de tres capas, de una combinación de valsartan, amlodipina, e hidroclorotiazida; y aditivos farmacéuticamente aceptables adecuados para la preparación de las formas de dosificación sólidas de valsartan; donde la amlodipina se proporciona en la forma

de besilato de amlodipina; en donde la forma de dosificación sólida toma la forma de una tableta de una sola capa; en donde la forma de dosificación sólida toma la forma de una tableta de dos capas; en donde la tableta de dos capas tiene el valsartan y la hidroclorotiazida en una primera capa, y la amlodipina en una segunda capa; en donde la tableta de dos capas tiene el valsartan en una primera capa, y la amlodipina y la hidroclorotiazida en una segunda capa; en donde el valsartan se emplea en una cantidad que está en el intervalo de aproximadamente 80 miligramos a aproximadamente 640 miligramos; en donde el valsartan se emplea en una cantidad seleccionada a partir de 160 miligramos y 320 miligramos; en donde la amlodipina se emplea en una cantidad que está en el intervalo de aproximadamente 2.5 miligramos a aproximadamente 20 miligramos; en donde la amlodipina se emplea en una cantidad seleccionada a partir de 5 miligramos y 10 miligramos; y, en donde la hidroclorotiazida se emplea en una cantidad que está en el intervalo de aproximadamente 6.25 miligramos a aproximadamente 50 miligramos.

2.3. En primera instancia, se debe advertir que algunas reivindicaciones también se refieren 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 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: WO03097045 publicada el 27 de noviembre de 2003.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una combinación de compuestos orgánicos, una composición farmacéutica y un equipo de partes que comprenden la combinación de compuestos orgánicos y un método de tratamiento o prevención de ciertas condiciones o enfermedades. Particularmente, en la página 12 (párrafo 5) de la anterioridad D1 se revelan dosis unitarias en tabletas o capsulas que comprende valsartan, amlodipina e hidroclorotiazida. Como tal la anterioridad revela que es útil para el tratamiento de la hipertensión fallas cardíacas congestivas, angina, infarto al miocardio, arterosclerosis, diabetes, insuficiencia renal, enfermedad vascular periférica, hipertrofia ventricular izquierda, disfunción cognitiva o fallas cardíacas crónicas. Por lo tanto, la materia aquí revelada no es novedosa dado que como lo demuestra el documento D1, ya era conocido y era parte del estado de la técnica una formulación tal y como se reivindica en la presente solicitud.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 133459 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.

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

- 2.7.1. **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, 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, 27 de junio de 2006 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una formas de dosificación sólidas de una sola capa, de dos capas, y de tres capas, de una combinación de valsartan, amlodipina, e hidroclorotiazida, sobre el cual busca protección en el capítulo reivindicatorio.
- 2.7.2. **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.



2.8. 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 tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“FORMAS DE DOSIFICACIÓN SÓLIDAS DE VALSARTAN, AMLODIPINA, E HIDROCLOROTIAZIDA, Y MÉTODOS PARA ELABORARLAS”**, cuyo titular es **NOVARTIS AG**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 604 del 29 de Mayo de 2009.

3. PRUEBAS

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

- D1: WO03097045 publicada el 27 de noviembre de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

- 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

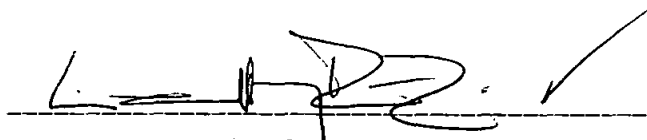
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
 2. Documento que acredite al representante legal de **GYNOPHARM S.A.**
 3. Recibo de caja del respectivo pago de tasa.
 4. Copias de los documentos:
- D1: WO03097045 publicada el 27 de noviembre de 2003.

6. NOTIFICACIONES

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,



CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

12

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 **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **08 133.459**, titulada "**FORMAS DE DOSIFICACION SOLIDAS DE VALSARTAN, AMLODIPINA, E HIDROCLOROTIAZIDA, Y METODOS PARA ELABORARLAS**", cuyo titular es **NOVARTIS AG**, publicada en la gaceta No. 604 del 29 de mayo de 2009.

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 25 días del mes de 8 de 2009.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

73

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 64,045
FECHA : AGOSTO 28 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-133459- -00003-0000

Fecha 2009-08-28 17:20:50 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve 378 FASENACIONAL
Act 400 OPOSIOBSERVTLR Folios. 46

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOFARM S.A.	RECIBO DE CAJA			56605	31/07/2009	491,000.00
GYNOFARM S.A.	RECIBO DE CAJA			59594	12/08/2009	1,012,000.00

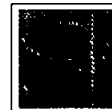
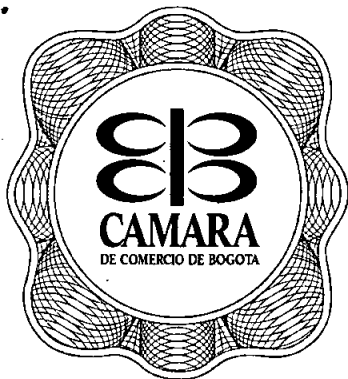
***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL/CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	
12	MARCAS Y LEMAS COMERCIALES	287,000.00
	TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



01

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/13

HORA: 11:10:21

OPERACION: 10BSC0813090

PAGINA: 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 Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara 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.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó 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

*** CONTINUA ***

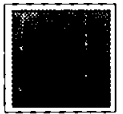
P R E M I O
COLOMBIANO
A LA CALIDAD
DE LA GESTION



01



* 8 3 7 3 5 0 1 0 *



95

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/13

HORA: 11:10:21

OPERACION: 10BSC0813090

PAGINA: 3

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 Acción

Autorizado

\$*****4,000,000,000 *****4,000,000 *****1,000

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

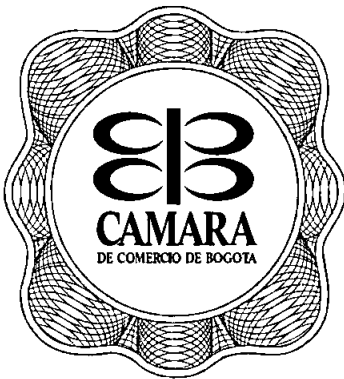
\$*****2,672,646,000 *****2,672,646 *****1,000

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 corres-

*** CONTINUA ***

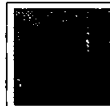
PREMIO
COPIADO
A LA CALIDAD
DE LA GESTION



01



* 8 3 7 3 5 0 1 1 *



26

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/13

HORA: 11:10:21

OPERACION: 10BSC0813090

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

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 repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, 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

*** CONTINUA ***

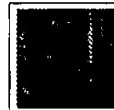
PREMIO
CROMBIANO
CALIDAD
GESTION



01



* 8 3 7 3 5 0 1 2 *



27

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/08/13

HORA: 11:10:21

OPERACION: 10BSC0813090

PAGINA: 7

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

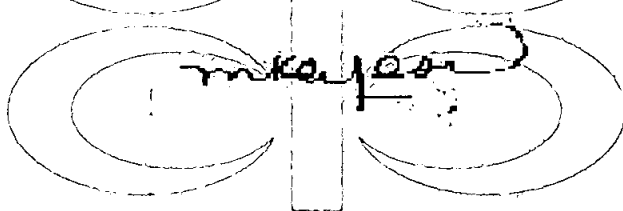
C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.



PREMIO
COLOMBIANO
LA CALIDAD
DE LA GESTIÓN

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 November 2003 (27.11.2003)

PCT

(10) International Publication Number
WO 03/097045 A1

- (51) International Patent Classification⁷: **A61K 31/4184**, 31/19, C07D 401/12, A61K 31/44, 31/196
- (74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (21) International Application Number: PCT/EP03/05180
- (22) International Filing Date: 16 May 2003 (16.05.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/381,547 17 May 2002 (17.05.2002) US
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).
- (71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (*for AT only*): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **SHETTY, Suraj, Shivappa** [US/US]; 12 Spring Street, Far Hills, NJ 07931 (US). **WEBB, Randy, Lee** [US/US]; 17 Honeyman Drive, Flemington, NJ 08822 (US).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 03/097045 A1

(54) Title: COMBINATION OF ORGANIC COMPOUNDS

(57) Abstract: The present invention relates to a combination of organic compounds, a pharmaceutical composition and a kit of parts comprising said combination of organic compounds and to a method of treatment or prevention of certain conditions or diseases.

Combination of Organic Compounds

The present invention relates to a combination of organic compounds that are antihypertensive agents with complementary modes of action for eliciting blood pressure-lowering, and also for attenuating the varied pathological sequelae of hypertension and several other cardiovascular disorders. Furthermore, this invention addresses the disparate responsiveness of humans to antihypertensive monotherapy, based on age and/or ethnicity (*Campo C, Segura J, Ruilope LM, J Clin Hypertens (Greenwich) 2002 Jan, 4(1):35-40*). Finally, the choice of agents and their respective dosages in the combination regimen are designed to enhance tolerability by minimizing the risk of dose-dependent adverse effects associated with individual agents.

Numerous clinical studies have shown that lowering blood pressure in hypertensive patients reduces mortality and morbidity (Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38). Despite the availability and use of various classes of agents in the treatment of this medical condition, adequate control of blood pressure is not always achieved (Waeber B, Brunner HR, Am J Hypertens 1997, 10(7 Pt 2):131S-137S). Using a combination of agents is one way to achieve the desired therapeutic end-point. An arbitrary selection of antihypertensive agents of different classes for inclusion in a combination therapy regimen does not necessarily help achieve target levels of blood pressure in hypertensive mammals including humans (MacGregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Br Med J (Clin Res Ed), 284(6317):693-6). Therefore, a need for further development of methods of treatment, combinations, and pharmaceutical compositions clearly exists.

Specifically, the present invention relates to pharmaceutical compositions comprising (i) an angiotensin receptor (Type 1, AT₁) blocker (ARB) selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, and pharmaceutically acceptable salts thereof; (ii) a calcium channel blocker (CCB) selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, and

pharmaceutically acceptable salts thereof; and, (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, and pharmaceutically acceptable salts thereof where appropriate, i.e. if the diuretic compound is not already present as a pharmaceutically acceptable salt as e.g. in the case of hydrochlorothiazide; optionally in the presence of a pharmaceutically acceptable carrier. The invention further provides methods for treating hypertension and a variety of cardiovascular disorders enumerated below and their sequelae by administration of the pharmaceutical composition comprising (i) an angiotensin receptor blocker (ARB), (ii) a calcium channel blocker (CCB), (iii) and a diuretic to a mammal including humans.

Thus, the invention further relates to a pharmaceutical composition or a kit of parts, e.g. for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke which composition (or kit of part) comprises (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride,

spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two or three separate units: e.g. a pharmaceutical composition

comprising an ARB, an pharmaceutical composition comprising a CCB, and a pharmaceutical composition comprising a diuretic; or a pharmaceutical composition comprising an ARB and a diuretic, and a pharmaceutical composition comprising a CCB; or a pharmaceutical composition comprising a CCB and a diuretic, and a pharmaceutical composition comprising an ARB. Although the kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. parenteral valsartan formulation and oral amlodipine or hydrochlorothiazide formulations) or are administered at different dosage intervals, the administration of the single components of such a kit of parts may, without any restriction be effected simultaneously, sequentially or staggered with time.

In a preferred embodiment, the (commercial) product is a commercial package comprising as active ingredients the combination according to the present invention (in the form of two or three separate units of the components (i) to (iii)), together with instructions for its simultaneous, separate or sequential use, or any combination thereof, in the delay of progression or treatment of the diseases mentioned herein. A preferred commercial package, is where the ARB (i) and the diuretic (iii) are present in the form of Co-DIOVAN®, or where the ACE inhibitor (i), the CCB (ii) and the diuretic (iii) are present in the form of Co-DIOVAN® and NORVASC®.

The pharmaceutical preparations of the present invention 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 compounds. Pharmaceutical preparations for enteral or parenteral 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, which 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 compounds 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 that are commercially available. Normally, in the case of oral administration, an approximate daily dose of from about 20 mg to about 900 mg of active agents, i.e. ARB plus CCB plus diuretic, is to be estimated e.g. for a patient of approximately 75 kg in weight.

In the present invention preferred ARBs are those agents that have been marketed, as e.g. valsartan and losartan. The same applies to the CCBs employed in the present invention, of which amlodipine and felodipine are preferred. The most preferred diuretic is hydrochlorothiazide (HCTZ).

Very surprisingly is the finding that, a combination of (i) an ARB, (ii) a CCB, and (iii) a diuretic and in particular a combination comprising valsartan, amlodipine and HCTZ achieves greater therapeutic effect than the administration of valsartan, amlodipine, or HCTZ alone or in a combination of two of these agents. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days). The aforementioned combination treatment also unexpectedly reduces blood pressure in hypertensive mammals in a smooth and sustained fashion. The trough:peak blood pressure ratio demonstrated by this combination is close to unity leading to a more homogenous blood pressure control during the inter-dosing period. The combined regimen is almost completely devoid of either orthostatic hypotension or first-dose hypotension, and incidences of rebound hypertension after cessation of treatment are very rare. It can be shown that combination therapy according to the invention results in lessening of pulse pressure in hypertensive mammals.

Furthermore, this combination therapy can ameliorate endothelial dysfunction and improve vascular compliance and distensibility in hypertensive mammals. It can also slow the progression of cardiac, renal and cerebral end-organ damage in these mammals. Further benefits 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 to diminish the incidence of side effects. Surprisingly, the combination of valsartan, amlodipine and HCTZ significantly reduce the incidences of peripheral edema relative to those observed in mammals treated with amlodipine alone. Also, the undesirable effects of HCTZ on serum lipids, glucose, and uric acid levels are surprisingly attenuated in mammals treated with the combined regimens of valsartan, amlodipine and HCTZ.

In particular the combined administration of valsartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof, and HCTZ results in a significant response in a greater percentage of treated patients compared to monotherapy or combination therapy e.g. valsartan and HCTZ, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated. The combination treatment effectively lowers blood pressure in hypertensive patients in all age groups including pre and postmenopausal women. It can be shown that combination therapy with valsartan, amlodipine, and HCTZ results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) and lessening of pulse pressure through improved efficacy. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan, amlodipine, and HCTZ combination therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan, amlodipine, and HCTZ combination is also useful in treating atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), peripheral vascular disease, cognitive dysfunction, and stroke. Furthermore, the improvement in endothelial function with the combination therapy using valsartan, amlodipine, and HCTZ provides benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral

- 7 -

vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke. The combination regimen also surprisingly reduces the rate of progression of cardiac, renal and cerebral end-organ damage. By providing enhanced efficacy, safety and tolerability, the combination of drugs indicated in this invention also has the potential to promote patient compliance, a major consideration in the pharmacological treatment of hypertension.

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

The advantages of the present combinations are, for example, demonstrated in a clinical study or in the test procedure as essentially described hereinafter. Many clinical study protocols adapted to test our combinations are known by the person skilled in the art. An example of a clinical trial useful to demonstrate the unexpected advantages of our new combinations is described by Waeber B et al. (J Hypertens. 2001 Nov;19(11):2097-104. The same protocol is performed with our preferred combinations such as a combination, preferably fixed-dose combination, of valsartan 80mg, hydrochlorothiazide 12.5 mg, and amlodipine 5 mg. This protocol is hereby incorporated into the present application by reference to this publications.

Representative studies are carried out with a combination of valsartan, amlodipine, and HCTZ applying the following methodology. Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate - salt rat (DOCA-salt) and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The Acute Study Procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the Chronic Study Procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood

pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up to 6 weeks (approximately one week prior to DOCA-salt administration and for 5 weeks thereafter).

Rats are anesthetized with 2-3% isoflurane in oxygen inhalant followed by Amytal sodium (amobarbital) 100 mg/kg, ip. The level of anesthesia is assessed by a steady rhythmic breathing pattern.

Acute study procedure:

Rats undergo a unilateral nephrectomy at the time of DOCA implantation. Hair is clipped on the left flank and the back of the neck and scrubbed with sterile alcohol swabs and povidone/iodine. During surgery rats are placed on a heating pad to maintain body temperature at 37 °C.

A 20 mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15 mm incision is made on the back of the neck and a 3-week-release pellet (Innovative Research of America, Sarasota, Florida) containing deoxycorticosterone acetate (100 mg/kg) is implanted subcutaneously. The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular injection of procaine penicillin G (100,000 U) and buprenorphine (0.05 – 0.1 mg/kg) s.c. The rats are immediately placed on 1% NaCl + 0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood, and administration of test compounds. Rats are allowed to recover for 48

hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic study procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in M.K. Bazil, C. Krulan and R.L. Webb. Telemetric monitoring of cardiovascular parameters in conscious spontaneously hypertensive rats. *J.Cardiovasc. Pharmacol.* 22: 897-905, 1993.

Protocols are then set-up on the computer for measurement of blood pressure, heart rate, etc, at predetermined time points. Baseline data is collected at various time points and over various time intervals. For example, baseline or pre-dose values usually consist of data collection and averaging over 3 consecutive, 24-hour time periods prior to drug administration.

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 ml/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to 8 weeks, drugs are given via subcutaneously implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1 to 100 mg/kg/day, amlodipine dosages range from 1 to 75 mg/kg/day, and HCTZ dosages range from 1 to 75 mg/kg/day.

Additionally, SHR are utilized to study the effects of valsartan in combination with amlodipine, and HCTZ. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the RAAS or chronic salt depletion to activate the RAAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments are performed in spontaneously hypertensive rats (SHR) supplied by Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul,

Minnesota) is implanted into the lower abdominal aorta of all test animals between the ages of 14 to 16 weeks of age. All SHR are allowed to recover from the surgical implantation procedure for at least 2 weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24 hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24 hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12 hour light dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan, amlodipine, and HCTZ doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 1 to 100 mg/kg/day, dosages of amlodipine range from 1 to 75 mg/kg/day, and dosages of HCTZ range from 1 to 75 mg/kg/day. In most situations, a daily dose will not exceed 100 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1 to 30 mg/kg/day, and amlodipine and HCTZ are given in dosages below 50 mg/kg/day.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1 to 50 mg/kg/day and that of amlodipine and HCTZ does not exceed 75 mg/kg/day, respectively.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized, blood samples obtained for biochemical analysis and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are

weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan HD, Thibault G, Li JS, Schiffrin EL, *Circulation* 1999, 100 (22): 2267-2275. Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan HD, Park JB, Schiffrin, EL, *Hypertension*, 1999, 34(4 Part 2): 907-913. Assessment of vascular compliance and distensibility following treatment with the combination regimen is performed according to the methods described by Ceiler DL, Nelissen-Vrancken HJ, De Mey JG, Smits JF, *J Cardiovasc Pharmacol* 1998, 31(4):630-7. Amelioration of cardiac, renal, and cerebral injury secondary to hypertension is assessed after treatment with the combination regimen in salt-loaded stroke-prone spontaneously hypertensive rats according to the methods described by Nagura J, Yamamoto M, Hui C, Yasuda S, Hachisu M, Konno F, *Clin Exp Pharmacol Physiol* 1996, 23(3):229-35. Propensity of the combination therapy to elicit postural or orthostatic hypotension is assessed in SHRs by the methods described by Nabata H, Aono J, Ishizuka N, Sakai K, *Arch Int Pharmacodyn Ther* 1985, 277(1):104-18. Tendency to produce peripheral edema by the combination regimen was assessed by the methods described by Lacolley P, Poitevin P, Koen R, Levy BI, *J Hypertens* 1998, 16(3):349-55.

Valsartan is 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 or 640 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 or 640 mg daily. Preferably, valsartan is applied once a day or twice a day in heart failure patients 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 q.d. or b.i.d. administration in heart failure.

In case of amlodipine, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 1 mg to about 60 mg, preferably 2.5 to 20 mg, more preferably between 2.5 and 10 mg daily when administered orally.

In case of HCTZ, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 5 mg to about 200 mg preferably from about 50 mg to about 150 mg, even more preferably from about 25 mg to about 100 mg and even more preferably from about 5 mg to about 25 mg, administered orally once a day.

An example of a preferred composition, comprises an amount of Valsartan between 60 and 100 mg e.g. 80 mg, an amount of amlodipine between 2 and 12 mg e.g. 2.5 or 5 mg and an amount of HCTZ between 8 and 16 mg e.g. 12.5 mg.

Another example of a preferred composition, comprises an amount of Valsartan between 140 and 180 mg e.g. 160 mg, an amount of amlodipine between 2 and 12 mg e.g. 2.5 or 5 or 10 mg and an amount of HCTZ between 8 and 16 mg e.g. 12.5 mg.

Another example of a preferred composition comprises an amount of Valsartan between 140 and 180 mg e.g. 160 mg, an amount of amlodipine between 4 and 12 mg e.g. 5 mg or 10 mg, and an amount of HCTZ between 20 and 30 mg e.g. 25 mg.

The combination of (i) an ARB, (ii) a CCB, and (iii) a diuretic may, according to the present invention be manufactured and administered in free or fixed dose combinations of the respective pharmaceutically active agents. It may be advantageous to begin the treatment with free combinations that allow an easy adjustment of the administered dose of each individual agent. When the ideal dose regimen, which generally is dependent on the specific condition of the individual to be treated, the individuals weight, other medication administered to the individual and the like, is reached, a fixed dose combination may be administered in case where an administration once a day or e.g. twice or three times daily is possible and a sufficient control of blood pressure is achieved.

Presently it is preferred to combine two of the components (i) to (iii) and administer the third separately at the same or at a different time.

Valsartan is being marketed under the trade name Diovan®. A combination of valsartan and HCTZ is being marketed under the trade name Co-Diovan® and amlodipine is being

marketed under the trade name Norvasc®. All of these marketed products may be utilized in as such for combination therapy according to the present invention.

The following examples illustrate the invention described above and are not intended to restrict the scope of this invention in any way.

Formulation Example 1:

Composition and batch quantities for Diovan® tablets

Components	COMPOSITION PER UNIT (mg)				QUANTITY PER BATCH ¹ (kg)			
	40mg	80mg	160mg	320mg	40mg	80mg	160mg	320mg
Diovan Drug Substance	40.000	80.000	160.000	320.000	144.000	144.000	144.000	144.000
Microcrystalline Cellulose(NF,Ph.Eur.) Avicel PH102	27.000	54.000	108.000	216.000	97.200	97.200	97.200	97.200
Crospovidone (NF,Ph.Eur.)	7.500	15.000	30.000	60.000	27.000	27.000	27.000	27.000
Colloidal Anhydrous Silica (Ph.Eur.)/Colloidal silicon Dioxide (NF)/Aerosil 200	0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
Magnesium Stearate (NF,Ph.Eur.)	1.500	3.000	6.000	12.000	5.400	5.400	5.400	5.400
Blending								
Magnesium Stearate (NF,Ph.Eur.)	0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
Coating								
DIOLACK Gelb F32892	2.800				11.090 ²			
DIOLACK Blassrot F34899		6.000				12.420 ³		
DIOLACK Hellbraun F33172			9.000				9.720 ⁴	
DIOLACK Braun F16711				16.000				8.640 ⁴
Purified Water					62.843	70.380	55.080	48.960
Total Tablet/Batch Weight	80.300	161.000	319.000	636.000	289.080	289.800	287.100	286.200

¹A total of 2 subdivisions of granulation per batch

²A 10% excess of coating solution was manufactured to account for loss during coating.

³A 15% excess of coating solution was manufactured to account for loss during coating.

⁴A 20% excess of coating solution was manufactured to account for loss during coating.

Composition of Diolack

DIOLACK	HPMC USP/Ph.Eur (603)	PEG 8000 USP/Ph.Eur.	Titanium Dioxide (White) USP/Ph.Eur	Iron Oxide (Red) Ph.Fr./NF/ E172/CFR/ CI 77491	Iron Oxide (Yellow) Ph.Fr./NF/ E172/CFR/ CI 77492	Iron Oxide (Brown) Mixture of iron oxide red & black	Iron Oxide (Black) E172/CFR/ CI 77499
Gelb F32892	80.00 %	4.00 %	13.48 %	0.01 %	2.50 %	—	0.01 %
Blassrot F34899	80.00 %	4.00 %	15.50 %	0.40 %	0.10 %	—	—
Hellbraun F33172	80.00 %	4.00 %	9.34 %	0.25 %	6.40 %	—	0.01 %
Braun F16711	80.00 %	4.00 %	14.00 %	0.50 %	0.50 %	0.50 %	0.50 %

A mixture of Diovan drug substance, 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 sieved through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieved 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 the appropriate composition of Diolack in a perforated pan.

Formulation Example 2:

Composition and quantities for Co-Diovan® tablets

Components	COMPOSITION PER UNIT (mg)	COMPOSITION PER UNIT (mg)	COMPOSITION PER UNIT (mg)
Granulation			
Diovan Drug Substance	80.000	160.000	160.00
Esidrex Drug Substance (micro)	12.500	12.500	25.00
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	31.500	75.500	63.00
Crospovidone (NF, Ph.Eur.)	20.000	40.000	40.00
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.00	3.00
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	6.00
Blending			
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	3.00
Coating			
Opadry Black OOF17713	-	-	0.096
Opadry Red OOF15613	-	-	0.762
Opadry Yellow OOF12951	-	-	3.808
Opadry White OOF18296	-	-	5.334
Hydroxy propyl Methylcellulose	2.76	5.510	-
Iron Oxide Yellow	0.025	-	-
Iron Oxide Red	0.025	0.750	-
Polyethylene Glycol 8000	0.50	1.000	-
Talc	2.000	3.990	-
Titanium Dioxide	0.70	0.750	-
Total Tablet/Batch Weight	156.000	312.000	310.00

Composition of Opadry

OPADRY	HPMC USP/Ph.Eur (603)	PEG 4000 USP/Ph.Eur.	Talc USP/Ph.Eur	Titanium Dioxide USP/Ph.Eur (White)	Iron Oxide (Red) Ph.Fr./NF/ E172/CFR/ CI 77491	Iron Oxide (Yellow) Ph.Fr./NF/ E172/CFR/ CI 77492	IronOxide (Black) E172/CFR/ CI 77499
Opadry White OOF18296*	71.4 %	7.15 %	7.15 %	14.3 %	-	-	-
Opadry Red OOF15613*	71.4 %	7.15 %	7.15 %	-	14.3 %	-	-
Opadry Red OOF15613*	71.4 %	7.15 %	7.15 %	-	-	14.3 %	-
Opadry Black OOF17713*	71.4 %	7.15 %	7.15 %	-	-	-	14.3 %

A mixture of Diovan drug substance, Esidrex drug substance (micro), microcrystalline cellulose, crospovidone, colloidal anhydrous silica/Aerosil 200 and part of the 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 sieved through a screening mill. The final blend is made in a diffusion mixer under addition of the remaining part of the magnesium stearate, which is hand screened before. The whole mixture is compressed in a rotary tableting machine and the tablets are coated with a film by using the appropriate composition of Opadry in a perforated pan.

Formulation Example 3:

Composition and quantities for a combination of valsartan and amlodipine

Components	COMPOSITION PER UNIT (mg)	COMPOSITION (%)
Diovan Drug Substance	80.00	43.02
Amlodipine Drug Substance	6.94	3.73
Avicel 102 (I)	54.00	29.04
Avicel 102 (II)	20.00	10.76
Crospovidone (I)	15.00	8.07
Crospovidone (II)	4.0	2.15
Cab-O-Sil	1.50	0.81
Magnesium Stearate (I)	3.00	1.61
Magnesium Stearate (II)	1.50	0.81
	185.94	100.00

The tablet is manufactured e.g essentially as described in Formulation Example 1.

What is claimed is:

1. A pharmaceutical composition comprising
 - (i) an angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof,
 - (ii) a calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof, and
 - (iii) a diuretic or a pharmaceutically acceptable salt thereof.
2. A pharmaceutical composition according to claim 1, wherein (i) the angiotensin receptor blocker (ARB) is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731; (ii) the calcium channel blocker (CCB) is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil; and (iii) the diuretic is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide.
3. A pharmaceutical composition according to claim 2, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.
4. A pharmaceutical composition according to claim 3, wherein valsartan is contained in an amount from about 20 to about 640 mg, amlodipine is contained in an amount from about 1 mg to about 60 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 200 mg.
5. A pharmaceutical composition according to claim 4, wherein valsartan is contained in an amount from about 40 to about 320 mg, amlodipine is contained in an amount from

about 2.5 mg to about 10 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 25 mg.

6. A kit of parts comprising
 - (i) a pharmaceutical composition of an angiotensin receptor blocker (ARB),
 - (ii) a pharmaceutical composition of a calcium channel blocker (CCB), and
 - (iii) a pharmaceutical composition of a diureticin the form of two or three separate units of the components (i) to (iii).
7. A kit of parts according to claim 6, wherein (i) the angiotensin receptor blocker (ARB) is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731; (ii) the calcium channel blocker (CCB) is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil; and (iii) the diuretic is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide.
8. A kit of parts according to claim 7, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.
9. A kit of parts according to claim 8, wherein valsartan is contained in an amount from about 20 to about 640 mg, amlodipine is contained in an amount from about 1 mg to about 60 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 200 mg.
10. A kit of parts according to claim 9, wherein valsartan is contained in an amount from about 40 to about 320 mg, amlodipine is contained in an amount from about 2.5 mg to about 10 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 25 mg.

11. A method of treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.
12. A commercial package comprising
- (i) a pharmaceutical composition of an angiotensin receptor blocker (ARB),
 - (ii) a pharmaceutical composition of a calcium channel blocker (CCB), and
 - (iii) a pharmaceutical composition of a diuretic,
- in the form of two or three separate units of the components (i) to (iii),

391

together with instructions for simultaneous, separate or sequential use thereof for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke

13. A commercial package according to claim 12, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.
14. A commercial package according to claim 13, wherein the angiotensin receptor blocker (ARB) (i) and the diuretic (iii) are present in the form of Co-DIOVAN ® or wherein the angiotensin receptor blocker (ARB) (i), the CCB (ii) and the diuretic (iii) are present in the form of Co-DIOVAN ® and Norvasc ®.
15. The use of a combination according to any one of claims 1 to 5, or a kit of parts according to any one of claims 6 to 10, for the manufacture of a medicament for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy,

glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

16. The use of a combination according to any one of claims 1 to 5, or a kit of parts according to any one of claims 6 to 10, for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4184 A61K31/19 C07D401/12 A61K31/44 A61K31/196

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 100 04 651 A (DIERKES JUTTA ; LULEY CLAUS (DE); WESTPHAL SABINE (DE)) 16 August 2001 (2001-08-16) claim 1 table 1	1-3,6-8, 11-13, 15,16
X	DE 198 20 151 A (HEXAL AG) 11 November 1999 (1999-11-11) claims 1,5-7 page 1, line 12 - line 15 -/--	1,2,6,7, 11,12, 15,16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 August 2003

Date of mailing of the international search report

01/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Beranová, P

42

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MACGREGOR G A ET AL: "THE EFFICACY OF CANDESARTAN: AN ANGIOTENSIN II TYPE I RECEPTOR ANTAGONIST ALONE OR IN COMBINATION WITH AMLODIPINE OR IN COMBINATION WITH AMLODIPINE AND HYDROCHLOROTHIAZIDE IN PATIENTS WITH MODERATE-TO-SEVERE ESSENTIAL HYPERTENSION" AMERICAN JOURNAL OF HYPERTENSION, NEW YORK, NY, US, vol. 10, no. 4, PART 2, April 1997 (1997-04), page 112A XP000869500 * abstract *	1,2,6,7, 11,12, 15,16
X	MACGREGOR G A ET AL: "Efficacy of candesartan cilexetil alone or in combination with amlodipine and hydrochlorothiazide in moderate-to-severe hypertension" HYPERTENSION 2000 UNITED STATES, vol. 36, no. 3, 2000, pages 454-460, XP002251650 ISSN: 0194-911X page 455; figure 1 page 457, right-hand column, paragraph 1 * page 459, right-hand column, last paragraph *	1,2,6,7, 11,12, 15,16
X	OPARIL SUZANNE ET AL: "Efficacy and safety of Losartan/Hydrochlorothiazide in patients with severe hypertension." AMERICAN JOURNAL OF CARDIOLOGY, vol. 87, no. 6, 15 March 2001 (2001-03-15), pages 721-726, XP002251651 ISSN: 0002-9149 page 722, left-hand column, paragraph 2 page 726, right-hand column, paragraph 1	1,2,6,7, 11,12, 15,16
X	WO 92 20342 A (DU PONT) 26 November 1992 (1992-11-26) claims 1,6 page 5, line 28 -page 6, line 17	1,6,11, 12,15,16
X	US 5 656 650 A (WEINSTOCK JOSEPH) 12 August 1997 (1997-08-12) claims 1,4,17	1,6,11, 12,15,16

	---/---	

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OPARIL SUZANNE ET AL: "Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension." CLINICAL THERAPEUTICS, vol. 18, no. 4, 1996, pages 608-625, XP002251652 ISSN: 0149-2918 page 618, right-hand column, paragraph 2	1-16
Y	OHNISHI K ET AL: "Influence of the angiotensin II receptor antagonist losartan on diuretic-induced metabolic effects in elderly hypertensive patients: Comparison with a calcium channel blocker." INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 39, no. 10, October 2001 (2001-10), pages 417-422, XP008020851 ISSN: 0946-1965 * page 417, abstract * * page 418, Study design * * page 421, left-hand column, Discussion *	1-16

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 6, 12, 15 and 16 relate to compounds defined by reference to a desirable characteristic or property, namely "angiotensin receptor blocker", "calcium channel blocker" and "diuretic". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely Examples and the combination of valsartan, amlodipine and hydrochlorothiazide, as described on page 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 10004651	A	16-08-2001	DE 10004651 A1	16-08-2001
			AU 7285800 A	14-08-2001
			WO 0156609 A1	09-08-2001
DE 19820151	A	11-11-1999	DE 19820151 A1	11-11-1999
			AU 760550 B2	15-05-2003
			AU 3931199 A	23-11-1999
			BR 9910201 A	09-01-2001
			CA 2331414 A1	11-11-1999
			WO 9956734 A2	11-11-1999
			EP 1085858 A2	28-03-2001
			JP 2002513753 T	14-05-2002
WO 9220342	A	26-11-1992	AU 664375 B2	16-11-1995
			AU 2026992 A	30-12-1992
			CA 2103276 A1	16-11-1992
			CZ 9302351 A3	16-03-1994
			EP 0584250 A1	02-03-1994
			IE 921534 A1	18-11-1992
			IL 101858 A	04-08-1996
			JP 2930252 B2	03-08-1999
			JP 6508128 T	14-09-1994
			KR 222627 B1	01-10-1999
			MX 9202243 A1	01-11-1992
			NZ 242724 A	27-09-1994
			WO 9220342 A1	26-11-1992
			US 5492904 A	20-02-1996
			ZA 9203557 A	15-11-1993
US 5656650	A	12-08-1997	AT 177634 T	15-04-1999
			AU 656551 B2	09-02-1995
			AU 9178291 A	08-07-1992
			CA 2098176 A1	14-06-1992
			DE 69131021 D1	22-04-1999
			DE 69131021 T2	12-08-1999
			DK 565634 T3	27-09-1999
			EP 0565634 A1	20-10-1993
			ES 2130170 T3	01-07-1999
			GR 3030293 T3	30-09-1999
			HK 1012209 A1	12-05-2000
			JP 3398379 B2	21-04-2003
			JP 6503834 T	28-04-1994
			KR 222252 B1	01-10-1999
			WO 9210097 A1	25-06-1992