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Fecha 2015-09-17 16:17:35 Dep. 2020 DIR.NUEVASCR
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Act 412 REPOSPRESRECU Folios 54**Clarke, Modet & C^{va}**

COLOMBIA

P-3978

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

Re: Expediente No. 13.238.680
Solicitud de patente a nombre de **BORYUNG PHARMACEUTICAL CO., LTD.**

Yo, CAROLINA DAZA MONTALVO identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 6, obrando como apoderada sustituta de acuerdo con la sustitución adjunta de la sociedad **BORYUNG PHARMACEUTICAL CO., LTD.**, domiciliada en Seúl, Korea, solicitante de la patente de la referencia, interpongo recurso de reposición contra la resolución No. 38798 emitida el 30 de julio de 2015, expedida por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente para la solicitud contenida en el expediente de la referencia.

1. FUNDAMENTOS DEL RECURSO

En relación con los argumentos presentados por ese despacho en la resolución impugnada No. 38798 emitida el 30 de julio de 2015, es necesario señalar que carecen de un enfoque adecuado de conformidad con las normas, jurisprudencia y reglas técnicas que existen para evaluar la altura inventiva de una invención.

1.1 Violación de los artículos 14 y 18 de la Decisión 486 por una indebida aplicación de la norma basada en un error de interpretación de la misma.

El señor examinador indicó en la resolución No. 38798 que las reivindicaciones presentadas carecen de altura inventiva, en vista de los documentos D1 (WO 2007001066), D2 (WO 9955681) y D3 (WO 03024956).

Ahora bien, como se evidenciará más adelante, es deseo de la Solicitante presentar argumentos contra las declaraciones de ese Despacho indicando como primera medida que el examinador no realizó una adecuada interpretación del artículo 18 de la Decisión 486 y parte de premisas erradas, en cuanto a la supuesta igualdad o equivalencia entre la materia objeto de la presente invención y el estado de la técnica, y realiza un equivocado análisis del requisito en cuestión, para finalmente negar sin justificación la patente para la solicitud en comento.

Así las cosas, volvemos sobre el particular que el artículo 18 de la Decisión 486 establece que *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*.

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Sobre este particular, es necesario hacer énfasis sobre el hecho que el análisis de nivel inventivo **NO** es una comparación de los objetos de las anterioridades y la solicitud en estudio.

De hecho, el análisis de nivel inventivo debe ir más allá y tiene que demostrar la obviedad de la invención y establecer cómo la misma no contiene un salto cualitativo que demuestre su altura inventiva y que hubiese sido obvia para una persona versada en la materia.

En relación con lo anterior, atentamente nos permitimos decir que la Solicitante está en desacuerdo y es deseo de la Solicitante presentar argumentos en contra de estas declaraciones, con el fin de demostrar que la invención reclamada en la presente solicitud posee características técnicas que implicaron un paso inventivo durante su desarrollo.

(1) D1-D3 no enseña o sugiere el efecto sinérgico de la sal de potasio de fimasartan o hidrato de la misma y Besilato de amlodipina.

Respecto a lo señalado por el señor examinador en la resolución que se impugna en donde el efecto antihipertensivo superior de la presente invención es predecible de las enseñanzas de D1 y D2 o D1 y D3 porque D2 enseña que el fimasartan es 50 veces más activo que los bloqueadores del receptor de angiotensina II conocidos previamente, la Solicitante desea manifestar que, como lo indicó el señor examinador, una persona versada en la materia puede esperar que el efecto antihipertensivo de la combinación de sal de potasio de fimasartan o hidrato del mismo y besilato de amlodipina sea mayor que el de la combinación de otros bloqueadores del receptor de angiotensina II y besilato de amlodipina basados en la enseñanza de D2.

Sin embargo, **D1 y D2 o D1 y D3 solamente sugieren el efecto antihipertensivo aditivo de la sal de potasio de fimasartan o hidrato del mismo y besilato de amlodipina que es mayor que otras combinaciones. Ninguno de D1-D3 enseña o sugiere que la sal de potasio de fimasartan o hidrato del mismo y besilato de amlodipina trabajen sinérgicamente para reducir la presión arterial.**

Como se presenta en la Tabla 1 del capítulo descriptivo, las composiciones de la presente invención (Ejemplos 1 y 2), exhiben un efecto antihipertensivo (-55 y -75, respectivamente) **mayor que una suma simple** de los efectos antihipertensivos obtenidos cuando cada ingrediente se administró solo (Ejemplos comparativos 1, 2, 5 y 6). Esto se resume en la siguiente Tabla:

Ejemplo comparativo 1 (Fimasartan 3 mg/kg)	Ejemplo comparativo 5 (Amlodipina 0.5 mg/kg)	Suma simple del efecto antihipertensivo de los ejemplos comparativos 1 & 5	Ejemplo 1 (Fimasartan 3 mg/kg + Amlodipina 0.5 mg/kg)
-35	-13	-48	-55
Ejemplo comparativo 2 (Fimasartan 10 mg/kg)	Ejemplo comparativo 6 (Amlodipina 1.6 mg/kg)	Suma simple del efecto antihipertensivo de los ejemplos comparativos 2 & 6	Ejemplo 2 (Fimasartan 10 mg/kg + Amlodipina 1.6 mg/kg)
-50	-20	-70	-75

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Dicho efecto antihipertensivo sinérgico conseguido por las combinaciones reclamadas permite alcanzar un tratamiento efectivo aunque la administración de dosis sea más baja de lo requerido cuando cada componente se administra por separado. Las dosis más bajas pueden reducir los efectos secundarios adversos asociados con dosis más altas de los componentes individuales.

Por el contrario, la combinación de otros bloqueadores de los receptores de angiotensina II y besilato de amlodipina con frecuencia no muestra tal efecto antihipertensivo sinérgico. El capítulo descriptivo demuestra que, las composiciones que contienen Amlodipina en combinación con el bloqueador de la angiotensina II diferente a Fimasartan exhiben un valor antihipertensivo menor que el de una simple suma de los efectos antihipertensivos de los ingredientes individuales.

La Tabla 1 de la presente solicitud proporciona datos sobre las composiciones que contienen losartan potásico (Ejemplo comparativo 3) y valsartan (Ejemplo comparativo 4) y combinaciones de estos antagonistas de los receptores de la angiotensina II con amlodipina (Ejemplos comparativos 7 y 8). Los datos se muestran a continuación:

Ejemplo comparativo 3 (sal de potasio de losartan 10 mg/kg)	Ejemplo comparativo 6 (Amlodipina 1.6 mg/kg)	Suma simple del efecto antihipertensivo de los ejemplos comparativos 3 & 6	Ejemplo comparativo 7 (sal de potasio de losartan 10 mg/kg + Amlodipina 1.6 mg/kg)
-20	-20	-40	-32
Ejemplo comparativo 4 (valsartan 10 mg/kg)	Ejemplo comparativo 6 (Amlodipina 1.6 mg/kg)	Suma simple del efecto antihipertensivo de los ejemplos comparativos 4 & 6	Ejemplo 8 (valsartan 10 mg/kg + Amlodipina 1.6 mg/kg)
-32	-20	-52	-46

Como se muestra en la tabla anterior, las composiciones que comprenden losartan y amlodipina (Ejemplo comparativo 7) o combinación de valsartan y amlodipina (Ejemplo comparativo 8) **no presentan ningún efecto antihipertensivo sinérgico**. En lugar de ello, cada una de las combinaciones exhibe un efecto antihipertensivo que es menor que el que se consigue mediante la administración de los ingredientes individuales.

(2) Es muy difícil encontrar fármacos que actúan de forma sinérgica

Es bien conocido en el campo que una combinación de medicamentos del mismo tipo no siempre conduce a un efecto sinérgico y, a menudo da lugar a efectos secundarios negativos.

Por ejemplo, un β -bloqueador como atenolol es un fármaco antihipertensivo. Sin embargo, una combinación de un β -bloqueador y un bloqueador de angiotensina II no da lugar a un efecto anti-hipertensivo consistente e incluso provoca una complicación mediante el aumento de la frecuencia de la constricción bronquial.

Además, un diurético se utiliza a menudo para tratar la hipertensión, solo o con un bloqueador del receptor de la angiotensina II. Sin embargo, entre los diuréticos, se ha reportado la combinación de un diurético ahorrador de potasio como la espironolactona y un bloqueador del receptor de angiotensina II para causar hipercalemia.

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Otro ejemplo es, el inhibidor de la Enzima Convertidora de la Angiotensina (denominado en lo sucesivo inhibidor de la ACE) es un fármaco antihipertensivo bien conocido. Una combinación de un inhibidor de la ACE y un bloqueador del receptor de la angiotensina II se utiliza comúnmente para tratar la hipertensión. Sin embargo, no todas las combinaciones se pueden utilizar. Yusuf S. et al. informó que la combinación de telmisartán (un bloqueador del receptor de angiotensina II) y ramipril (un inhibidor de la ACE) causó un aumento del riesgo de síntomas de hipotensión, síncope, y disfunción renal como se presenta a continuación:

Telmisartan, ramipril, or both in patients at high risk for vascular events.

ONTARGET Investigators Yusuf S, Ten KK, Poque J, Ovali L, Copland I, Schumacher H, Danesais G, Sleight P, Anderson C

Collaborators (369)

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada. yusufs@mcmaster.ca

Abstract

BACKGROUND: In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting-enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. We compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes.

METHODS: After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

RESULTS: Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, $P < 0.001$) and angioedema (0.1% vs. 0.3%, $P = 0.01$) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, $P < 0.001$); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, $P < 0.001$), syncope (0.3% vs. 0.2%, $P = 0.03$), and renal dysfunction (13.5% vs. 10.2%, $P < 0.001$).

CONCLUSIONS: Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit. (ClinicalTrials.gov number, NCT00153101 [ClinicalTrials.gov].)

(telmisartan, ramipril, or both in patients at high risk for vascular events. (N Engl J Med. 2008 Apr 10;358(15):154/-59. doi: 10.1056/NEJMoa0801317. Epub 2008 Mar 31.)

Teniendo en cuenta lo anterior, es obvio que la combinación de dos fármacos que interactúan de forma sinérgica y no causen ningún efecto secundario es muy duro. Por lo tanto, el efecto sinérgico de la sal de potasio de fimasartan o hidrato del mismo y besilato de amlodipina no se puede esperar de la divulgación de D1-D3.

Con base en el análisis anterior, ni D1 ni D2 ni D3, ya sea solos o en combinación, enseñan o sugieren la presente invención, toda vez que estos documentos fallan en enseñar todas las características esenciales de la invención, y la manera como se solucionó el problema técnico en cuestión. Por lo tanto, se le solicita respetuosamente al examinador retire la objeción de nivel inventivo.

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Finalmente, es deseo de la Solicitante informar, sin apartarse del principio de independencia entre oficinas de Patentes en el mundo, que la presente invención ha sido concedida en las oficinas de Japón con el número de patente 5782178 (2015.07.04), Estados Unidos de América con el número de patente US 8,765,776 B2 (2014.07.01), Australia con el número de patente 2011365756 (2015.07.30), Marruecos con el número de patente 35107 (2015.05.02), Canadá, Ucrania, Vietnam con el número de patente VN 13960 B1 (2015.04.06), República de Corea con el número de patente KR 10-1168136 B1 (2012.07.17) los cuales se adjuntan a este memorial.

En este sentido, respetuosamente nos permitimos decir que consideramos que el señor examinador ha hecho un análisis no permitido para la evaluación del nivel inventivo, por lo que se ha incumplido con los artículos 14 y 18 de la decisión 486 de la Comunidad Andina de Naciones, por lo que procede la reposición del presente trámite.

2. Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

a) Que de conformidad con lo previsto por los artículos 3, 42 y 80 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de este recurso.

b) Que se declare infundada la oposición presentada por Laboratorio Franco Colombiano, Lafrancol S.A.S.

c) Que se revoque la resolución No. 38798 emitida el 30 de julio de 2015, expedida por el Superintendente de Industria y Comercio y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante.

Señor Superintendente,


CAROLINA DAZA MONTALVO
C.C. 66.783.790 de Palmira Valle
TP-141563 CSJ
notificaciones@clarkemodet.com.co

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

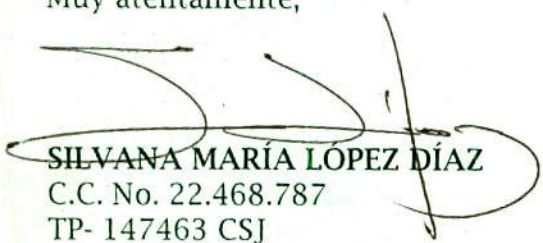
Re: Expediente No. 13.238.680

Solicitud de patente a nombre de BORYUNG PHARMACEUTICAL CO., LTD.

RECURSO DE REPOSICIÓN

Yo, SILVANA MARÍA LÓPEZ DÍAZ, identificada como aparece al pie de mi firma, domiciliada en Bogotá, atentamente informo a usted que sustituyo el poder con que obro, a la doctora CAROLINA DAZA MONTALVO, domiciliada en Bogotá, identificada con la Cédula de Ciudadanía No.66.783.790 de Palmira Valle y portadora de la tarjeta profesional No.TP-141563 del CSJ, con las mismas facultades que me fueron conferidas para este caso.

Muy atentamente,

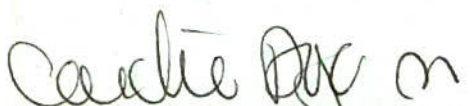


SILVANA MARÍA LÓPEZ DÍAZ

C.C. No. 22.468.787

TP- 147463 CSJ

Acepto sustitución



CAROLINA DAZA MONTALVO

C.C. 66.783.790 de Palmira Valle

TP-141563 CSJ



PRESENTACION PERSONAL

NOTARIA 11

El anterior escrito fue presentado ante el
NOTARIO ONCE (E) DEL CIRCULO DE BOGOTA D.C.

Personalmente por: Silvana Rion

LOPEZ DIAZ

quien exhibio la C.C. 22 468787 de BAJO

y Tarjeta Profesional No. 187463

Fecha:

Firma:

[Handwritten signature]



Mauricio Mora Tejada
NOTARIO (E)

26 JUN 2015



Clarke, Modet & Cº

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ANEXOS

- Certificado de Patente de Japón
- Patente de invención KR 10-1168136 B1
 - Decisión de concesión de Canadá
 - Decisión de concesión de Ucrania
- Documento que demuestra la concesión en Marruecos
 - Patente de invención US 8,765,776 B2
 - Patente de invención VN 13960 B1

特 許 証

(CERTIFICATE OF PATENT)

特許第5782178号

(PATENT NUMBER)

発明の名称
(TITLE OF THE INVENTION)

血圧降下用薬学的組成物

特許権者
(PATENTEE)

大韓民国、110-450 ソウル、 チョン
グローク、ウォンナムードン、 66-21
国籍 大韓民国
ボリョン ファーマスーティカル カ
ンパニー リミテッド

発明者
(INVENTOR)

キム、スン ホ
キム、ジ ハン
ユ、キュン サン

出願番号
(APPLICATION NUMBER)

特願2014-505053

その他別紙記載

出願日
(FILING DATE)

平成23年 8月 8日(August 8, 2011)

登録日
(REGISTRATION DATE)

平成27年 7月24日(July 24, 2015)

この発明は、特許するものと確定し、特許原簿に登録されたことを証する。
(THIS IS TO CERTIFY THAT THE PATENT IS REGISTERED ON THE REGISTER OF THE JAPAN PATENT OFFICE.)

平成27年 7月24日(July 24, 2015)

特許庁長官
(COMMISSIONER, JAPAN PATENT OFFICE)

伊藤 仁



特 許 証

(CERTIFICATE OF PATENT)

(続葉 1)

特許第 5 7 8 2 1 7 8 号 (PATENT NUMBER)

特願 2 0 1 4 - 5 0 5 0 5 3 (APPLICATION NUMBER)

発明者
(INVENTOR)

チャン、イン ジン
シン、サン グ
ユン、ソ ヒョン
チョ、ジュ ヨン
キム、テ ウン
イ、ソ チョン
ペク、ス ヒ
チ、ヨン ハ
リ、ジュ ハン
ナム、キュン ワン
キム、チェ ハク

[以下余白]

特許証送付先

住 所

〒541-0044

大阪府大阪市中央区伏見町四丁目1番1号
明治安田生命大阪御堂筋ビル 高島国際特許
事務所

氏 名

高島 一

様

特許権設定登録通知書

特許番号 第5782178号
登録日 平成27年 7月24日
出願番号 特願2014-505053
出願日 平成23年 8月 8日
請求項の数 14
納付年分 第 3年分まで
受領金額 15,300円
受領日 平成27年 7月16日

重 要 特許料の納付について

- ・特許権を維持するには、存続期間の満了（特許出願の日から20年）までの各年について所定の特許料の納付が必要です。
なお、第4年分以降の納付に関しては、特許庁から納付についての通知は送付いたしませんので、納付期限の管理はご自身でお願いします。

この通知を保管し、右側の特許料納付期限日の表で納付期限を確認してください。（自動納付制度もありますので、特許庁ホームページを参照してください。）

- ・第4年以降の各年分の特許料は、登録日の翌日を起算日として、納付済年分の満了日（以下「納付期限日」という）までに、次の年分の納付が必要です。
- ・納付期限日までに納付できなかったときは、その期間の経過後6ヶ月以内であれば特許料を追納することができます。
- ・追納する場合は、納付すべき特許料のほか、その特許料と同額の割増特許料が必要です。
- ・追納できる期間内に納付しないときは、その特許権は、納付期限日にさかのぼって消滅したものとみなされます。
- ・特許料納付書の様式及び特許料の額については、以下を参照してください。

特許庁ホームページ

<http://www.jpo.go.jp/index.j.htm>

特許料納付期限日

納付年分	納付期限日
第 4 年分	平成30年 7月24日
第 5 年分	平成31年 7月24日
第 6 年分	平成32年 7月24日
第 7 年分	平成33年 7月24日
第 8 年分	平成34年 7月24日
第 9 年分	平成35年 7月24日
第10年分	平成36年 7月24日
第11年分	平成37年 7月24日
第12年分	平成38年 7月24日
第13年分	平成39年 7月24日
第14年分	平成40年 7月24日
第15年分	平成41年 7月24日
第16年分	平成42年 7月24日
第17年分	平成43年 7月24日

（注）納付期限日が行政機関の休日にあたるときは、その日の翌日が期間の末日となります。

問い合わせ先 審査業務課登録室
電話 03(3581)1101（代表）
特許担当 内線 2708

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	(19) 대한민국특허청(KR) (12) 등록특허공보(B1)	(45) 공고일자 2012년07월24일 (11) 등록번호 10-1168136 (24) 등록일자 2012년07월17일
(51) 국제특허분류(Int. Cl.) A61K 31/505 (2006.01) A61K 31/41 (2006.01) A61P 9/12 (2006.01) A61P 9/00 (2006.01) (21) 출원번호 10-2011-0078417 (22) 출원일자 2011년08월08일 심사청구일자 2011년08월08일 (56) 선행기술조사문헌 KR1020100048137 A* *는 심사관에 의하여 인용된 문헌		(73) 특허권자 보령제약 주식회사 서울특별시 종로구 창경궁로 136 (원남동) (72) 발명자 김승호 서울특별시 용산구 이태원로27다길 35, 외인주택 2호 (이태원동) 김지한 서울특별시 영등포구 대림로7길 9-1 (대림동) (뒷면에 계속) (74) 대리인 안소영
전체 청구항 수 : 총 5 항		심사관 : 이수정

(54) 발명의 명칭 혈압 강하용 약제학적 조성물

(57) 요약

본 발명은 안지오텐신-2-수용체 차단제로서 피다살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물을 포함하는 혈압 강하용 약제학적 조성물을 제공한다.

11

(72) 발명자

김제학

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특허청구의 범위

청구항 1

안지오텐신-2-수용체 차단제로서 피마살탄 칼륨염 또는 이의 수화물 30 mg 및
칼슘 채널 차단제로서 아로디핀 베실레이트염 5 mg 을 포함하는 혈압 강하용 약제학적 조성물.

청구항 2

삭제

청구항 3

삭제

청구항 4

제1항에 있어서, 안지오텐신-2-수용체 차단제가 피마살탄 삼수물 칼륨염인 혈압 강하용 약제학적 조성물.

청구항 5

삭제

청구항 6

삭제

청구항 7

삭제

청구항 8

삭제

청구항 9

삭제

청구항 10

삭제

청구항 11

삭제

청구항 12

제1항에 있어서, 약제학적 조성물이 경구투여 제형인 혈압 강하용 약제학적 조성물.

청구항 13

제12항에 있어서, 제형이 단일정제인 혈압 강하용 약제학적 조성물.

청구항 14

안지오텐신-2-수용체 차단제로서 피마살탄 칼륨염 또는 이의 수화물 30 mg 및
칼슘 채널 차단제로서 아로디핀 베실레이트염 5 mg 을 포함하는,
고혈압의 예방, 완화 또는 치료용 약제학적 조성물.

청구항 15

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삭제

명세서

기술분야

[0001] 본 발명은 혈압 강하용 약제학적 조성물에 관한 것이다.

배경기술

[0002] 고혈압은 가장 일반적인 심혈관계 질환의 하나로서, 통상 혈압이 140/90mmHg인 경우 고혈압으로 진단된다. 최근 들어, 고혈압 등 성인병 환자가 급격히 증가하고 있으며, 고혈압에 의해 급성 심장병 또는 심근 경색 등을 초래할 수 있으므로 보다 효과적인 고혈압 치료제의 개발이 계속적으로 요구되고 있다.

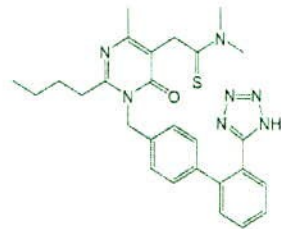
[0003] 고혈압 치료제의 다수 임상시험에서 고혈압 환자의 혈압을 저하시키는 것이 심장병 또는 심근경색증의 치사율 및 이환율을 감소시키는 것으로 나타났다(Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38). 이러한 의학적 상태를 치료하기 위해서 다양한 종류의 약물을 사용하고 이를 응용하여 투여하는 것에도 불구하고, 혈압이 적절한 조절이 항상 이루어지지 않고 있다(Waeber B, Brunner HR, Am. J. Hypertens 1997, 10(7 Pt 2):131S-137S).

[0004] 항고혈압제 약물의 여러 가지 응용된 투여 형태 중, 약물의 조합제제 또는 병용요법을 사용하는 것은 목적하는 치료학적 성과에 도달하기 위한 한 가지 방법이다. 한편, 병용요법 처방에 포함시키기 위해서 다양한 부류의 항고혈압제를 임의로 선택하는 것이 인간을 비롯한 고혈압 포유동물에게 목적하는 혈압 수치에 도달하는 것을 반드시 도와주는 것은 아니다(MacGregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Br Med J (Clin Res Ed). 284 (6317): 693-6).

[0005] 따라서, 치료의 방법, 조합제제 및 약제학적 조성물을 더 개발할 필요성이 명백히 존재한다.

[0006] 피마살탄(Fimasartan)은 2-n-부틸-5-디메틸아미노티오펜일메틸-6-메틸-3-[[2'-(1H-테트라졸-5-일)비페닐-4-일]메틸]피리미딘-4(3H)-온(2-n-Butyl-5-dimethylaminothiobenzylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one)으로, 하기 구조식을 가지며, 안지오텐신-2-수용체 차단제(Angiotensin II Receptor Blocker,ARB) 계열의 혈압 강하제로 현재 카나브(KANARB)명으로 의약품 허가가 승인되었다.

[0007] [피마살탄]



[0008]

[0009] 경?중증도의 본태성 고혈압 환자에서 피마살탄 칼륨 60mg 내지 120mg의 혈압 강하 효과를 ARB 계열의 대표적 화합물인 로사탄(Losartan)과 비교하기 위해 무작위배정, 양측눈가림 임상시험을 실시한 결과, 12주 시점의 좌위 DBP변화량이 기저치(baseline) 대비 피마살탄 군에서는 -11.26 ± 7.53 mm Hg이, 로사탄 군에서는 -8.56 ± 7.72 mmHg의 혈압강하 효과가 나타나는 등 12 또는 24주 투여 후의 혈압강하 효과가 로사탄에 비해 우월한 것이 확인되었다(A Randomized, Double-blind, Losartan-controlled, Parallel Group Comparison Dose Titration Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Fimasartan (BR-A-657?K) 60mg ~ 120mg in Patients with Mild to Moderate Essential Hypertension (Phase III)).

[0010] 아로디핀(Amlodipine)은 칼슘채널차단제(Calcium Channel Blocker, CCB)로서 칼슘이온이 심장 및 말초혈관 평활근의 세포막으로 유입되는 것을 차단하여, 혈관평활근을 직접 이완시켜 항고혈압 작용효과를 나타낸다. 아로디핀의 협심증을 완화시키는 정확한 작용기전은 완전하게 확립되어 있지는 않으나 다음과 같은 2가지 작용기전에 의해 전제 허혈성 증상을 감소시켜 주는 역할을 하는 것으로 밝혀졌다.

[0011] 첫 번째로, 아로디핀은 말초동맥을 확장시켜 총말초혈관 저항(후부하)을 감소시킴으로써 심장에 대한 부담을

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떨어주고, 심박수를 안정화시켜 심근의 에너지 소모량 및 산소요구량을 감소시킨다.

- [0012] 두 번째로, 암로디핀은 허혈부위와 정상부위의 주관상동맥 및 그 밖의 관상세동맥을 확장시키는 것으로 추측된다. 이러한 혈관 확장은 관상동맥 경련이 있는 환자의 심근허혈부위에 산소운반을 증가시켜 주는 역할을 한다.
- [0013] 최근 고혈압 치료를 위해 칼슘채널차단제인 암로디핀과 ARB계열의 화합물과의 복합제가 활발히 연구되고 있으나, 이러한 복합제는 경우에 따라 두 약물간의 상호작용 유발과 각 약물의 부작용을 증가시키는 부수적인 문제점을 초래하기도 한다.
- [0014] 이에, 본 발명자들은 암로디핀과 ARB계열 화합물의 단순한 약물복합제의 문제점을 인식하고 이를 해결하기 위하여 연구한 결과 본 발명을 완성하였다.

선행기술문헌

특허문헌

- [0015] (특허문헌 0001) [문헌 1] KR1989-0011854 1989.08.22., All pages
(특허문헌 0002) [문헌 2] WO00/16773 1999.09.08., All pages
(특허문헌 0003) [문헌 3] KR2001-0013626 2001.02.26., All pages
(특허문헌 0004) [문헌 4] KR2001-0079517 2001.08.22., All pages
(특허문헌 0005) [문헌 5] KR2001-0090193 2001.10.18., All pages
(특허문헌 0006) [문헌 6] KR2004-0032639 2004.04.17., All pages
(특허문헌 0007) [문헌 7] KR2010-0048137 2010.05.11., All pages

비특허문헌

- [0016] (비특허문헌 0001) [문헌 8] Yoo SD et.al., Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry. Biomed Chromatogr. 2011 Jan 26; doi:10.1002/bmc. 1592. Epub ahead of print (검색일:2011.07.28)
(비특허문헌 0002) [문헌 9] Yu KS, et.al., Effect of multiple doses of fimasartan, an angiotensin II receptor antagonist, on the steady-state pharmacokinetics of digoxin in healthy volunteers. Int J Clin Pharmacol Ther. 2011 May;49(5):321-7
(비특허문헌 0003) [문헌 10] Yu KS et.al., The Effect of the Newly Developed Angiotensin Receptor II Antagonist Fimasartan on the Pharmacokinetics of Atorvastatin in relation to OATP1B1 in Healthy Male Volunteers. J Cardiovasc Pharmacol. 2011 Jul 14. Epub ahead of print (검색일:2011.07.28)

발명의 내용

해결하려는 과제

- [0017] 본 발명의 목적은 고혈압 예방, 완화 및 치료뿐만 아니라, 고혈압 및/또는 고지혈증에 기인한 합병증의 예방, 완화 또는 치료에 효과적인 혈압강하용 약제학적 조성물을 제공하는데 있다.

과제의 해결 수단

- [0018] 본 발명은 안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물을 포함하는 혈압 강하용 약제학적 조성물을 제공한다.

- [0019] 본 발명에서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물은 결정형이거나 무정형일 수 있으며, 본 발명은 이들의 결정형 및/또는 무정형을 포함한다.
- [0020] 본 발명에서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물은 결정형이거나 무정형일 수 있으며, 본 발명은 이들의 결정형 및/또는 무정형을 포함한다.
- [0021] 본 발명에서, 약제학적으로 허용되는 염은 통상적으로 의학 제조회사가 의약품 제조하는데 사용하는 무기산 염, 유기산염, 금속염을 의미하며, "무기산"으로는 염산, 브롬산, 황산, 인산 등을 사용할 수 있고, "유기산"으로는 구연산, 초산, 젖산, 주석산, 푸마르산, 포름산, 프로피온산, 옥살산, 트리플루오로아세트산, 메탄술폰산, 벤젠술폰산, 말레인산, 벤조산, 글루콘산, 글리콜산, 숙신산, 4-모폴린에탄술폰산, 캠프술폰산, 4-니트로벤젠술폰산, 히드록시-0-술폰산, 4-톨루엔술폰산, 칼복투론산, 엠보산, 글루탐산, 아스파르트산, 아디페이트염, 캄실레이트염 또는 베실레이트염 등을 사용할 수 있으며, "금속"에는 나트륨, 칼륨, 칼슘, 마그네슘, 등이 있다.
- [0022] 본 발명에서, 안지오텐신-2-수용체 차단제가 피마살탄 칼륨염, 염산염, 칼슘염, 황산염, 아디페이트염, 캄실레이트염 또는 베실레이트염인 것이 바람직하며, 피마살탄 칼륨염 또는 피마살탄 삼수물 칼륨염이 보다 더 바람직하다. 이들은 시중에서 구입할 수 있으며, 공지된 방법으로 제조할 수 있다(예를 들어, 대한민국 특허등록번호 제0354654호 및 제0521980호 등).
- [0023] 본 발명에서, 칼슘 채널 차단제가 암로디핀 베실레이트염, 황산염, 캄실레이트염, 염산염, 칼륨염, 칼슘염 또는 아디페이트염인 것이 바람직하며, 암로디핀 베실레이트염이 보다 더 바람직하고, 이들은 시중에서 구입할 수 있으며, 공지된 방법으로 제조할 수 있다(예를 들어, 미국특허등록번호 제4572909).
- [0024] 본 발명에서, "용매화물" 중 용매는 유기화합물 제조에 사용되는 통상의 유기용매를 의미하며, 예를 들어, 메탄올, 에탄올, 1-프로판올, 2-프로판올, 1-부탄올, 2-부탄올, 1-아세테이트, 아세톤, 초산, 아니솔, 테트라히드로푸란, 메틸아세테이트, 에틸아세테이트, 프로필아세테이트, 이소프로필아세테이트, 이소부틸아세테이트, n-부틸아세테이트, 디메틸설폭사이드, 펜탄, 헵탄 등이 있으나, 이들의 예로 본 발명의 용매화물이 제한되는 것은 아니다.
- [0025] 본 발명에서, "수화물" 및 "용매화물"은 피마살탄 또는 암로디핀의 1몰에 대하여 0.25 내지 10몰비로 함유될 수 있으며, 예를 들어 0.5몰, 1몰, 1.5몰, 2몰, 2.5몰, 3몰, 5몰 등일 수 있으나, 이들의 예로 본 발명이 제한되는 것은 아니다.
- [0026] 본 발명의 조성물은 안지오텐신-2-수용체 차단제를 0.5 내지 240mg을 함유할 수 있으며, 50 내지 180mg 함유하는 것이 바람직하며, 60 내지 120mg 함유하는 것이 보다 더 바람직하다.
- [0027] 또한, 본 발명의 조성물은 칼슘 채널 차단제를 0.1 내지 20mg 함유할 수 있으며, 5 내지 15mg 함유하는 것이 바람직하며, 5 내지 10mg을 함유하는 것이 보다 더 바람직하다.
- [0028] 한편, 약제학적 조성물에 포함된 이들 약물에 대한 상용 고용량(즉, 약제학적으로 허용되는 1회당 높은 투여 용량)은 예를 들어 60kg 정도 체중의 일반 성인을 기준으로 피마살탄은 최대 240mg이하이고 암로디핀은 최대 20mg이하인 것으로 알려져 있다.
- [0029] 본 명세서 전체에서, "약제학적 조성물"이라 함은 명시적인 다른 기재가 없는 한, 한번에 복용 또는 투여되는 정제, 캡슐 또는 주사제와 같은 단일 단위 투여 형태뿐만 아니라, 2회 이상으로 나누어 투여되는 복수의 단위 투여 형태도 포괄하여 지칭할 수 있는 것으로 해석된다. 예를 들어 "안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물을 포함하는 약제학적 조성물"이라 함은 이들 2가지 활성 성분을 함께 포함하는 단일 단위 투여 형태뿐만 아니라, 각각이 하나씩의 활성 성분을 포함하는 두 개의 단위 투여 형태를 함께 지칭할 수도 있는 것으로 해석된다. 즉, 이들 두 개의 단위 투여 형태가 동시 또는 일정 시간 이하의 간격을 두고 투여되어, 이들 단위 투여 형태 각각에 포함된 2가지 활성 성분의 유효량이 체내에서 함께 존재해 상승 작용을 일으키는 경우, 상기 두 개의 단위 투여 형태를 포괄하여 "안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물을 포함하는 약제학적 조성물"의 범주에 속하는 것으로 지칭될 수 있다.
- [0030] 본 발명의 조성물은 투여를 위해서 상기한 성분 이외에 추가로 약제학적으로 허용 가능한 담체를 1종 이상 포

함하여 제조할 수 있다. 약제학적으로 허용 가능한 담체는 식염수, 멸균수, 링거액, 완충 식염수, 텍스트로즈 용액, 말토 덱스트린 용액, 글리세롤, 에탄올 및 이들 성분 중 1 성분 이상을 혼합하여 사용할 수 있으며, 필요에 따라 항산화제, 완충액, 정균제 등 다른 통상의 첨가제를 첨가할 수 있다.

[0031] 또한 회석제, 분산제, 계면활성제, 결합제 및 윤활제를 부가적으로 첨가하여 수용액, 현탁액, 유탁액 등과 같은 주사용 제형, 환약, 캡슐, 과립 또는 정제로 제제화할 수 있다. 더 나아가 당 분야의 적절한 방법으로 또는 Remington's Pharmaceutical Science, Mack Publishing Company, Easton PA에 개시되어 있는 방법을 이용하여 각 질환에 따라 또는 성분에 따라 바람직하게 제제화 할 수 있다.

[0032] 본 발명의 조성물은 목적하는 방법에 따라 경구 투여하거나 비경구 투여(예를 들어 정맥 내, 피하, 복강 내 또는 국소에 적용) 할 수 있으며, 투여량은 환자의 체중, 연령, 성별, 건강상태, 식이, 투여시간, 투여방법, 배설율 및 질환의 중증도 등에 따라 그 범위가 다양하다. 본 발명 조성물은 하루 일회 내지 수회에 나누어 투여할 수 있다.

[0033] 본 발명의 조성물은 수용액, 현탁액, 유탁액 등과 같은 주사용 제형, 환약, 캡슐, 과립 또는 정제, 또는 키트 형태의 경구 투여용 제형일 수 있으며, 경구투여용이 보다 바람직하고, 단일정제인 것이 보다 더 바람직하다.

[0034] 또한, 본 발명의 조성물은 상승된 혈압강하 효과로 인하여, 고혈압, 심부전증, 관동맥심질환, 허혈성 심질환, 허혈성 말초 순환계 질환, 고혈압성 신부전, 뇌졸중 또는 동맥 경화증의 예방, 완화 또는 치료에 사용될 수 있다.

[0035] 따라서, 본 발명은 안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물을 포함하는 고혈압, 심부전증, 관동맥심질환, 허혈성 심질환, 허혈성 말초 순환계 질환, 고혈압성 신부전, 뇌졸중 또는 동맥 경화증의 예방, 완화 또는 치료용 약제학적 조성물을 제공한다.

[0036] 또한, 본 발명은 안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물의 유효량을 포함하는 고혈압, 심부전증, 관동맥심질환, 허혈성 심질환, 허혈성 말초 순환계 질환, 고혈압성 신부전, 뇌졸중 또는 동맥 경화증의 예방, 완화 또는 치료를 요하는 인간을 포함하는 포유류에게 투여함으로써, 상기 질환의 예방, 완화 또는 치료하는 방법을 제공한다.

[0037] 또한, 본 발명은 고혈압, 심부전증, 관동맥심질환, 허혈성 심질환, 허혈성 말초 순환계 질환, 고혈압성 신부전, 뇌졸중 또는 동맥 경화증의 예방, 완화 또는 치료를 위한 약제학적 제조를 위한 안지오텐신-2-수용체 차단제로서 피마살탄, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물; 및 칼슘 채널 차단제로서 암로디핀, 이의 이성질체, 이의 약제학적으로 허용되는 염, 이들의 용매화물 또는 이들의 수화물의 유효량을 포함하는 조성물의 용도를 제공한다.

발명의 효과

[0038] 본 발명의 조성물은 각 활성 성분의 동일 투여량의 혈압 강하 수치의 단순한 합보다 상승된 혈압 강하 효과를 나타낸다. 따라서, 본 발명의 조성물은 각 활성 성분의 사용량보다 낮은 함량 또는 투여량의 사용이 가능하므로, 각 활성 성분의 과용에 따른 부작용을 감소시키면서 보다 효과적으로 고혈압 등을 치료 또는 예방할 수 있다.

발명을 실시하기 위한 구체적인 내용

[0039] 이하, 본 발명의 이해를 돕기 위하여 실시예 및 실험예를 제시한다. 하기의 실시예 및 실험예는 본 발명을 보다 쉽게 이해하기 위하여 제공되는 것일 뿐, 이들에 의해 본 발명의 내용이 한정되는 것은 아니다.

[0040] <실험예> 본 발명의 조성물의 혈압 강하 효과 확인

[0041] 본 연구에서는 본태성 고혈압 쥐에 시험 약물인 피마살탄 삼수물, 칼륨염과 로자탄 칼륨염, 발사르탄, 암로디핀 베실레이트염을 각각 그리고 암로디핀 베실레이트염과의 병용으로 4주간 반복 경구 투여하면서 혈압, 심박수 및 체중변화를 측정하여 각 약물의 장기간 투여에 의한 강압작용을 파악하고 효과적이고 안정적인 혈압 유지 정도를 확인하고, 단일 투여와 복합 투여와의 차이점을 파악하려 하였으며 이를 통하여 각 약물 사이의 강압 작용 정도를 비교, 평가하고자 하였다.

- [0042] (1) 시험 재료 및 방법
- [0043] ① 실험동물
- [0044] Charles River Japan (CRJ)으로부터 수컷 SHR 8주령 (230~250 g)을 공급받아 평균혈압이 160~170 mmHg 이상이 되는 18~19주령 (340~ 380 g)까지 순화기간을 적용한 후 시험에 사용하였다. 시험 전 순화기간을 통해 면밀히 관찰 하여 상태가 양호한 동물을 선정하였으며, 각 시험군당 8마리씩 사용하였으며(n=8) 선정된 동물은 간접 혈압 측정장치(CODA-6)를 이용하여 혈압 상승을 확인한 동물에 한하여 시험군에 적용하였다. 이 때 본시험 적용 전 측정에서 정상 SHR 혈압 범위를 벗어나는 개체(평균혈압으로서 140mmHg 이하 이거나 220mmHg 이상인 측정값을 나타낸 개체)는 시험에서 제외하였다.
- [0045] ② 약물군의 설정 및 투여방법
- [0046] 본시험에서 실험 쥐에 투여되는 약물의 최종 용량은 기초시험 및 예비시험을 거쳐 유의성 있는 강압 효과를 나타낼 수 있는 적절한 용량으로 설정하였다. 예비시험에서 각 약물별로 저, 중, 고 용량을 설정하고 시험 결과 투여 전 고혈압 위의 혈압에서 약물 투여 후 20~50mmHg 정도로 유의성 있게 혈압을 떨어뜨릴 수 있는 용량 (임상 상용량은 20~25%에 해당하는 용량)을 단독투여군의 적정 용량으로 선정하였다. 한편, 복합제 투여군에서는 문헌검토결과 4주 투여에서 독성을 나타내지 않고 안정적인 상태에서 강압작용만 나타낼 수 있을 만한 용량을 설정하였다. 모든 투여 용량은 기 수행된 시험에서 사용한 용량을 참고하였으며 최종 본시험에 사용한 용량 및 약물 투여군은 다음과 같다.
- [0047] ARB 화합물로서 로사탄 칼륨염, 발사르탄 및 피마살탄 삼수물 칼륨염을 각각 Zhejiang Huahai Pharmaceutical로부터 구입하여 사용하였다. 로사탄 칼륨염은 10mg/kg을 L군으로 설정하였으며, 발사르탄 10mg/kg 을 V군으로 설정하였고, 피마살탄 삼수물 칼륨염의 경우 3mg/kg을 F1군으로, 10mg/kg 을 F2군으로 설정하였다.
- [0048] 칼슘 채널 차단제로서 암로디핀 베실레이트염 (자체 합성, 미합중국특허등록번호 제4572909)을 사용하였으며, 암로디핀 베실레이트염 0.5 mg/kg 을 A1 군으로 설정하였고, 1.6 mg/kg 용량을 A2군으로 설정하였다. 시험물 질과 비교약물은 모두 0.5% CMC-Na(carboxymethylcellulose sodium salt; Sigma)로 현탁하여 사용하였으며 대조군의 경우 0.5% CMC 만 투여하였다.
- [0049] ③ 시험방법
- [0050] - 투여: 투여 시에는 조제물을 중탕하여 온도를 35℃로 적정하게 맞춘 후, 5 mL/kg의 용량으로 위зон테를 사용하여 강제 경구투여 하였다.
- [0051] - 혈압측정: 랫트의 혈압은 랫트를 고정하여 가온 장치 내에서 40℃ 정도(고정틀 내의 온도 37℃ 기준)의 온도로 13분간 가온함으로써 꼬리 혈관을 노장시키고, 꼬리에 연결한 한 쌍의 cuff 를 통해 본체의 software로 혈압을 측정하는 CODA-6 장비를 사용하였다. CODA-6 (Kent Scientific Corporation)를 통한 간접혈압측정법은 기존에 사용하던 physiograph, power lab과 같은 동맥 cannulation을 통한 직접혈압측정방법으로는 수행할 수 없는 반복 투여를 수행 하여야 하는 장기간 혈압측정 시험을 가능하게 하였다. 측정은 4주 반복 투여에 의한 약물의 투여 용량에 따른 소실폐턴과 본래 혈압으로의 회복 정도를 확인하기 위하여 최종 투여 종료 후 일주일 동안 매일 1회 혈압을 측정하였다.
- [0052] 혈압 변화 양상은 평균혈압 (MAP) 변화를 중심으로 확인하였으며 이 완기, 수축기 혈압과 심박수, 체중변화 등의 양상을 기타 변화로 시험결과에 참고하였다.
- [0053] (2) 결과 처리 및 통계 분석
- [0054] 본 실험에서 얻은 측정치의 통계학적 분석은 통계처리 프로그램인 SPSS 를 이용하여 one-way ANOVA에서 유의한 F 값이 관찰되는 항목에 대하여 대조군과 용량군 사이의 유의수준 $p < 0.001$, 0.01, 0.05 범위로 비교하였다.
- [0055] 4주 반복투여 효력시험에서 대조군을 포함한 모든 군에서 체중 증가는 비약하게 나타났다. 시험 초기에는 오히려 감소하는 경향을 보였으나, 시험 중반 이후 체중의 유지를 확인하였다. 이는 약물에 의한 직접적인 영향이라기 보다는 간접 혈압 측정 과정에서 가온과 고정 등의 스트레스가 수반되어 나타나는 증상으로 사료되었다.
- [0056] 측정 결과 산출된 각 약물 투여군의 투여 약물의 종류 및 약물 용량 및 이와 함께, 각 약물 투여군에서 얻어진 혈압 강압치, 즉, 약물 투여에 따른 4주간의 혈압 강하 정도를 투여 전 혈압 기준으로 계산하여 그 계산값

을 [표 1]에 나타내었다.

표 1

[0057]

투여 전 혈압과 비교한 4주 연속투여 결과 강압 정도(mmHg)		
약물투여군 (약물 종류 및 용량)	평균	표준오차
실시예1(F1+A1)	-55	2.255
실시예2(F2+A2)	-75	2.536
비교예1(F1)	-35	1.375
비교예2(F2)	-50	2.135
비교예3(L)	-20	1.256
비교예4(V)	-32	2.862
비교예5(A1)	-13	1.105
비교예6(A2)	-20	1.325
비교예7(L+A2)	-32	2.268
비교예8(V+A2)	-46	2.675

[0058]

상기 [표 1]에서 알 수 있듯이, 비교예 1 이 비교예 3 및 비교예 4에 비해 임상 상용량(피마살탄 삼수물 칼륨염의 임상 상용량= 60mg, 로자탄 칼륨염의 임상 상용량= 50mg, 발사르탄 임상 상용량=80mg) 대비 작은 용량으로 투여하였음에도 불구하고 보다 우수한 혈압 강하 효과를 나타냄을 확인할 수 있었다.

[0059]

또한, 본 발명의 조성물인 피마살탄과 아로디핀의 복합제인 실시예 1 및 2는 각각의 성분을 단독으로 투여한 혈압강하 효과의 단순한 합보다 더 큰 혈압강하효과를 나타내었다. 예를 들어, 아로디핀 베실레이트 0.5mg/Kg 단독 투여시(비교예5) -13mmHg이고 피마살탄 삼수화물 칼륨염 3mg/Kg 단독 투여시 (비교예 1) -35mmHg이나, 이 둘의 복합제제인 실시예 1의 경우 -55mmHg로 이 둘의 혈압강하효과의 단순한 수치의 합보다 더 상승된 혈압강하 효과를 나타내었으며, 이 효과는 표준오차를 고려하더라도 유의있는 수치이다. 또한, 아로디핀 베실레이트 1.6mg/Kg 단독 투여시(비교예6) -20mmHg이고 피마살탄 삼수화물 칼륨염 10mg/Kg 단독 투여시 (비교예 2) -50mmHg이나, 이들의 복합제제인 실시예 2의 경우 -75mmHg로 이 둘의 혈압강하효과의 단순한 수치의 합보다 더 상승된 혈압강하 효과를 나타내었다. 이러한 효과는, 다른 ARB계 화합물과 아로디핀과의 복합제가 복합제의 각 단독 성분의 혈압강하 수치의 단순한 합의 값 보다 더 작은 혈압강하 값을 나타낸다는 상기 결과와 비교 했을 때(비교예 7 및 8) 예상치 못한 현저한 효과라는 것이 확인된다.

[0060]

따라서, 본 발명의 조성물은 각 활성 성분의 단독 혈압강하 효과 보다 상승된 혈압 강하효과를 나타내므로 (synergy effect) 각 활성 성분의 함량 보다 감소시켜 각 활성 성분의 과용에 따른 부작용의 위험성 또한 크게 줄일 수 있으며, 각 활성 성분의 병용요법에 따른 환자의 의학 복용의 불편함을 해소시킬 수 있다.

[0061]

<제조예> 본 발명의 조성물(정제) 제조

[0062]

본 발명의 조성물을 하기 [표2]에 기재된 바와 같은 성분 및 그 함량을 함유하는 정제로 제조하였으며, 이를 제조예 1 내지 4로 나타내었다.

표 2

[0063]

성분	제조예1 (mg/1정)	제조예2 (mg/1정)	제조예3 (mg/1정)	제조예4 (mg/1정)
피마살탄 삼수화물 칼륨염	66.01	132.02	66.01	132.02
아로디핀 베실레이트	6.99	6.99	13.98	13.98
옥수수전분	46	98.99	39.01	92
미결정셀룰로오스	16	32	16	32
크로스포비론	10	20	10	20
히드록시프로필셀룰로오스	3.5	7	3.5	7
스테아르산마그네슘	1.5	3	1.5	3
1정 총중량 (mg)	150	300	150	300

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[0064] <정제의 제조방법>

[0065] 피마살탄 삼수화물, 칼륨염, 암로디핀 베실레이트염, 옥수수전분, 미결정셀룰로오스, 크로스포비돈을 고속 혼합기에 투입한 후 혼합하였다. 따로 히드록시프로필셀룰로오스와 적량의 정제수를 혼합하여 결합액을 만들고, 전혼합된 분말이 들어 있는 고속 혼합기에 투입하여 과립을 제조한 후 건조기에서 건조했다. 건조된 과립을 20호체로 체질한 후 스테아르산마그네슘을 첨가하고 혼합하여 최종 혼합물을 얻었다. 최종 혼합물을 회전식 타정기를 이용하여 압착하여 제조예 1 내지 4에 해당하는 각각의 정제를 제조하였다.



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AUG 26 2015

Cassan Maclean

Date : 2015/08/21

Classification :
A61K 31/41

CASSAN MACLEAN
307 Gilmour Street
OTTAWA Ontario
K2P 0P7

AVIS D'ACCEPTATION/NOTICE OF ALLOWANCE

Date de dépôt/Filing date : 2011/08/08

N° de demande/Application No. : 2,832,758

Votre référence/
Your Reference : 42671-0013

Titre de l'invention/
Title of Invention : ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION

Propriétaire(s)/Owner(s) : BORYUNG PHARMACEUTICAL CO., LTD.

Revendications/Claims : 014

Examiné tel que modifié/
Examined as amended : 2015/04/07

La demande de brevet susmentionnée a été jugée acceptable.

Il faut acquitter la taxe finale de TROIS CENTS DOLLARS (300\$), ou CENT CINQUANTE DOLLARS (150\$) si le requérant a le droit de revendiquer le statut de petite entité et a soumis une déclaration de petite entité, dans les six mois suivant la date du présent avis. Faute de quoi la demande sera réputée abandonnée conformément à l'alinéa 73(1)f) de la Loi sur les brevets.

Une taxe additionnelle de six dollars (6\$) par page excédant 100 pages du mémoire descriptif et dessins devra aussi être payée.

Le brevet sera délivré au nom du dernier propriétaire inscrit à nos dossiers à qui a fourni une documentation acceptable, au plus tard la date du paiement de la taxe finale, conformément à l'article 41 des Règles sur les brevets.

La réponse au présent avis doit comprendre l'identification complète de la demande et la date de l'avis.

La publication des brevets canadiens délivrés dans la Gazette du Bureau des brevets peut comprendre aussi une note concernant la mise en vente d'un brevet ou de sa licence. Si vous désirez profiter de ce service gratuit, veuillez l'indiquer au moment de payer la taxe finale.

The above application for patent has been found allowable.

The final fee of THREE HUNDRED DOLLARS (\$300), or ONE HUNDRED AND FIFTY DOLLARS (\$150) where the applicant is entitled to claim small entity status and has submitted a small entity declaration, must be paid within six months following the date of this notice. Otherwise, the application will be deemed to be abandoned pursuant to paragraph 73(1)(f) of the Patent Act.

An additional fee of six dollars (\$6.00) per page over 100 pages of specification and drawings must also be paid.

The patent shall issue to the last registered owner who has submitted acceptable documentation on or before the date that the final fee is paid (as pursuant to Section 41 of the Patent Rules).

A reply to this notice must include full identification of the application including the date of the notice.

The publication of issued Canadian patents in the Patent Office Record can also include an indication that the patent is available for licence or sale. If you wish to take advantage of this free service, please indicate this when paying the final fee.

Commissaire aux brevets/Commissioner of Patents

Canada

OPIC  CIPO

21

ДЕРЖАВНА СЛУЖБА ІНТЕЛЕКТУАЛЬНОЇ ВЛАСНОСТІ УКРАЇНИ
 ДЕРЖАВНЕ ПІДПРИЄМСТВО
 "УКРАЇНСЬКИЙ ІНСТИТУТ ІНТЕЛЕКТУАЛЬНОЇ ВЛАСНОСТІ"
 (УКРПАТЕНТ)

вул. Глазунова, 1, м. Київ-42, 01601, Україна Тел.: (044) 494-05-05 Факс: (044) 494-05-06
 E-mail: office@ukrpatent.org

№ 16303/ЗА/15

Висновок, затверджений Державною службою інтелектуальної власності України, набув статусу **рішення про видачу патенту на винахід**

Адреса для листування
 Михайлюк Ганна Валентинівна, вул.
 Бобруйська, буд. 46, м. Харків, 61054,
 Україна

Стосується заявки № а 2013 12969
 / при листуванні просимо посилатися на цей № /

«ЗАТВЕРДЖУЮ»

Начальник управління
 правового забезпечення промислової власності
 Державної служби інтелектуальної власності України



І.О. Шатова

Висновок про відповідність винаходу умовам патентоздатності за результатами кваліфікаційної експертизи

(21) Реєстраційний номер заявки **а 2013 12969**

(22) Дата подання **08.08.2011**

ПРІОРИТЕТ ЗАЯВЛЕНО :

за датою подання попередньої заявки в іноземній державі

(31) 10-2011-0033856

(32) 12.04.2011

(33) KR

(86) Номер та дата подання міжнародної заявки PCT/KR2011/005754 08.08.2011

(85) Дата прийняття заявки до розгляду за національною процедурою 08.11.2013

(71) Заявник(и)

БОРЮН ФАРМАСЬЮТИКАЛ КО., ЛТД. (KR)

(72) Повне ім'я винахідника(ів)

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(74) Представник у справах інтелектуальної власності

Михайлюк Ганна Валентинівна

(51) МПК

A61K 31/44 (2006.01)

A61K 31/505 (2006.01)

A61P 9/12 (2006.01)

(54) Назва винаходу

ПРОТИГІПЕРТОНІЧНА ФАРМАЦЕВТИЧНА КОМПОЗИЦІЯ

За результатами кваліфікаційної експертизи, проведеної відділом Державного підприємства "Український інститут інтелектуальної власності", встановлено, що заявлений винахід **відповідає умовам патентоздатності**.

Обсяг правової охорони визначається формулою винаходу, що додається.

Перелік документів попереднього рівня техніки, прийнятих до уваги експертизою, за кодом (56)

YI, SO JEONG. ET AL.: 'Pharmacokinetic interaction of Fimasartan, a new angiotensin II receptor antagonist, with Amlodipine in healthy volunteers.' JOURNAL OF CARDIOVASCULAR PHARMACOLOGY. vol. 57, no. ISSUE, 09 March 2011, pages 682 - 689

FERRI, C. ET AL.: 'Role of combination therapy in the treatment of hypertension: focus on valsartan plus amlodipine.' ADVANCES IN THERAPY. vol. 25, no. 4, 2008, pages 300-320

STANGIER, J.: 'Pharmacokinetics of repeated oral doses of amlodipine and amlodipine plus telmisartan in healthy volunteers.' THE JOURNAL OF CLINICAL PHARMACOLOGY. vol. 40, no. 12, 2000, pages 1347 - 1354

Державна реєстрація патенту України на винахід відповідно до ч. 2 ст. 22 Закону буде здійснена за умови сплати державного мита за його видачу і збору за публікації про видачу патенту. Згідно з Порядком сплати зборів за дії, пов'язані з охороною прав на об'єкти інтелектуальної власності, затвердженим постановою Кабінету Міністрів України від 23.12.2004 р. № 1716 із змінами, внесеними постановою Кабінету Міністрів України від 19.09.2007 № 1148, (далі - Порядок), розмір цього збору (код 12400) становить 240 грн, оскільки заявка містить сумарно 19 аркушів опису, креслень, формули винаходу і реферату.

Додаток до рішення: формула винаходу на 1 арк.

Головний експерт



В.В. Руденко

Телефон

494-05-62

(57)

1. Протигіпертонічна фармацевтична композиція, що включає:
калієвий тригідрат фімасартану як блокатор рецепторів ангіотензину II і
бесилат амлодипіну як блокатор кальцієвих каналів.
2. Протигіпертонічна фармацевтична композиція за п. 1, де вміст блокатора рецепторів ангіотензину II знаходиться в діапазоні від 0,5 до 240 мг, а вміст блокатора кальцієвих каналів знаходиться в діапазоні від 0,1 до 20 мг.
3. Протигіпертонічна фармацевтична композиція за п. 2, де вміст блокатора рецепторів ангіотензину II знаходиться в діапазоні від 50 до 180 мг.
4. Протигіпертонічна фармацевтична композиція за п. 3, де вміст блокатора рецепторів ангіотензину II знаходиться в діапазоні від 60 до 120 мг.
5. Протигіпертонічна фармацевтична композиція за п. 2, де вміст блокатора кальцієвих каналів знаходиться в діапазоні від 5 до 15 мг.
6. Протигіпертонічна фармацевтична композиція за п. 5, де вміст блокатора кальцієвих каналів знаходиться в діапазоні від 5 до 10 мг.
7. Протигіпертонічна фармацевтична композиція за п. 1, де фармацевтична композиція являє собою пероральну лікарську форму.
8. Протигіпертонічна фармацевтична композиція за п. 7, де лікарська форма являє собою окрему таблетку.
9. Фармацевтична композиція для профілактики, полегшення або лікування гіпертензії, серцевої недостатності, коронарної хвороби серця, ішемічної хвороби серця, ішемічного захворювання периферичних судин, гіпертензивної ниркової недостатності, апоплексії головного мозку або артеріосклерозу, що включає калієвий тригідрат фімасартану як блокатор рецепторів ангіотензину II і бесилат амлодипіну як блокатор кальцієвих каналів.

THE STATE INTELLECTUAL PROPERTY SERVICE OF UKRAINE
STATE ENTERPRISE

UKRAINIAN INSTITUTE OF INDUSTRIAL PROPERTY

vul. Glazunova, 1, m. Kyiv-42, 01601, Ukraine Phone: (044) 494-05-05 Fax: (044) 494-05-06

E-mail: office@ukrpatent.org

The conclusion is approved by the State Intellectual Property Service of Ukraine and has a power of a

Decision to grant a patent for the invention

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Ukraine

Application No. a 2013 12969

/please, refer to this No. in your future correspondence/

«APPROVED»

Chief of the judicial support department of
industrial property of the State Intellectual
Property Service of Ukraine

/signature/

I.O. Shatova

**Conclusion about conformity of the invention to requirements of patentability
according to the results of the substantive examination**

(21) Application No. a 2013 12969

(22) Date of Filing 08.08.2011

THE PRIORITY HAS BEEN GRANTED:

on the date of filing of the prior application with a foreign state

(31) 10-2011-0033856 (32) 12.04.2011 (33) KR

(86) PCT Application number and filing date PCT/KR2011/005754 08.08.2011

(85) Date of the application entry into the national phase 08.11.2013

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25

- (51) IPC
A61K 31/44 (2006.01)
A61K 31/505 (2006.01)
A61P 9/12 (2006.01)

- (54) Title of the Invention
ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION

As a result of the substantive examination of the State Enterprise "Ukrainian Institute of Industrial Property", it has been determined that the claimed invention **meets the requirements of patentability**.

The scope of protection is determined by the set of claims, which is attached.

The list of prior art documents taken into consideration by the examination board (56)

YI, SO JEONG, ET AL.: 'Pharmacokinetic interaction of Fimasartan, a new angiotensin II receptor antagonist, with Amlodipine in healthy volunteers.' JOURNAL OF CARDIOVASCULAR PHARMACOLOGY. vol. 57, no. ISSUE. 09 March 2011, pages 682 – 689

FERRI, C. ET AL.: 'Role of combination therapy in the treatment of hypertension: focus on valsartan plus amlodipine.' ADVANCES IN THERAPY. vol. 25, no. 4, 2008, pages 300-320

STANGIER, J.: 'Pharmacokinetics of repeated oral doses of amlodipine and amlodipine plus telmisartan in healthy volunteers.' THE JOURNAL OF CLINICAL PHARMACOLOGY. vol. 40, no. 12, 2000, pages 1347 - 1354

According to the Section 2 of Art. 22 of the Patent Law, the official registration of a patent for the invention will be effected provided that the official registration fee for issue of the Patent and publication fee are paid. In accordance with the Rules on payment of fees for actions related to the protection of rights to intellectual property objects approved by the Decision of the Cabinet of Ministers of December 23, 2004, No. 1716, with amendments introduced by the Decision of the Cabinet of Ministers of September 19, 2007 No. 1148, (further the Rules), the fee for publication (code 12400) is 240 UAH, because the application contains in total 19 pages of description, drawings, claims and abstract.

Enclosure to the decision: claims on 1 page.

Chief expert

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(57)

1. An antihypertensive pharmaceutical composition, comprising:
fimasartan potassium trihydrate as an angiotensin II receptor blocker and
amlodipine besylate as a calcium channel blocker.
2. The antihypertensive pharmaceutical composition according to claim 1, wherein
the content of the angiotensin II receptor blocker is in the range of 0,5 to 240 mg, and the
content of the calcium channel blocker is in the range of 0,1 to 20 mg.
3. The antihypertensive pharmaceutical composition according to claim 2, wherein
the content of the angiotensin II receptor blocker is in the range of 50 to 180 mg.
4. The antihypertensive pharmaceutical composition according to claim 3, wherein
the content of the angiotensin II receptor blocker is in the range of 60 to 120 mg.
5. The antihypertensive pharmaceutical composition according to claim 2, wherein
the content of the calcium channel blocker is in the range of 5 to 15 mg.
6. The antihypertensive pharmaceutical composition according to claim 5, wherein
the content of the calcium channel blocker is in the range of 5 to 10 mg.
7. The antihypertensive pharmaceutical composition according to claim 1, wherein
the pharmaceutical composition is an oral dosage form.
8. The antihypertensive pharmaceutical composition according to claim 7, wherein
the dosage form is a single tablet.
9. A pharmaceutical composition for the prevention, alleviation or treatment of
hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic
peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis,
comprising fimasartan potassium trihydrate as an angiotensin II receptor blocker and
amlodipine besylate as a calcium channel blocker.

아 Country MA (모로코)

국가코드 MA (모로코)

번호 Patent Number 35107(2014.05.02)

종류 Kind of Document B1(Granted patent [From 01-01-2007 onwards]) [문헌종류 코드보기](#)

번호 Application Number 36404 (2013.11.08)

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Abstract

La présente invention concerne une composition pharmaceutique antihypertensive contenant du finasartan, l'un de ses sels pharmaceutiquement acceptables, solvate que bloqueur du récepteur de l'angiotensine ii; et de l'amlodipine, l'un de ses isomères, sels pharmaceutiquement acceptables, solvates ou hydrates en tant que calciques.

[French](#)



US008765776B2

(12) **United States Patent**
Kim et al.

(10) **Patent No.:** **US 8,765,776 B2**
(45) **Date of Patent:** **Jul. 1, 2014**

- (54) **ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION**
- (75) Inventors: **Seung Ho Kim**, Seoul (KR); **Ji Han Kim**, Seoul (KR); **Je Hak Kim**, Anyang-si (KR); **Kyung Wan Nam**, Gunpo-si (KR); **Yong Ha Chl**, Yongin-si (KR); **Joo Han Lee**, Seoul (KR); **Soo Heui Paik**, Ansan-si (KR); **So Jeong Yi**, Seoul (KR); **Tae Eun Kim**, Seoul (KR); **Seo Hyun Yoon**, Seoul (KR); **Joo Youn Cho**, Seoul (KR); **Sang Goo Shin**, Seoul (KR); **In Jin Jang**, Seoul (KR); **Kyung Sang Yu**, Seoul (KR)
- (73) Assignee: **Boryung Pharmaceutical Co., Ltd.**, Seoul (KR)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 211 days.
- (21) Appl. No.: **13/205,545**
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- (52) **U.S. Cl.**
USPC **514/269**; 514/349; 544/319; 546/299
- (58) **Field of Classification Search**
USPC 514/269; 349; 544/319; 546/299
See application file for complete search history.
- (56) **References Cited**

U.S. PATENT DOCUMENTS

4,572,909 A	2/1986	Campbell et al.	514/356
5,869,476 A	2/1999	Paik et al.	514/183
6,294,542 B1	9/2001	Lee et al.	514/269
7,309,788 B2	12/2007	Kim et al.	544/319

FOREIGN PATENT DOCUMENTS

EP	0 253 310	1/1988
KR	1989-0011854	8/1989
KR	2001-0079517	8/2001
KR	2001-0090193	10/2001
KR	10-0354654	9/2002
KR	2004-0032639	4/2004

KR	10-0521980	10/2005
KR	2010-0048137	5/2010
KR	2011-0086293	7/2011
WO	WO 99/55681	11/1999
WO	WO 00/02543	1/2000
WO	WO 00/16773	3/2000
WO	WO 03024956 A1 *	3/2003
WO	WO 2007001066 A1 *	1/2007
WO	WO 2012/141385	10/2012

OTHER PUBLICATIONS

Letter Written Disclosure of the Supplemental Information Disclosure Statement for the above-referenced application, mailed on Jan. 19, 2012, 2 pages.

Adis R&D Insight database, "Fimasartan," [No authors listed] Am J Cardiovasc Drugs 11(4):249-252 (2011).

Boryung Pharmaceutical Co., Ltd., "Fimasartan: new generation of ARBs," Published on Jun. 2010 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:kobio.org [11 pages].

Chi et al., "Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oral administration in the fasted and fed states in healthy subjects" Am J Cardiovasc Drugs 11(5):335-346 (2011).

ClinicalTrials.gov, "A clinical study to evaluate efficacy and safety of fimasartan/hydrochlorothiazide combination-therapy," Boryung Pharmaceutical Co., Ltd. Published on Oct. 10, 2010 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:clinicaltrials.gov/ct2/show/NCT01258673 [1 page].

ClinicalTrials.gov, "A therapeutic exploratory clinical study to evaluate the antihypertensive efficacy of fimasartan (BR-A-657•K) during 24 hours in patients with mild to moderate essential hypertension," Boryung Pharmaceutical Co., Ltd. Published on Jun. 16, 2009 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:clinicaltrials.gov/ct2/show/NCT00922241 [1 page].

ClinicalTrials.gov, "Efficacy, safety and pharmacodynamic/pharmacokinetic study of fimasartan (BR-A-657•K)," Boryung Pharmaceutical Co., Ltd. Published on Jul. 10, 2009 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:clinicaltrials.gov/ct2/show/NCT00937651 [4 pages].

ClinicalTrials.gov, "Fimasartan (BR-A-657) multiple oral dose in healthy subjects," Boryung Pharmaceutical Co., Ltd. Published on Dec. 14, 2010 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:clinicaltrialsfeeds.org/clinical-trials/show/NCT01289899 [1 page].

ClinicalTrials.gov, "Study to compare and assess the safety and pharmacokinetic characteristics after oral administration of fimasartan (BR-A-657•K) in healthy elderly and young male volunteers," Boryung Pharmaceutical Co., Ltd. Published on Jul. 6, 2009 [online][retrieved on Nov. 22, 2011] Retrieved from:<URL:txooo.im/ct2/show/NCT00937534 [3 pages].

(Continued)

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(57) **ABSTRACT**

Provided is an antihypertensive pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker, and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

20 Claims, No Drawings

(56)

References Cited

OTHER PUBLICATIONS

- ClinicalTrials.gov, "A study to evaluate the pharmacokinetic drug interaction after oral concurrent administration of fimasartan and amlodipine in healthy male volunteers," Boryung Pharmaceutical Co., Ltd. Published on Jul. 10, 2009 [online] [retrieved on Nov. 22, 2011] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01258673 [3 pages].
- Collins et al., "Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context," *Lancet* 335(8693):827-838 (1990).
- Derwent English abstract for WO 2000/016773 (equivalent document for KR 10-0354654), published Sep. 8, 1999 entitled: "Composition for reducing treating hypertension or platelet aggregation disorders, contains angiotensin II receptor antagonist and platelet anti-aggregation agent," Dialog File No. 351, Accession No. 9957323 [3 pages].
- English language abstract of Korean Patent Publication No. KR 2001-0090193 (Item AG), Korean Intellectual Property Office, 2 pages.
- English language abstract of Korean Patent Publication No. KR 2004-0032639 (Item AH), issued as Korean Patent No. KR 0521980 (Item AL), Korean Intellectual Property Office, 2 pages.
- English language abstract of Korean Patent Publication No. KR 2010-0048137 (Item AI), Korean Intellectual Property Office, 1 page.
- English language abstract of Korean Patent Publication No. KR 2011-0086293 (Item AJ), Korean Intellectual Property Office, 1 page.
- MacGregor et al., "Captopril in essential hypertension: contrasting effects of adding hydrochlorothiazide or propranolol," *Br Med J. (Clin Res Ed)* 284(6317):693-696 (1982).
- Shin et al., "Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry," *Biomed Chromatogr.* Jan. 26, 2011[Epub ahead of print]—Abstract only 1 page.
- Shin et al., "The effect of the newly developed angiotensin receptor II antagonist fimasartan on the pharmacokinetics of atorvastatin in relation to OATP1B1 in healthy male volunteers," *J Cardiovasc Pharmacol.* Jul. 14, 2011[Epub ahead of print]—Abstract only 1 page.
- Waeber, B. and H. Brunner, "Combination antihypertensive therapy: does it have a role in rational therapy?" *Am J Hypertens.* 10(7 Pt 2):131S-137S (1997).
- Yi et al., "Effect of multiple doses of fimasartan, an angiotensin II receptor antagonist, on the steady-state pharmacokinetics of digoxin in healthy volunteers," *Int J Clin Pharmacol Ther.* 49(5):321-327 (2011).
- Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, mailed on Jun. 5, 2013, 2 pages.
- "Kanarb (Fimasartan)" brochure, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/include/download.asp?strUpFile=english.jpg [retrieved on May 31, 2013], 1 page.
- Chrysant et al., "The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACT, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study," *Clinical Therapeutics* 30(4):587-604 (2008).
- Clinical Trial: "A multicenter, phase 3 study to evaluate the antihypertensive efficacy and safety of Fimasartan (BR-A-657-K) 30mg compared to placebo in patients with mild to moderate essential hypertension (fimasartan)," Boryung Pharmaceutical Co., Ltd. Retrieved from: <URL: clinicaltrials.gov/ct2/show/NCT01672476 [accessed May 31, 2013; First Received Aug. 26, 2012; last updated Sep. 4, 2012] 5 pages.
- Clinical Trial: "A randomized, double-blind, placebo-controlled, 3x3 factorial design, phase II study to evaluate the antihypertensive efficacy and safety of combination of fimasartan and amlodipine in patients with essential hypertension," Boryung Pharmaceutical Co., Ltd. Retrieved from: <URL: clinicaltrials.gov/ct2/show/NCT01518998?term=NCT01518998 [accessed May 31, 2013; First Received Jan. 24, 2012; last updated Mar. 26, 2013] 5 pages.
- Clinical Trial: "Clinical trials for single oral dose of 60mg fimasartan and single IV infusion of 30mg Fimasartan to evaluate the absolute bioavailability of Kanarb® tablet (Fimasartan) in healthy subjects," Boryung Pharmaceutical Co., Ltd. Retrieved from: <URL: clinicaltrials.gov/ct2/show/NCT01671020 [accessed May 31, 2013; First Received Aug. 20, 2012; last updated Aug. 22, 2012] 2 pages.
- Ferri et al., "Role of combination therapy in the treatment of hypertension: focus on valsartan plus amlodipine," *Advances in Therapy.* 25(4):299-319 (2008).
- Gu et al., "The effect of fimasartan, an angiotensin receptor type 1 blocker, on the pharmacokinetics and pharmacodynamics of warfarin in healthy Korean male volunteers: a one-sequence, two-period crossover clinical trial," *Clin Ther.* 34(7):1592-1600 (2012).
- Jeon et al., "Assessment of the drug-drug interactions between fimasartan and hydrochlorothiazide in healthy volunteers," *J Cardiovasc Pharmacol.* 59(1):84-91 (2012).
- Kanarb website, Clinical Trials—Overview, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/clinical_trials/overview.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Clinical Trials—Results, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/clinical_trials/results.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Fimasartan—History, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/fimasartan/history.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Fimasartan—Kanarb, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/fimasartan/kanarb.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Fimasartan—Overview, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/fimasartan/overview.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Nonclinical trials—Overview, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/non_clinical_trials/overview.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Nonclinical trials—Pharmacokinetics, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/non_clinical_trials/Pharmacokinetics.asp [retrieved on May 31, 2013] 1 page.
- Kanarb website, Nonclinical trials—Pharmacology, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/non_clinical_trials/pharmacology.asp [retrieved on May 31, 2013] 2 pages.
- Kanarb website, Nonclinical trials—Toxicology, Boryung Pharmaceutical Co., Ltd., Retrieved from: <URL: test.kanarb.com/non_clinical_trials/toxicology.asp [retrieved on May 31, 2013] 1 page.
- Kim et al., "Fimasartan, a novel angiotensin II receptor antagonist," *Arch Pharm Res.* 35(7):1123-1126 (2012).
- Kim et al., "Increased Systemic Exposure of Fimasartan, an Angiotensin II Receptor Antagonist, by Ketoconazole and Rifampicin," *The Journal of Clinical Pharmacology* 53(1):75-81 (2013).
- Kim et al., "Synthesis and antihypertensive activity of pyrimidin-4(3H)-one derivatives as losartan analogue for new angiotensin II receptor type 1 (AT1) antagonists," *Bioorg Med Chem Lett.* 22(4):1649-1654 (2012).
- Lee et al., "Effect of age on the pharmacokinetics of fimasartan (BR-A-657)," *Expert Opin Drug Metab Toxicol.* 7(11):1337-1344 (2011) (Abstract Only).
- Ryu et al., "Fimasartan, anti-hypertension drug, suppressed inducible nitric oxide synthase expressions via nuclear factor-kappa B and activator protein-1 inactivation," *Biol Pharm Bull.* 36(3):467-474 (2013).
- Shin et al., "Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry," *Biomed Chromatogr.* 25(11):1208-1214 (2011).
- Shin et al., "The effect of the newly developed angiotensin receptor II antagonist fimasartan on the pharmacokinetics of atorvastatin in relation to OATP1B1 in healthy male volunteers," *J Cardiovasc Pharmacol.* 58(5):492-499 (2011).

30

(56)

References Cited

OTHER PUBLICATIONS

- Stangier et al., "Pharmacokinetics of repeated oral doses of amlodipine and amlodipine plus telmisartan in healthy volunteers," *The Journal of Clinical Pharmacology* 40(12):1347-1354 (2000).
- Yi et al., "Pharmacokinetic interaction of fimasartan, a new angiotensin II receptor antagonist, with amlodipine in healthy volunteers," *J Cardiovasc Pharmacol* 57(6):682-689 (2011).
- International Search Report, issued Apr. 4, 2012, in connection with corresponding International Application No. PCT/KR2011-005754, 4 pages.
- Letter/Written Disclosure of the Information Disclosure Statement for the above-referenced application, mailed on Dec. 4, 2013, 2 pages.
- Boryung Pharmaceutical Co., Ltd., "R&D Pipeline, Fimasartan," Published on Oct. 11, 2005 [online][retrieved on Nov. 11, 2013] Retrieved from: <URL:boryung.co.kr/englishV2/rnd/rnd43.asp>, 1 page.
- Chi et al., "Pharmacological characterization of BR-A-657, a highly potent nonpeptide angiotensin II receptor antagonist," *Biol Pharm Bull* 36(7):1208-1215 (2013).
- Clinical Trial: "A clinical trial to compare and evaluate the pharmacokinetic characteristics and the safety of Fimasartan in hepatic impairment patients and healthy volunteers," first received Jun. 17, 2010; last updated Jan. 2, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01146938?term=fimasartan&rank=10>, 3 pages.
- Clinical Trial: "A clinical trial to compare and evaluate the pharmacokinetic characteristics and the safety of Fimasartan in renal patients and healthy volunteers," first received Jun. 21, 2010; last updated Jan. 6, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01148368?term=fimasartan&rank=13>, 3 pages.
- Clinical Trial: "A clinical trial to evaluate the effect of Fimasartan on pharmacodynamics, pharmacokinetics, and the safety of warfarin in healthy male volunteers," first received Jul. 10, 2009; last updated Oct. 7, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00938132?term=fimasartan&rank=27>, 2 pages.
- Clinical Trial: "A randomized trial of angiotensin Receptor blocker, Fimasartan, in aortic stenosis (ALFA Trial)," Boryung Pharmaceutical Co., first received Apr. 29, 2012; last updated Apr. 30, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01589380?term=fimasartan&rank=7>, 6 pages.
- Clinical Trial: "A study to assess food effect on the pharmacokinetics of Fimasartan in healthy male volunteers," Boryung Pharmaceutical Co., Ltd., first received Nov. 2, 2009; last updated Dec. 23, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01007409?term=fimasartan&rank=15>, 2 pages.
- Clinical Trial: "A study to evaluate the effect of atorvastatin on the pharmacokinetics of Fimasartan in healthy male volunteers," Boryung Pharmaceutical Co., Ltd., first received Oct. 7, 2009; [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00991705?term=fimasartan&rank=21>, 3 pages.
- Clinical Trial: "A study to evaluate the effect of Fimasartan on pharmacokinetics, and the safety of digoxin in healthy male volunteers," Boryung Pharmaceutical Co., Ltd., first received Oct. 7, 2009; last updated Nov. 2, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00991783?term=fimasartan&rank=23>, 2 pages.
- Clinical Trial: "A study to evaluate the effect of Ketoconazole and Rifampicin on the pharmacokinetics of Fimasartan in healthy male volunteers," Boryung Pharmaceutical Co., Ltd., first received Jul. 10, 2009; last updated Oct. 7, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00938262?term=fimasartan&rank=26>, 2 pages.
- Clinical Trial: "A trial of Fimasartan for early diastolic heart failure (FINE)," Boryung Pharmaceutical Co., Ltd., first received Sep. 20, 2012; last updated Nov. 19, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01691118?term=fimasartan&rank=25>, 4 pages.
- Clinical Trial: "A valsartan 80 mg-referenced, therapeutic exploratory clinical study to evaluate the antihypertensive efficacy of Fimasartan 30 mg during 24 hours in patients with mild to moderate essential hypertension," Boryung Pharmaceutical Co., Ltd., first received May 31, 2013; last updated Jun. 13, 2013 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01878201?term=fimasartan&rank=12>, 4 pages.
- Clinical Trial: "Antihypertensive efficacy and tolerability and determine the adequate antihypertensive dosage of Fimasartan in mild to moderate essential hypertension patients," Boryung Pharmaceutical Co., Ltd., first received Jun. 16, 2009; last updated Jun. 17, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00923611?term=fimasartan&rank=9>, 4 pages.
- Clinical Trial: "Clinical study to evaluate the antihypertensive efficacy and changes of neurohormonal markers of Fimasartan and Atenolol with exaggerated blood pressure response during exercise in essential hypertensive patients," Boryung Pharmaceutical Co., Ltd., first received Nov. 19, 2012; last updated May 28, 2013 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01736488?term=fimasartan&rank=4>, 4 pages.
- Clinical Trial: "Clinical Study to evaluate the antihypertensive efficacy and safety of Fimasartan in Hypertension patients," Boryung Pharmaceutical Co., Ltd., first received Jun. 16, 2009; last updated Oct. 17, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00922480?term=fimasartan&rank=24>, 4 pages.
- Clinical Trial: "Effect of Fimasartan for modification of Atheroma vulnerability in DEFERred Coronary Disease (FIMA-DEFER)," Boryung Pharmaceutical Co., Ltd., first received Jun. 24, 2011; last updated Aug. 7, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01384747?term=fimasartan&rank=20>, 4 pages.
- Clinical Trial: "Fimasartan (BR-A-657) single oral dose in healthy subjects," Boryung Pharmaceutical Co., Ltd., first received Dec. 13, 2010; last updated Feb. 3, 2011 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01289886?term=fimasartan&rank=19>, 3 pages.
- Clinical Trial: "Study to compare and assess the safety and pharmacokinetic characteristics after oral administration of Fimasartan (BR-A-657K) in healthy elderly and young male volunteers," Boryung Pharmaceutical Co., Ltd., first received Jul. 6, 2009; last updated Nov. 2, 2009 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT00937534?term=fimasartan&rank=3>, 3 pages.
- Clinical Trial: "The clinical study to evaluate the efficacy and safety of Fimasartan in patients with mild to moderate essential hypertension," Boryung Pharmaceutical Co., Ltd., first received May 31, 2010; last updated Aug. 22, 2012 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01135212?term=fimasartan&rank=8>, 4 pages.
- Clinical Trial: "To evaluate the pharmacokinetic interactions and safety between Fimasartan and Rosuvastatin," Boryung Pharmaceutical Co., Ltd., first received Aug. 8, 2013; last updated Oct. 20, 2013 [online][retrieved on Nov. 12, 2013] Retrieved from: <URL:clinicaltrials.gov/ct2/show/NCT01921946?term=fimasartan&rank=17>, 3 pages.
- Heart and Stroke Foundation Press Release, "Guideline alert for blood pressure patients as treatment combo fails," Published Jan. 16, 2009 [online][retrieved on Nov. 22, 2013] Retrieved from: <URL:heartandstroke.com/site/apps/nfnet/content2.aspx?c=iklQLcMWJtE&b=3485819&ct=6501933>, 1 page.
- Ontarget Investigators et al., "Telmisartan, ramipril, or both in patients at high risk for vascular events," *N Engl J Med* 358(15):1547-1559 (2008).
- International Preliminary Report on Patentability, issued Oct. 15, 2013, in connection with corresponding International Application No. PCT/CR2011/005754, 6 pages.

* cited by examiner

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ANTIHYPERTENSIVE PHARMACEUTICAL
COMPOSITION

RELATED APPLICATIONS

Benefit of priority is claimed to Korean Patent Application No. 10-2011-0033856, to Seung Ho KIM, Ji Han KIM, Je Hak KIM, Kyung Wan NAM, Yong Ha CHI, Joo Han LEE and Soo Heui PAK, entitled "ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION," filed Apr. 12, 2011, the subject matter of which is incorporated by reference in its entirety.

TECHNICAL FIELD

The present invention relates to an antihypertensive pharmaceutical composition.

BACKGROUND ART

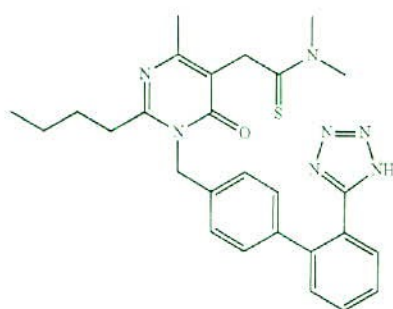
Hypertension is one of the most common cardiovascular diseases. Typically, a person is diagnosed with hypertension when his/her blood pressure is in a range of 140/90 mmHg. Recently, the incidence of lifestyle-related diseases such as hypertension has rapidly increased. As hypertension may result in the occurrence of acute heart diseases or myocardial infarction, there is a continued need for development of a more effective antihypertensive agent.

According to various clinical trials of antihypertensive agents, it was found that lowering of blood pressure of hypertensive patients leads to a decrease in mortality and morbidity of heart diseases or myocardial infarction (Collins R, Peto R, MacMahon S, Hebert P, Fiebach N II, Eberlein K A, Godwin J, Qizilbash N, Taylor J O, Hennekens C II, Lancet 1990, 335(8693):827-38). Although a variety of drugs have been used and administered for the purpose of treating such a clinical condition, suitable control of blood pressure is not always successful (Waeber B, Brunner HR, Am. J. Hypertens 1997, 10(7 Pt 2): 131S-137S).

Among various applicable administration modes of antihypertensive drugs, a combination preparation or combination therapy of drugs is one method for achieving desired therapeutic results. On the other hand, arbitrary selection of various classes of antihypertensive agents for application of drugs to combination therapy prescription does not always provide help to achieve a desired blood pressure level in a hypertensive mammal including a human (MacGregor G A, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones J C, Br Med J (Clin Res Ed), 284 (6317): 693-6).

To this end, there is an obvious need for further development of therapeutic methods, combination preparations and pharmaceutical compositions against hypertension.

Fimasartan, which is chemically defined as 2-n-butyl-5-dimethylaminothiocarbonyl-methyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one and has the following structural formula:



[Fimasartan]

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is an antihypertensive agent of the angiotensin II receptor blocker (ARB) class and has currently been approved as a pharmaceutical product under brand name of KANARB®.

According to the randomized double-blind clinical testing conducted for the comparison of antihypertensive effects in patients with mild to moderate essential hypertension, at a dose of 60 mg to 120 mg of drugs between Fimasartan potassium and Losartan which is a representative compound of the ARB class, it was demonstrated that antihypertensive effects in terms of changes in diastolic blood pressure (DBP) in the sitting position at Week 12 of drug administration were respectively -11.26 ± 7.53 mmHg for the Fimasartan-treated group and -8.56 ± 7.72 mmHg for the Losartan-treated group, relative to a baseline, thus showing that antihypertensive effects after 12- or 24-week administration were higher in Fimasartan than Losartan (A Randomized, Double-blind, Losartan-controlled, Parallel Group Comparison Dose Titration Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Fimasartan (BR-A-657.K) 60 mg-120 mg in Patients with Mild to Moderate Essential Hypertension (Phase III)).

Amlodipine is a calcium channel blocker (CCB), and blocks an inflow of calcium ions to cell membranes of cardiac and peripheral vascular smooth muscles and therefore directly relaxes vascular smooth muscles to exhibit antihypertensive effects. Although the action mechanism by which Amlodipine mitigates angina pectoris has not been fully understood, it was found that the following two action mechanisms function to relieve ischemic symptoms.

First, Amlodipine dilates peripheral arteries to decrease the total peripheral resistance (after-load), thus leading to decreased cardiac work, and stabilizes a heart rate to decrease cardiac energy consumption and oxygen demand.

Second, it is believed that Amlodipine dilates main coronary arteries and other coronary arterioles of ischemic lesions and normal regions. Such vasodilation plays a role to increase delivery of oxygen to myocardial ischemic lesions of patients with coronary artery convulsion.

Although active research for the treatment of hypertension has recently been focused on a combination preparation of Amlodipine, which is a calcium channel blocker, with a compound belonging to the ARB class, such a combination preparation may present additional problems in some cases, such as by causing drug-to-drug interaction and increased adverse side effects of individual drugs.

To this end, the inventors of the present invention have recognized problems of simple combination preparations of Amlodipine and ARB class compounds and conducted a variety of extensive and intensive studies to address the foregoing problems. As a result, the present invention has been completed.

[Related technique]

1. KR 1989-0011854 A 1989 Aug. 22

2. WO 00/16773 1999 Sep. 8

3. KR 2001-0013626 A 2001 Feb. 26

4. KR 2001-0079517 A 2001 Aug. 22

5. KR 2001-0090193 A 2001 Oct. 18

6. KR 2004-0032639 2004 Apr. 17

7. KR 2010-0048137 2010 May 11

8. Yoo S D et al., Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry, *Biomed Chromatogr.* 2011 Jan. 26. doi:10.1002/bmc.1592. Epub ahead of print

9. Yu K S. et al., Effect of multiple doses of fimasartan, an angiotensin II receptor antagonist, on the steady-state phar-

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macokinetics of digoxin in healthy volunteers. *Int J Clin Pharmacol Ther*. 2011 May; 49(5):321-327

10. Yu K S et al., The Effect of the Newly Developed Angiotensin Receptor II Antagonist Fimasartan on the Pharmacokinetics of Atorvastatin in relation to OATP1B1 in Healthy Male Volunteers. *J Cardiovasc Pharmacol*. 2011 Jul. 14. (Epub ahead of print)

DISCLOSURE OF THE INVENTION

Technical Problem

Therefore, the present invention is intended to provide an antihypertensive pharmaceutical composition which is effective not only for the prevention, alleviation and treatment of hypertension, but also for the prevention, alleviation or treatment of complications of hypertension and/or hyperlipidemia.

Technical Solution

The present invention provides an antihypertensive pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

In the present invention, Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

In the present invention, Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt with an inorganic acid, organic acid or metal, which has been conventionally used in the preparation of pharmaceutical products by pharmaceutical manufacturers. Examples of the inorganic acid include hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid. Examples of the organic acid include citric acid, acetic acid, lactic acid, tartaric acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid (besylate), maleic acid, benzoic acid, gluconic acid, glycolic acid, succinic acid, 4-morpholineethanesulfonic acid, camphorsulfonic acid (camsylate), 4-nitrobenzenesulfonic acid, hydroxy-o-sulfonic acid, 4-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid, aspartic acid and adipic acid (adipate). Examples of the metal include sodium, potassium, calcium and magnesium.

In the present invention, the angiotensin II receptor blocker is preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate, and more preferably a Fimasartan potassium salt or Fimasartan potassium trihydrate. These materials are commercially available or otherwise may be prepared by using a known method (for example, see Korean Patent Nos. 0354654 and 0521980).

In the present invention, the calcium channel blocker is preferably an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate, and more preferably Amlodipine besylate. These materials are

commercially available or otherwise may be prepared by using a known method (for example, see U.S. Pat. No. 4,572,909).

In the present invention, the solvent in the "solvate" refers to a common organic solvent which has been used in the preparation of organic compounds. Examples of the solvent include, but are not limited to, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-acetate, acetone, acetic acid, anisole, tetrahydrofuran, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, n-butyl acetate, dimethyl sulfoxide, pentane, and heptane.

In the present invention, the content of "hydrate" and "solvate" may be in a range of 0.25 to 10 moles relative to 1 mole of Fimasartan or Amlodipine, for example, 0.5 moles, 1 mole, 1.5 moles, 2 moles, 2.5 moles, 3 moles or 5 moles, but the present invention is not limited thereto.

The composition of the present invention may contain an angiotensin II receptor blocker in an amount of 0.5 to 240 mg, preferably 50 to 180 mg, and more preferably 60 to 120 mg.

Further, the composition of the present invention may contain a calcium channel blocker in an amount of 0.1 to 20 mg, preferably 5 to 15 mg, and more preferably 5 to 10 mg.

On the other hand, it is known that a conventional high dose (that is, pharmaceutically acceptable high dose/administration) of these drugs contained in a pharmaceutical composition is a maximum of 240 mg or less for Fimasartan and a maximum of 20 mg or less for Amlodipine, for an ordinary adult weighing 60 kg.

Throughout the specification, unless otherwise specifically indicated, the term "pharmaceutical composition" is intended to generally cover not only a single dosage form which is taken or administered at one single dose, such as tablet, capsule or injection, but also plural dosage forms which are administered at two or more divided doses. For example, the term "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker" is interpreted to designate not only a single dosage form containing these two active ingredients all together, but also two dosage forms in which each contains one active ingredient. That is, where these two dosage forms are simultaneously administered or are consecutively administered at regular intervals and therefore effective amounts of two active ingredients contained in each of these dosage forms coexist in vivo to bring about synergistic effects, these two dosage forms also fall within the scope of the "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker".

The composition of the present invention may further contain one or more pharmaceutically acceptable carriers besides the aforesaid ingredients, to be formulated into a variety of dosage forms for desired applications. Examples of the pharmaceutically acceptable carrier include saline, sterile water, Ringer's solution, buffered physiological saline, dextrose solution, maltodextrin solution, glycerol, and ethanol. These materials may be used alone or in any combination thereof. If necessary, other conventional additives may be added such as antioxidants, buffers and bacteriostatic agents.

Further, diluents, dispersants, surfactants, binders and lubricants may be additionally added to prepare injectable formulations such as aqueous solutions, suspensions, and

emulsions, or oral formulations such as pills, capsules, granules, and tablets. Furthermore, the agent may be preferably formulated into a desired dosage form, depending on diseases to be treated and ingredients, using any appropriate method known in the art, or the method as disclosed in "Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa.

The composition of the present invention may be administered via oral routes or parenteral routes (for example, intravenously, subcutaneously, intraperitoneally, or locally), depending on desired applications. The dose of the composition may vary depending on weight, age, gender, health status, and dietary habits of patients, administration times and routes, excretion rates, and severity of disease. The composition of the present invention may be administered once or several times a day.

The composition of the present invention may be an injectable formulation such as aqueous solution, suspension or emulsion, or an oral formulation such as pill, capsule, granule or tablet or in the form of a kit. An oral dosage form is preferable and a single tablet is more preferable.

Further, the composition of the present invention, due to having an enhanced antihypertensive effect, may be used for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

Therefore, the present invention provides a pharmaceutical composition for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

Further, the present invention provides a method for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, including administering a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker to a mammal, including a human, in need thereof.

The present invention provides a method for preventing or treating a hypertension, comprising administering the antihypertensive pharmaceutical composition of the present invention to a mammal including a human.

In the method for preventing or treating a hypertension of the present invention, the antihypertensive pharmaceutical composition is comprised Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

In the method for preventing or treating a hypertension of the present invention, the sort or content of each of the angiotensin II receptor blocker and the calcium channel blocker is the same as described above regarding the antihypertensive pharmaceutical composition of present invention.

In the method for preventing or treating a hypertension of the present invention, the angiotensin II receptor blocker is

preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate and more preferably is a Fimasartan potassium salt.

In the method for preventing or treating a hypertension of the present invention, the calcium channel blocker is preferably an Amlodipine besylate.

In the method for preventing or treating a hypertension of the present invention, the content of the angiotensin II receptor blocker is preferably in the range of 0.5 to 240 mg, and the content of the calcium channel blocker is in the range of 0.1 to 20 mg.

Further, the present invention provides a use of a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker, for manufacturing a pharmaceutical preparation for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

Advantageous Effects

The composition of the present invention exhibits an enhanced antihypertensive effect greater than the simple sum of antihypertensive values of the same doses of individual active ingredients. Accordingly, the composition of the present invention enables the use of individual active ingredients at a content or dose lower than that upon separate use thereof, and thus can provide more effective treatment or prevention of hypertension or the like while reducing adverse side effects due to an overdose of individual active ingredients.

MODE FOR INVENTION

Now, the present invention will be described in more detail with reference to the following Examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

EXPERIMENTAL EXAMPLE

Antihypertensive Effects of Inventive Composition

This study is intended to examine antihypertensive action of individual drugs. For this purpose, test drugs, i.e., Fimasartan potassium trihydrate, Losartan potassium salt, Valsartan, Amlodipine besylate, a combination of Fimasartan potassium trihydrate with Amlodipine besylate, a combination of Losartan potassium salt with Amlodipine besylate, and a combination of Valsartan with Amlodipine besylate were repeatedly and orally administered for 4 weeks to rats with essential hypertension. Changes in blood pressure, heart rate and body weight of animals were measured to investigate the antihypertensive action by long-term administration of individual drugs, confirm the maintenance degree of effective and stable blood pressure, and examine the difference between single administration and combined administration of drugs. In this manner, the antihypertensive action was compared and evaluated between the individual drugs.

(1) Test Material and Method

1 Experimental Animals

8-week old male spontaneously hypertensive rats (SHR), weighing 230 to 250 g, were purchased from Charles River Japan (CRJ). The animals were used in the test, after being

subjected to an acclimation period until the animals were 18 to 19-week old (340 to 380 g) to reach a mean blood pressure of 160 to 170 mmHg. Animals with a good condition were selected by minute observation over the acclimation period prior to the test, and divided into individual test groups, each consisting of 8 animals (n=8). Only the selected animals, from which a rise in blood pressure was confirmed using a non-invasive blood pressure monitoring system (CODA-6), were assigned to the test group. Through the measurement of SHR blood pressure prior to application of the main test, SHR individuals having blood pressure outside a blood pressure range (individuals exhibiting a mean blood pressure below 140 mmHg or above 220 mmHg as measured) of normal SHR were excluded from the test.

2 Establishment of Drug-Treated Groups and Administration Method

A suitable dose capable of exhibiting a significant antihypertensive effect through a basic test and a preliminary test was taken as a final dose of drugs administered to experimental rats in this test. Low, medium and high doses of the drugs according to individual drugs were established in the preliminary test. Then, based on the test results, a dose capable of achieving significant lowering of a blood pressure from the blood pressure of hypertensive rats prior to administration of the drugs to a range of 20 to 50 mmHg after administration of the drugs (a dose corresponding to 20 to 25% of a usual clinical dose) was taken as an optimal dose of the single administration group. On the other hand, based on the review results from the literature, a dose capable of showing a stable antihypertensive action without causing toxicity at 4-week administration was set for the combination preparation-administered group. All the doses referred to those used in the already performed test. Doses and drug-administered groups used in the final main test are as follows.

As an ARB compound, Losartan potassium salt, Valsartan and Fimasartan potassium trihydrate were respectively purchased and used from Zhejiang Huahai Pharmaceutical Co., Ltd. 10 mg/kg of Losartan potassium salt was taken as an L group, and 10 mg/kg of Valsartan was taken as a V group. With regard to Fimasartan potassium trihydrate, 3 mg/kg was taken as an F1 group, and 10 mg/kg was taken as an F2 group.

As a calcium channel blocker, Amlodipine besylate (home-made by the method described in U.S. Pat. No. 4,572,909) was used. 0.5 mg/kg of Amlodipine besylate was taken as an A1 group, and a dose of 1.6 mg/kg was taken as an A2 group. The test materials and the comparative drugs were each suspended in 0.5% carboxymethylcellulose sodium salt (CMC—Na, Sigma) prior to using. As a control group, 0.5% CMC alone was administered.

3 Test Method

Administration: Upon carrying out the administration, the drug preparation was heated to a suitable temperature of 35° in a water bath, followed by forced oral administration of 5 mL/kg via a stomach sonde.

Measurement of blood pressure: Blood pressure of rats was measured as follows. Rats were restrained and placed in a heating device which was then heated to a temperature of about 40° (based on the temperature of 37° in a restraining cage) over 13 minutes, such that the tail blood vessels were engorged, and the blood pressure of rats was measured using CODA-6 equipment that monitors a blood pressure by means of the software of the main body through a pair of cuffs attached to the tail. The non-invasive blood pressure measuring method via CODA-6 (Kent Scientific Corporation) enables a long-term blood pressure measuring test that should involve repeated administration of test materials, which is not

feasible with a direct blood pressure measuring method through arterial cannulation, such as conventionally used physiograph or power lab. In order to confirm a disappearance pattern in response to doses of drugs by 4-week repeated administration and a degree of recovery to initial blood pressure, the blood pressure was measured once a day for 1 week after the final administration was completed.

Changes in blood pressure were confirmed with focusing on changes in mean arterial pressure (MAP), and changes in diastolic and systolic blood pressure, heart rate, and body weight were used as references for other changes in the experimental results.

(2) Results Processing and Statistical Analysis

Statistical analysis of the measurement values obtained in this experiment was carried out using a statistical program SPSS. For items where a significant F value is observed in one-way ANOVA, the comparison was made at significant levels of p<0.001, 0.01 and 0.05 between the control group and the experimental groups with a different dose of drugs.

In the 4-week repeated administration efficacy test, all of the groups including the control group exhibited a slight increase in body weight. The body weight tended to decrease at the early stage of the test, but the maintenance of the body weight was confirmed after the middle stage of the test. This was believed to be a symptom resulting from exposure to stress during the indirect blood pressure measurement, such as heating and restraint, not direct effects due to drugs.

Based on the measured results, kinds and doses of the drugs administered to the individual drug-administered groups, in conjunction with antihypertensive values obtained in the individual drug-administered groups, that is, the antihypertensive degree over 4 weeks in response to the drug administration, as calculated based on the blood pressure prior to administration of drugs, are given in Table 1 below.

TABLE 1

Antihypertensive degree (mmHg) with consecutive 4-week administration of drugs, as compared to blood pressure prior to administration		
Drug-administered groups (kinds and doses of drugs)	Mean	Standard error
Example 1 (F1 + A1)	-55	2.258
Example 2 (F2 + A2)	-75	2.536
Comparative Example 1 (F1)	-35	1.375
Comparative Example 2 (F2)	-50	2.135
Comparative Example 3 (L)	-20	1.256
Comparative Example 4 (V)	-32	2.862
Comparative Example 5 (A1)	-13	1.105
Comparative Example 6 (A2)	-20	1.325
Comparative Example 7 (L + A2)	-32	2.268
Comparative Example 8 (V + A2)	-46	2.675

As shown in Table 1 above, it can be seen that Comparative Example 1 exhibited a superior antihypertensive effect even with administration of a dose lower than a usual clinical dose (usual clinical dose of Fimasartan potassium trihydrate=60 mg, usual clinical dose of Losartan potassium salt=50 mg, and usual clinical dose of Valsartan=80 mg), as compared to Comparative Example 3 and Comparative Example 4.

Further, Examples 1 and 2, which use a combination preparation of Fimasartan and Amlodipine that is the composition of the present invention, exhibited an antihypertensive effect

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greater than a simple sum of antihypertensive effects obtained when each ingredient alone was administered. For example, as compared to an antihypertensive value of -13 mmHg for single administration of 0.5 mg/Kg of Amlodipine besylate (Comparative Example 5) and an antihypertensive value of -35 mmHg for single administration of 3 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 1), Example 1 corresponding to a combination preparation of both drugs (Amlodipine besylate and Fimasartan potassium trihydrate) exhibited an antihypertensive value of -55 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two drugs. This effect is a significant numerical value even upon taking into consideration a standard error. Further, as compared to an antihypertensive value of -20 mmHg for single administration of 1.6 mg/Kg of Amlodipine besylate (Comparative Example 6) and an antihypertensive value of -50 mmHg for single administration of 10 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 2), Example 2 corresponding to a combination preparation of both drugs exhibited an antihypertensive value of -75 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two drugs. This effect is confirmed to be an unexpected remarkable effect, when compared with the foregoing results (Comparative Examples 7 and 8) wherein a combination preparation of another ARB compound and Amlodipine exhibited an antihypertensive value smaller than a simple sum of antihypertensive values of individual ingredients of the combination preparation.

As described above, since the composition of the present invention exhibits an antihypertensive effect greater than the sum of antihypertensive effects obtained when each active ingredient alone was administered (synergistic effect), the risk of adverse side effects due to an overdose of individual active ingredients can also be greatly reduced by further decreasing the content of each active ingredient, and inconveniences associated with medication of patients upon performing combination therapy of individual active ingredients can be solved

PREPARATION EXAMPLE

Preparation of Composition (Tablet) of the Present Invention

The composition of the present invention was formulated into tablets containing ingredients and contents thereof as described in Table 2 below, each of which is expressed as Preparation Examples 1 to 4.

TABLE 2

Ingredients	Preparation Example 1 (mg/tablet)	Preparation Example 2 (mg/tablet)	Preparation Example 3 (mg/tablet)	Preparation Example 4 (mg/tablet)
Fimasartan potassium trihydrate	66.01	132.02	66.01	132.02
Amlodipine besylate	6.99	6.99	13.98	13.98
Corn starch	46	98.99	39.01	92
Microcrystalline cellulose	16	32	16	32
Croscovidone	10	20	10	20

TABLE 2-continued

Ingredients	Preparation Example 1 (mg/tablet)	Preparation Example 2 (mg/tablet)	Preparation Example 3 (mg/tablet)	Preparation Example 4 (mg/tablet)
Hydroxypropylcellulose	3.5	7	3.5	7
Magnesium stearate	1.5	3	1.5	3
Total weight/tablet (mg)	150	300	150	300

Preparation of Tablets

Fimasartan potassium trihydrate, Amlodipine besylate, corn starch, microcrystalline cellulose and croscovidone were placed in a high-speed mixer, followed by mixing. In addition, hydroxypropylcellulose and purified water (q.s.) were mixed to prepare a binding solution which was then added to the high-speed mixer where the pre-mixed powder was placed, followed by granulation. The resulting granules were dried in a drier. The dried granules were sieved through a No. 20 sieve and magnesium stearate was added thereto, followed by mixing to obtain a final mixture. The final mixture was compressed into tablets corresponding to Preparation Examples 1 to 4, using a rotary tablet press.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

What is claimed is:

1. An antihypertensive pharmaceutical composition, comprising:
Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and
Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.
2. The antihypertensive pharmaceutical composition of claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate.
3. The antihypertensive pharmaceutical composition of claim 2, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt.
4. The antihypertensive pharmaceutical composition of claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium trihydrate.
5. The antihypertensive pharmaceutical composition of claim 1, wherein the calcium channel blocker is an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate.
6. The antihypertensive pharmaceutical composition of claim 5, wherein the calcium channel blocker is an Amlodipine besylate.
7. The antihypertensive pharmaceutical composition of claim 1, wherein the amount of the angiotensin II receptor blocker is in the range of 0.5 to 240 mg, and the amount of the calcium channel blocker is in the range of 0.1 to 20 mg.
8. The antihypertensive pharmaceutical composition of claim 7, wherein the amount of the angiotensin II receptor blocker is in the range of 50 to 180 mg.
9. The antihypertensive pharmaceutical composition of claim 8, wherein the amount of the angiotensin II receptor blocker is in the range of 60 to 120 mg.

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10. The antihypertensive pharmaceutical composition of claim 7, wherein the amount of the calcium channel blocker is in the range of 5 to 15 mg.

11. The antihypertensive pharmaceutical composition of claim 10, wherein the amount of the calcium channel blocker is in the range of 5 to 10 mg.

12. The antihypertensive pharmaceutical composition of claim 1, wherein the pharmaceutical composition is an oral dosage form.

13. The antihypertensive pharmaceutical composition of claim 12, wherein the dosage form is a single tablet.

14. A method for the alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, comprising administering simultaneously or consecutively to a mammal in need thereof:

Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and

Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

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15. A method for treating a hypertension, comprising administering to a mammal an antihypertensive pharmaceutical composition comprising:

Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and

Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

16. The method of claim 15, wherein the mammal is a human.

17. The method of claim 15, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate.

18. The method of claim 17, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt.

19. The method of claim 15, wherein the calcium channel blocker is an Amlodipine besylate.

20. The method of claim 15, wherein the amount of the angiotensin II receptor blocker is in the range of 0.5 to 240 mg, and the amount of the calcium channel blocker is in the range of 0.1 to 20 mg.

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SOCIALIST REPUBLIC OF VIETNAM
MINISTRY OF SCIENCE AND TECHNOLOGY
NATIONAL OFFICE OF INTELLECTUAL PROPERTY

PATENT FOR INVENTION

No. **13960**

Title of Invention : ANTIHYPERTENSIVE PHARMACEUTICAL
COMPOSITION

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of National Office of Intellectual Property
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(54) Title of Invention: ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION

(57) Abstract:

The present invention provides an antihypertensive pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

Technical Field of the Invention

The present invention relates to an antihypertensive pharmaceutical composition.

Background of the Invention

Hypertension is one of the most common cardiovascular diseases. Typically, a person is diagnosed with hypertension when his/her blood pressure is in a range of 140/90 mmHg. Recently, the incidence of lifestyle-related diseases such as hypertension has rapidly increased. As hypertension may result in the occurrence of acute heart diseases or myocardial infarction, there is a continued need for development of a more effective antihypertensive agent.

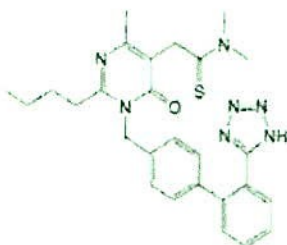
According to various clinical trials of antihypertensive agents, it was found that lowering of blood pressure of hypertensive patients leads to a decrease in mortality and morbidity of heart diseases or myocardial infarction (Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38). Although a variety of drugs have been used and administered for the purpose of treating such a clinical condition, suitable control of blood pressure is not always successful (Waeber B, Brunner HR, Am. J. Hypertens 1997, 10(7 Pt 2):131S-137S).

Among various applicable administration modes of antihypertensive drugs, a combination preparation or combination therapy of drugs is one method for achieving desired therapeutic results. On the other hand, arbitrary selection of various classes of antihypertensive agents for application of drugs to combination therapy prescription does not always provide help to achieve a desired blood pressure level in a hypertensive mammal including a human (MacGregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Br Med J (Clin Res Ed), 284 (6317): 693-6).

To this end, there is an obvious need for further development of therapeutic methods, combination preparations and pharmaceutical compositions against hypertension.

Fimasartan, which is chemically defined as 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]pyrimidin-4(3H)-one and has the following structural formula, is an antihypertensive agent of the angiotensin II receptor blocker (ARB) class and has currently been approved as a pharmaceutical product under brand name of KANARB.

[Fimasartan]



According to the randomized double-blind clinical testing conducted for the comparison of antihypertensive effects in patients with mild to moderate essential hypertension, at a dose of 60 mg to 120 mg of drugs between Fimasartan potassium and Losartan which is a representative compound of the ARB class, it was demonstrated that antihypertensive effects in terms of changes in diastolic blood pressure (DBP) in the sitting position at Week 12 of drug administration were respectively -11.26 ± 7.53 mmHg for the Fimasartan-treated group and -8.56 ± 7.72 mmHg for the Losartan-treated group, relative to a baseline, thus showing that antihypertensive effects after 12- or 24-week administration were higher in Fimasartan than Losartan (A Randomized, Double-blind, Losartan-controlled, Parallel Group Comparison Dose Titration Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Fimasartan (BR-A-657-K) 60mg ~ 120mg in Patients with Mild to Moderate Essential Hypertension (Phase III)).

Amlodipine is a calcium channel blocker (CCB), and blocks an inflow of calcium ions to cell membranes of cardiac and peripheral vascular smooth muscles and therefore directly relaxes vascular smooth muscles to exhibit antihypertensive effects. Although the action mechanism by which Amlodipine mitigates angina pectoris has not been fully understood, it was found that the following two action mechanisms function to relieve ischemic symptoms.

First, Amlodipine dilates peripheral arteries to decrease the total peripheral resistance (after-load), thus leading to decreased cardiac work, and stabilizes a heart rate to decrease cardiac energy consumption and oxygen demand."

Second, it is believed that Amlodipine dilates main coronary arteries and other coronary arterioles of ischemic lesions and normal regions. Such vasodilation plays a role to increase delivery of oxygen to myocardial ischemic lesions of patients with coronary artery convulsion.

Although active research for the treatment of hypertension has recently been focused on a combination preparation of Amlodipine, which is a calcium channel blocker, with a compound belonging to the ARB class, such a combination

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preparation may present additional problems in some cases, such as by causing drug-to-drug interaction and increased adverse side effects of individual drugs.

To this end, the inventors of the present invention have recognized problems of simple combination preparations of Amlodipine and ARB class compounds and conducted a variety of extensive and intensive studies to address the foregoing problems. As a result, the present invention has been completed.

Related technique

1. KR 1989-0011854 A 1989.08.22.,
2. WO 00/16773 1999.09.08.,
3. KR 2001-0013626 A 2001.02.26.,
4. KR 2001-0079517 A 2001.08.22.,
5. KR 2001-0090193 A 2001.10.18.,
6. KR 2004-0032639 2004.04.17.,
7. KR 2010-0048137 2010.05.11.,
8. Yoo SD et.al., Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry, *Biomed Chromatogr.* 2011 Jan 26. doi:10.1002/bmc. 1592. Epub ahead of print
9. Yu KS, et.al., Effect of multiple doses of fimasartan, an angiotensin II receptor antagonist, on the steady-state pharmacokinetics of digoxin in healthy volunteers. *Int J Clin Pharmacol Ther.* 2011 May;49(5):321-7
10. Yu KS et.al., The Effect of the Newly Developed Angiotensin Receptor II Antagonist Fimasartan on the Pharmacokinetics of Atorvastatin in relation to OATP1B1 in Healthy Male Volunteers. *J Cardiovasc Pharmacol.* 2011 Jul 14. Epub ahead of print

Summary of the Invention

Therefore, the present invention is intended to provide an antihypertensive pharmaceutical composition which is effective not only for the prevention, alleviation and treatment of hypertension, but also for the prevention, alleviation or treatment of complications of hypertension and/or hyperlipidemia.

The present invention provides an antihypertensive pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

Detailed Description of the Invention

In the present invention, Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

In the present invention, Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt with an inorganic acid, organic acid or metal, which has been conventionally used in the preparation of pharmaceutical products by pharmaceutical manufacturers. Examples of the inorganic acid include hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid. Examples of the organic acid include citric acid, acetic acid, lactic acid, tartaric acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid(besylate), maleic acid, benzoic acid, gluconic acid, glycolic acid, succinic acid, 4-morpholineethanesulfonic acid, camphorsulfonic acid(camsylate), 4-nitrobenzenesulfonic acid, hydroxy-o-sulfonic acid, 4-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid, aspartic acid and adipic acid(adipate). Examples of the metal include sodium, potassium, calcium and magnesium.

In the present invention, the angiotensin II receptor blocker is preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate, and more preferably a Fimasartan potassium salt or Fimasartan potassium trihydrate. These materials are commercially available or otherwise may be prepared by using a known method (for example, see Korean Patent Nos. 0354654 and 0521980).

In the present invention, the calcium channel blocker is preferably an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate, and more preferably Amlodipine besylate. These materials are commercially available or otherwise may be prepared by using a known method (for example, see US Patent No. 4572909).

In the present invention, the solvent in the "solvate" refers to a common organic solvent which has been used in the preparation of organic compounds. Examples of the solvent include, but are not limited to, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-acetate, acetone, acetic acid, anisole, tetrahydrofuran, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, n-butyl

acetate, dimethyl sulfoxide, pentane, and heptane.

In the present invention, the content of "hydrate" and "solvate" may be in a range of 0.25 to 10 moles relative to 1 mole of Fimasartan or Amlodipine, for example, 0.5 moles, 1 mole, 1.5 moles, 2 moles, 2.5 moles, 3 moles or 5 moles, but the present invention is not limited thereto.

The composition of the present invention may contain an angiotensin II receptor blocker in an amount of 0.5 to 240 mg, preferably 50 to 180 mg, and more preferably 60 to 120 mg.

Further, the composition of the present invention may contain a calcium channel blocker in an amount of 0.1 to 20 mg, preferably 5 to 15 mg, and more preferably 5 to 10 mg.

On the other hand, it is known that a conventional high dose (that is, pharmaceutically acceptable high dose/administration) of these drugs contained in a pharmaceutical composition is a maximum of 240 mg or less for Fimasartan and a maximum of 20 mg or less for Amlodipine, for an ordinary adult weighing 60 kg.

Throughout the specification, unless otherwise specifically indicated, the term "pharmaceutical composition" is intended to generally cover not only a single dosage form which is taken or administered at one single dose, such as tablet, capsule or injection, but also plural dosage forms which are administered at two or more divided doses. For example, the term "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker" is interpreted to designate not only a single dosage form containing these two active ingredients all together, but also two dosage forms in which each contains one active ingredient. That is, where these two dosage forms are simultaneously administered or are consecutively administered at regular intervals and therefore effective amounts of two active ingredients contained in each of these dosage forms coexist *in vivo* to bring about synergistic effects, these two dosage forms also fall within the scope of the "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker".

The composition of the present invention may further contain one or more pharmaceutically acceptable carriers besides the aforesaid ingredients, to be

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formulated into a variety of dosage forms for desired applications. Examples of the pharmaceutically acceptable carrier include saline, sterile water, Ringer's solution, buffered physiological saline, dextrose solution, maltodextrin solution, glycerol, and ethanol. These materials may be used alone or in any combination thereof. If necessary, other conventional additives may be added such as antioxidants, buffers and bacteriostatic agents.

Further, diluents, dispersants, surfactants, binders and lubricants may be additionally added to prepare injectable formulations such as aqueous solutions, suspensions, and emulsions, or oral formulations such as pills, capsules, granules, and tablets. Furthermore, the agent may be preferably formulated into a desired dosage form, depending on diseases to be treated and ingredients, using any appropriate method known in the art, or the method as disclosed in "Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

The composition of the present invention may be administered via oral routes or parenteral routes (for example, intravenously, subcutaneously, intraperitoneally, or locally), depending on desired applications. The dose of the composition may vary depending on weight, age, gender, health status, and dietary habits of patients, administration times and routes, excretion rates, and severity of disease. The composition of the present invention may be administered once or several times a day.

The composition of the present invention may be an injectable formulation such as aqueous solution, suspension or emulsion, or an oral formulation such as pill, capsule, granule or tablet or in the form of a kit. An oral dosage form is preferable and a single tablet is more preferable.

Further, the composition of the present invention, due to having an enhanced antihypertensive effect, may be used for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

Therefore, the present invention provides a pharmaceutical composition for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

Further, the present invention provides a method for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, including administering a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker to a mammal, including a human, in need thereof.

The present invention provides a method for preventing or treating a hypertension, comprising administering the antihypertensive pharmaceutical composition of the present invention to a mammal including a human.

In the method for preventing or treating a hypertension of the present invention, the antihypertensive pharmaceutical composition is comprised Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

In the method for preventing or treating a hypertension of the present invention, the sort or content of each of the angiotensin II receptor blocker and the calcium channel blocker is the same as described above regarding the antihypertensive pharmaceutical composition of present invention.

In the method for preventing or treating a hypertension of the present invention, the angiotensin II receptor blocker is preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate and more preferably is a Fimasartan potassium salt.

In the method for preventing or treating a hypertension of the present invention, the calcium channel blocker is preferably an Amlodipine besylate.

In the method for preventing or treating a hypertension of the present invention, the content of the angiotensin II receptor blocker is preferably in the range of 0.5 to 240 mg, and the content of the calcium channel blocker is in the range of 0.1 to 20 mg.

Further, the present invention provides a use of a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker, for manufacturing

a pharmaceutical preparation for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

Advantageous Effects

The composition of the present invention exhibits an enhanced antihypertensive effect greater than the simple sum of antihypertensive values of the same doses of individual active ingredients. Accordingly, the composition of the present invention enables the use of individual active ingredients at a content or dose lower than that upon separate use thereof, and thus can provide more effective treatment or prevention of hypertension or the like while reducing adverse side effects due to an overdose of individual active ingredients.

Examples

Now, the present invention will be described in more detail with reference to the following Examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

Experimental Example: antihypertensive effects of inventive composition

This study is intended to examine antihypertensive action of individual drugs. For this purpose, test drugs, i.e., Fimasartan potassium trihydrate, Losartan potassium salt, Valsartan, Amlodipine besylate, a combination of Fimasartan potassium trihydrate with Amlodipine besylate, a combination of Losartan potassium salt with Amlodipine besylate, and a combination of Valsartan with Amlodipine besylate were repeatedly and orally administered for 4 weeks to rats with essential hypertension. Changes in blood pressure, heart rate and body weight of animals were measured to investigate the antihypertensive action by long-term administration of individual drugs, confirm the maintenance degree of effective and stable blood pressure, and examine the difference between single administration and combined administration of drugs. In this manner, the antihypertensive action was compared and evaluated between the individual drugs.

(1) Test material and method

1. Experimental animals

8-week old male spontaneously hypertensive rats (SHR), weighing 230 to 250 g, were purchased from Charles River Japan (CRJ). The animals were used in the test,

after being subjected to an acclimation period until the animals were 18 to 19-week old (340 to 380 g) to reach a mean blood pressure of 160 to 170 mmHg. Animals with a good condition were selected by minute observation over the acclimation period prior to the test, and divided into individual test groups, each consisting of 8 animals ($n=8$). Only the selected animals, from which a rise in blood pressure was confirmed using a non-invasive blood pressure monitoring system (CODA-6), were assigned to the test group. Through the measurement of SHR blood pressure prior to application of the main test, SHR individuals having blood pressure outside a blood pressure range (individuals exhibiting a mean blood pressure below 140 mmHg or above 220 mmHg as measured) of normal SHR were excluded from the test.

2. Establishment of drug-treated groups and administration method

A suitable dose capable of exhibiting a significant antihypertensive effect through a basic test and a preliminary test was taken as a final dose of drugs administered to experimental rats in this test. Low, medium and high doses of the drugs according to individual drugs were established in the preliminary test. Then, based on the test results, a dose capable of achieving significant lowering of a blood pressure from the blood pressure of hypertensive rats prior to administration of the drugs to a range of 20 to 50 mmHg after administration of the drugs (a dose corresponding to 20 to 25% of a usual clinical dose) was taken as an optimal dose of the single administration group. On the other hand, based on the review results from the literature, a dose capable of showing a stable antihypertensive action without causing toxicity at 4-week administration was set for the combination preparation-administered group. All the doses referred to those used in the already performed test. Doses and drug-administered groups used in the final main test are as follows.

As an ARB compound, Losartan potassium salt, Valsartan and Fimasartan potassium trihydrate were respectively purchased and used from Zhejiang Huahai Pharmaceutical Co., Ltd. 10 mg/kg of Losartan potassium salt was taken as an L group, and 10 mg/kg of Valsartan was taken as a V group. With regard to Fimasartan potassium trihydrate, 3 mg/kg was taken as an F1 group, and 10 mg/kg was taken as an F2 group.

As a calcium channel blocker, Amlodipine besylate (home-made by the method described in US Patent No. 4572909) was used. 0.5 mg/kg of Amlodipine besylate was taken as an A1 group, and a dose of 1.6 mg/kg was taken as an A2 group. The test materials and the comparative drugs were each suspended in 0.5% carboxymethylcellulose sodium salt (CMC-Na, Sigma) prior to using. As a control group, 0.5% CMC alone was administered.

3. Test method

- **Administration:** Upon carrying out the administration, the drug preparation was heated to a suitable temperature of 35°C in a water bath, followed by forced oral administration of 5 mL/kg via a stomach sonde.

- **Measurement of blood pressure:** Blood pressure of rats was measured as follows. Rats were restrained and placed in a heating device which was then heated to a temperature of about 40°C (based on the temperature of 37°C in a restraining cage) over 13 minutes, such that the tail blood vessels were engorged, and the blood pressure of rats was measured using CODA-6 equipment that monitors a blood pressure by means of the software of the main body through a pair of cuffs attached to the tail. The non-invasive blood pressure measuring method via CODA-6 (Kent Scientific Corporation) enables a long-term blood pressure measuring test that should involve repeated administration of test materials, which is not feasible with a direct blood pressure measuring method through arterial cannulation, such as conventionally used physiograph or power lab. In order to confirm a disappearance pattern in response to doses of drugs by 4-week repeated administration and a degree of recovery to initial blood pressure, the blood pressure was measured once a day for 1 week after the final administration was completed.

Changes in blood pressure were confirmed with focusing on changes in mean arterial pressure (MAP), and changes in diastolic and systolic blood pressure, heart rate, and body weight were used as references for other changes in the experimental results.

(2) Results processing and statistical analysis

Statistical analysis of the measurement values obtained in this experiment was carried out using a statistical program SPSS. For items where a significant F value is observed in one-way ANOVA, the comparison was made at significant levels of $p < 0.001$, 0.01 and 0.05 between the control group and the experimental groups with a different dose of drugs.

In the 4-week repeated administration efficacy test, all of the groups including the control group exhibited a slight increase in body weight. The body weight tended to decrease at the early stage of the test, but the maintenance of the body weight was confirmed after the middle stage of the test. This was believed to be a symptom resulting from exposure to stress during the indirect blood pressure measurement, such as heating and restraint, not direct effects due to drugs.

Based on the measured results, kinds and doses of the drugs administered to the individual drug-administered groups, in conjunction with antihypertensive values

obtained in the individual drug-administered groups, that is, the antihypertensive degree over 4 weeks in response to the drug administration, as calculated based on the blood pressure prior to administration of drugs, are given in Table 1 below.

[Table 1]

Antihypertensive degree (mmHg) with consecutive 4-week administration of drugs, as compared to blood pressure prior to administration		
Drug-administered groups (kinds and doses of drugs)	Mean	Standard error
Example 1 (F1+A1)	-55	2.255
Example 2 (F2+A2)	-75	2.536
Comparative Example 1 (F1)	-35	1.375
Comparative Example 2 (F2)	-50	2.135
Comparative Example 3 (L)	-20	1.256
Comparative Example 4 (V)	-32	2.862
Comparative Example 5 (A1)	-13	1.105
Comparative Example 6 (A2)	-20	1.325
Comparative Example 7 (L+A2)	-32	2.268
Comparative Example 8 (V+A2)	-46	2.675

As shown in Table 1 above, it can be seen that Comparative Example 1 exhibited a superior antihypertensive effect even with administration of a dose lower than a usual clinical dose (usual clinical dose of Fimasartan potassium trihydrate = 60 mg, usual clinical dose of Losartan potassium salt = 50 mg, and usual clinical dose of Valsartan = 80 mg), as compared to Comparative Example 3 and Comparative Example 4.

Further, Examples 1 and 2, which use a combination preparation of Fimasartan and Amlodipine that is the composition of the present invention, exhibited an antihypertensive effect greater than a simple sum of antihypertensive effects obtained when each ingredient alone was administered. For example, as compared to an antihypertensive value of -13 mmHg for single administration of 0.5 mg/Kg of Amlodipine besylate (Comparative Example 5) and an antihypertensive value of -35 mmHg for single administration of 3 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 1), Example 1 corresponding to a combination preparation of both drugs (Amlodipine besylate and Fimasartan potassium trihydrate) exhibited an antihypertensive value of -55 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two

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drugs. This effect is a significant numerical value even upon taking into consideration a standard error. Further, as compared to an antihypertensive value of -20 mmHg for single administration of 1.6 mg/Kg of Amlodipine besylate (Comparative Example 6) and an antihypertensive value of -50 mmHg for single administration of 10 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 2), Example 2 corresponding to a combination preparation of both drugs exhibited an antihypertensive value of -75 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two drugs. This effect is confirmed to be an unexpected remarkable effect, when compared with the foregoing results (Comparative Examples 7 and 8) wherein a combination preparation of another ARB compound and Amlodipine exhibited an antihypertensive value smaller than a simple sum of antihypertensive values of individual ingredients of the combination preparation.

As described above, since the composition of the present invention exhibits an antihypertensive effect greater than the sum of antihypertensive effects obtained when each active ingredient alone was administered (synergistic effect), the risk of adverse side effects due to an overdose of individual active ingredients can also be greatly reduced by further decreasing the content of each active ingredient, and inconveniences associated with medication of patients upon performing combination therapy of individual active ingredients can be solved.

Preparation Example: Preparation of composition (tablet) of the present invention

The composition of the present invention was formulated into tablets containing ingredients and contents thereof as described in Table 2 below, each of which is expressed as Preparation Examples 1 to 4.

[Table 2]

Ingredients	Preparation Example 1 (mg/tablet)	Preparation Example 2 (mg/tablet)	Preparation Example 3 (mg/tablet)	Preparation Example 4 (mg/tablet)
Fimasartan potassium trihydrate	66.01	132.02	66.01	132.02
Amlodipine besylate	6.99	6.99	13.98	13.98
Corn starch	46	98.99	39.01	92
Microcrystalline cellulose	16	32	16	32
Crospovidone	10	20	10	20
Hydroxypropylcellulose	3.5	7	3.5	7
Magnesium stearate	1.5	3	1.5	3
Total weight/tablet (mg)	150	300	150	300

<Preparation of tablets>

Fimasartan potassium trihydrate, Amlodipine besylate, corn starch, microcrystalline cellulose and crospovidone were placed in a high-speed mixer, followed by mixing. In addition, hydroxypropylcellulose and purified water (q.s.) were mixed to prepare a binding solution which was then added to the high-speed mixer where the pre-mixed powder was placed, followed by granulation. The resulting granules were dried in a drier. The dried granules were sieved through a No. 20 sieve and magnesium stearate was added thereto, followed by mixing to obtain a final mixture. The final mixture was compressed into tablets corresponding to Preparation Examples 1 to 4, using a rotary tablet press.

CLAIMS

1. An antihypertensive pharmaceutical composition, comprising:
Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and
Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.
2. The antihypertensive pharmaceutical composition according to claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate.
3. The antihypertensive pharmaceutical composition according to claim 2, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt.
4. The antihypertensive pharmaceutical composition according to claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium trihydrate.
5. The antihypertensive pharmaceutical composition according to claim 1, wherein the calcium channel blocker is an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate.
6. The antihypertensive pharmaceutical composition according to claim 5, wherein the calcium channel blocker is an Amlodipine besylate.
7. The antihypertensive pharmaceutical composition according to claim 1, wherein the content of the angiotensin II receptor blocker is in the range of 0.5 to 240 mg, and the content of the calcium channel blocker is in the range of 0.1 to 20 mg.
8. The antihypertensive pharmaceutical composition according to claim 7, wherein the content of the angiotensin II receptor blocker is in the range of 50 to 180 mg.
9. The antihypertensive pharmaceutical composition according to claim 8, wherein the content of the angiotensin II receptor blocker is in the range of 60 to 120 mg.
10. The antihypertensive pharmaceutical composition according to claim 7, wherein

the content of the calcium channel blocker is in the range of 5 to 15 mg.

11. The antihypertensive pharmaceutical composition according to claim 10, wherein the content of the calcium channel blocker is in the range of 5 to 10 mg.

12. The antihypertensive pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is an oral dosage form.

13. The antihypertensive pharmaceutical composition according to claim 12, wherein the dosage form is a single tablet.

14. A pharmaceutical composition for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, comprising Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.