CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTÁ 8, COLOMBIA

Teléfono: (57-1) 347 3611
Telefax: (57-1) 211 8650
(57-1) 700 4814
Fax in U.S.A.: (1-305) 675 7743

www.cavelier.com
cavelier@cavelier.com

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-037959- -00014-0000
Fecha: 2012-07-09 17:09:53 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 61

Señor Superintendente
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 412

Referencia	:	Expediente **No. 07.037.959**
Asunto	:	Solicitud de Patente para: **COMPRIMIDO BICAPA QUE COMPRENDE TERLMISARTÁN Y AMLODIPINO**
Solicitante	:	**BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Fecha de Solicitud	:	17 de Abril de 2007

NOTARÍA SEXTA DE BOGOTÁ

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, abogada con Tarjeta Profesional No. 23.555, obrando como apoderada de **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución **No. 31916** de fecha 25 de Mayo de 2012, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"COMPRIMIDO BICAPA QUE COMPRENDE TERLMISARTÁN Y AMLODIPINO"** a favor de **BOEHRINGER INGELHEIM INTERNATIONAL GMBH.**

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución **No. 31916** de fecha 25 de Mayo de 2012, me fue notificada mediante edicto **No. 16471** desfijado el veintinueve (29) de Junio de dos mil doce (2012), por lo que el término para interponer el recurso de reposición vence el nueve (09) de Julio de dos mil doce (2012). En consecuencia, me encuentro dentro de la oportunidad legal.

III. FUNDAMENTO DE LA RESOLUCIÓN No. 31916

Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:

3.1. Declarar fundada la oposición presentada por la Doctora Eliana Isaura Moreno Bohórquez, en la calidad de apoderada de la sociedad Gynopharm S.A.

3.2. Negar el privilegio de patente para la invención **"COMPRIMIDO BICAPA QUE COMPRENDE TERLMISARTÁN Y AMLODIPINO".**

3.3. En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:

"La diferencia entre la invención definida en la reivindicación 1 y la composición del documento D2, consiste en que en la presente solicitud la combinación de agentes antihipertensivos corresponde a telmisartán y amlodipino, en lugar de bebazepril y amlodipino que propone D2."

"La diferencia entre la invención definida en la reivindicación 1 y la composición del documento D1 consiste en que la combinación de antihipertensivos propuesta en la anterioridad consiste en lacidipino y telmisartan, en lugar de telmisartán amlodipino de la presente solicitud."

"El efecto que logra el incluir telmisartán en lugar de benazepril en la formulación revelada en el documento D2, es que se obtiene una combinación antihipertensiva adicional a partir de compuestos que son altamente reconocidos por su propiedades modulares de los niveles de tensión arterial y cuyos mecanismos de acción están suficientemente divulgados en el estado de la técnica. La descripción carece de información que permita establecer el efecto técnico sorprendente o inesperado al combinar telmisartán y amlodipino, que logre el mismo efecto hipotensor que se obtienen de la administración de cada uno de estos agentes de manera individual. En consecuencia, la formulación presentada corresponde tan solo a una nueva formulación de estos agentes que ahora se encuentran combinados en una misma forma farmacéutica, pero que no proporciona ningún efecto ventajoso o inusual.

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

4.1. Revocar la Resolución **31916** de fecha 25 de Mayo de 2012, y en su lugar:

Declarar infundada la oposición presentada por la Doctora Eliana Isaura Moreno Bohórquez, en la calidad de apoderada de la sociedad Gynopharm S.A., y

Conceder el privilegio de patente de invención para **"COMPRIMIDO BICAPA QUE COMPRENDE TERLMISARTÁN Y AMLODIPINO"** a favor de **BOEHRINGER INGELHEIM INTERNATIONAL GMBH.**

V. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, ya que la presente solicitud posee nivel inventivo a la luz de las enseñanzas de los documentos WO 00/27397 (D1) y US 6 162 802 (D2).

La anterior afirmación tiene justificación jurídica y técnica por las siguientes razones:

5.1. Violación del artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina:

De acuerdo con el artículo 18 de la Decisión 486:

"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."

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con

NOTARÍA SEXTA BOGOTÁ

respecto al arte previo es un indicio de nivel inventivo, por cuanto aportan un salto tecnológico en la regla técnica.

A este respecto manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

Inicialmente, resulta necesario poner de presente que el telmisartán es un **antagonista de los receptores de angiotensina II**, mientras que el benzapril corresponde a un **inhibidor de la enzima convertidora de angiotensina** (IECA); por lo que dichos documentos tratan compuestos diferentes y corresponden a clases completamente diferentes, debido a su efecto biológico y características químicas y físicas.

En vista de lo anterior, su Despacho debe considerar que la anterioridad D1 (WO 00/27397) enseña específicamente la combinación de telmisartán con lacidipina (favor referirse a los ejemplos 1, 3a a 3d y 4), contrario a la formulación de comprimido bicapa reclamada en la presente solicitud. En este sentido, únicamente el ejemplo 2 de dicha anterioridad menciona la comprensión separada para producir comprimidos bicapa, pero no hace referencia alguna a capas separadas en dicha preparación. Adicionalmente, D1 no presenta enseñanza o indicio alguno que lleve a una persona versada en la materia a combinar el telmisartán con un bloqueador del canal del calcio, ni mucho menos hace mención específica a la amlodipina.

NOTARÍA SEXTA DE BOGOTÁ

Por el contrario, las enseñanzas relacionadas con la combinación de telmisartán como lacidipina alejan de la presente invención, y no existe motivación alguna para reemplazar lacidipina por amlodipina en un comprimido bicapa.

Ahora bien, a pesar que el documento D2 enseña comprimidos de amlodipina y belazepril, no existe motivación alguna en dicho documento que lleve a combinar amlodipina con telmisartán, y mucho menos en un comprimido bicapa. Aún más, y teniendo en cuenta el problema de estabilidad causado por la incompatibilidad de la amlodipina con los componentes básicos de las formulaciones de telmisartán, como es mencionado en el resumen de la invención de la presente solicitud, una persona versada en la materia evitaría usar telmisartán específicamente, ya que existe un gran número de otros antagonistas del receptor de la angiotensina II que se pueden utilizar. Sin embargo, y de manera sorprendente, los inventores encontraron que la capa de amlodipina en un comprimido bicapa que consiste de una capa de telmisartán y de amlodipina era lo suficientemente estable, a pesar de estar en contacto directo con los excipientes básicos necesarios para formar una capa de telmisartán.

NOTARÍA SEXTA DE BOGOTÁ

Adicionalmente, el documento D2 no llevaría a la formación de comprimidos bicapa, como es afirmado en la resolución impugnada, sino que en su lugar dicho documento claramente indica que la separación física de dos sustancias en una sola forma de dosificación se puede lograr en "miles de maneras conocidas en la técnica, tales como los comprimidos bicapa, píldoras recubiertas de un agente incorporado en una capa de la otra, por gránulos recubiertos separados de cada agente en una cápsula o tableta, gránulos revestidos de un agente en cápsula junto con el polvo del otro agente, cada agente microencapsulado por separado y luego mezclado juntos para su uso en una tableta o cápsula, el uso de un dispositivo transdérmico de doble o múltiple compartimientos, etc." (véase la columna 3 líneas 51-58 de D2).

Finalmente, D2 enseña específicamente, que "un comprimido recubierto de benazepril en combinación con polvo de amlodipina en una cápsula resulta la forma oral más deseable" (véase la columna 3 líneas 59-62 de D3), es decir, D2 enseña que la forma de dosificación deseada es una diferente a la de los comprimidos bicapas. En otras palabras, la persona medianamente versada en la materia encargada de preparar un comprimido de dos capas no habría consultado D2, porque D2 no contiene una enseñanza en particular de un comprimido bicapas, y mucho menos un comprimido de dos capas que consiste en capas separadas para telmisartán y amlodipino.

NOTARÍA SEXTA DE BOGOTÁ

Por lo tanto, y contrario a las afirmaciones del Señor Examinador, resulta claro que sobre la base de las enseñanzas de D1 y D2, el experto no sabría cómo modificar las formulaciones de D2 reemplazando el benazepril por telmisartán, como es enseñado en D1. Así las cosas, contrario a las consideraciones del Examinador, una persona versada en la materia no tendría ningún incentivo a considerar dicho documento al estar enfrentado al problema que se presenta en la solicitud. De esta manera se desvirtúa lo manifestado por su Despacho con respecto a que la presente invención no había superado un prejuicio técnico y por ende, queda acreditado el nivel inventivo de la misma.

Por último, se desea poner de presente que aunque nos encontramos de acuerdo con la soberanía y autonomía de su Oficina para realizar el examen de patentabilidad de las solicitudes de patentes, consideramos relevantes tener de presente que la solicitud bajo estudio ha sido otorgada por varias jurisdicciones, incluyendo Australia, Canadá, la Oficina de Patentes Eurásica, Indonesia. Nueva Zelanda, Singapur, Taiwán, Ucrania, Vietnam, y Sur África.

5.2. Conclusión

En línea con los argumentos presentados y con las disposiciones de la legislación actual en materia de patentes, consideramos que el estudio de patentabilidad no fue correctamente realizado y que contrario a lo que afirma el Examinador, los comprimidos bicapa reivindicados en la presente solicitud sí presentan nivel inventivo, teniendo en cuenta que la presente invención responde a una necesidad, presenta ventajas reales, y resulta inesperado a partir de las enseñanzas de las anterioridades citadas, ya que una persona conocedora en la materia no esperaría que la combinación de telmisartán con amlodipina en un comprimido bicapa permitiera solucionar los problemas de estabilidad producidos por la incompatibilidad del amlodipina con los constituyentes de la formulación de telmisartán.

Por lo tanto, la decisión tomada en este sentido debe ser revocada, dado que la solicitud en estudio cumple con los requerimientos de patentabilidad tal como exige la Decisión 486 de la Comunidad Andina.

VI. PETICIONES

Ruego a Usted entonces, lo siguiente:

6.1. Revocar la Resolución **31916** de fecha 25 de Mayo de 2012, y en su lugar:

Declarar infundada la oposición presentada por la Doctora Eliana Isaura Moreno Bohórquez, en la calidad de apoderada de la sociedad Gynopharm S.A., y

Conceder el privilegio de patente de invención para **"COMPRIMIDO BICAPA QUE COMPRENDE TERLMISARTÁN Y AMLODIPINO"** a favor de **BOEHRINGER INGELHEIM INTERNATIONAL GMBH.**

VII. NOMBRE Y DIRECCIÓN DEL RECURRENTE

El nombre y la dirección del recurrente son:

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Binger Strasse 173,
55216 Ingelheim am Rhein,
Alemania

NOTARÍA SEXTA DE BOGOTÁ

VIII. ANEXOS

Copia de la patentes otorgadas en Australia, Canadá, por la Oficina de Patentes Eurásica, Indonesia. Nueva Zelanda, Singapur, Taiwán, Ucrania, Vietnam, y Sur África para la presente invención.

VIII. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaria de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4°, de esta ciudad de Bogotá, D.C.

Señor Superintendente,

Luz Clemencia Páez

LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

NOTARÍA SEXTA DE BOGOTÁ

COLO-09255-841-072-3
COLO-09255-264-006-9
LLG\LLG\ID-221159\WPCL9255
No. M-2012-221159\LLG

RECONOCIMIENTO Y PRESENTACION PERSONAL

09 JUL 2012

Luz. Clemencia.
Suarez de paez

C.C. 35.456.344 USA
T.P. 23.555

que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

Luz Clemencia Suárez
TP# 23555 CSJ

REPÚBLICA DE COLOMBIA
Amparo Quintero Arturo
NOTARIA
NOTARIA SEXTA DE BOGOTÁ

1-1800-AU

Australian Government
IP Australia

LETTERS PATENT

STANDARD PATENT

2005300787

I, Fatima Beattie, the Commissioner of Patents, grant a Standard Patent with the following particulars:

Name and Address of Patentee(s):

Boehringer Ingelheim International GmbH
Binger Strasse 173, Ingelheim/Rhein, 55216, Germany

Name of Actual Inventor(s):

Eisenreich, Wolfram.

Title of Invention:

Bilayer tablet comprising telmisartan and amlodipine

Term of Letters Patent:

Twenty years from 29 October 2005

Priority Details :

Number	*Date*	*Filed with*
04026234.7	5 November 2004	EP

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

Dated this 8th day of September 2011

Fatima Beattie
Commissioner of Patents

PATENTS ACT 1990

(12) **STANDARD PATENT**
(19) **AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 2005300787 B2**

(54) Title
Bilayer tablet comprising telmisartan and amlodipine

(51) International Patent Classification(s)
A61K 9/20 (2006.01)
A61K 31/4184 (2006.01)
A61K 31/4422 (2006.01)
A61P 3/10 (2006.01)
A61P 9/00 (2006.01)
A61P 9/04 (2006.01)
A61P 9/08 (2006.01)
A61P 9/10 (2006.01)
A61P 9/12 (2006.01)
A61P 25/28 (2006.01)

(21) Application No: **2005300787**

(22) Date of Filing: **2005.10.29**

(87) WIPO No: **WO06/048208**

(30) Priority Data

(31) Number	(32) Date	(33) Country
04026234.7	**2004.11.05**	**EP**

(43) Publication Date : **2006.05.11**
(44) Accepted Journal Date : **2011.05.26**

(71) Applicant(s)
Boehringer Ingelheim International GmbH

(72) Inventor(s)
Eisenreich, Wolfram

(74) Agent/Attorney
Davies Collison Cave, 1 Nicholson Street, Melbourne, VIC, 3000

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. *The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.*

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. *The tablet of claim 1, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.*

9. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

10. The tablet of claim 9, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

11. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

12. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

13. The tablet of claim 1 packaged in a moisture proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles.

14. A method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

15. The method of claim 14 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

16 ... omnibus claims

POA-1800 CA

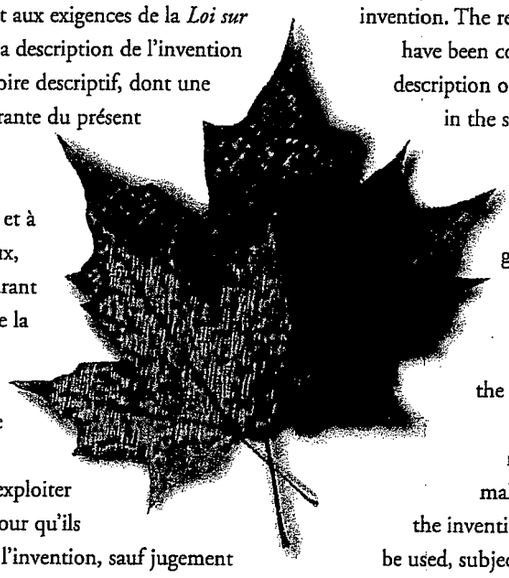
Office de la propriété intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An Agency of Industry Canada

Brevet canadien / Canadian Patent

Le commissaire aux brevets a reçu une demande de délivrance de brevet visant une invention. Ladite requête satisfait aux exigences de la *Loi sur les brevets*. Le titre et la description de l'invention figurent dans le mémoire descriptif, dont une copie fait partie intégrante du présent document.

Le présent brevet confère à son titulaire et à ses représentants légaux, pour une période expirant vingt ans à compter de la date du dépôt de la demande au Canada, le droit, la faculté et le privilège exclusif de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce rendu par un tribunal compétent, et sous réserve du paiement des taxes périodiques.



The Commissioner of Patents has received a petition for the grant of a patent for an invention. The requirements of the *Patent Act* have been complied with. The title and a description of the invention are contained in the specification, a copy of which forms an integral part of this document.

The present patent grants to its owner and to the legal representatives of its owner, for a term which expires twenty years from the filing date of the application in Canada, the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used, subject to adjudication before any court of competent jurisdiction, and subject to the payment of maintenance fees.

BREVET CANADIEN **2,582,049** CANADIAN PATENT

Date à laquelle le brevet a été accordé et délivré	**2010/08/24**	Date on which the patent was granted and issued
Date du dépôt de la demande	**2005/10/29**	Filing date of the application
Date à laquelle la demande est devenue accessible au public pour consultation	**2006/05/11**	Date on which the application was made available for public inspection

Commissaire aux brevets / Commissioner of Patents

Canada

3256 (CIPO 91) 09/09

OPIC CIPO

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

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2582049 C 2010/08/24

(11)(21) 2 582 049

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2005/10/29
(87) Date publication PCT/PCT Publication Date: 2006/05/11
(45) Date de délivrance/Issue Date: 2010/08/24
(85) Entrée phase nationale/National Entry: 2007/03/26
(86) N° demande PCT/PCT Application No.: EP 2005/011596
(87) N° publication PCT/PCT Publication No.: 2006/048208
(30) Priorité/Priority: 2004/11/05 (EP04026234.7)

(51) Cl.Int./Int.Cl. *A61K 9/20* (2006.01),
A61K 31/4184 (2006.01), *A61K 31/4422* (2006.01),
A61P 25/28 (2006.01), *A61P 3/10* (2006.01),
A61P 9/00 (2006.01), *A61P 9/04* (2006.01),
A61P 9/08 (2006.01), *A61P 9/10* (2006.01),
A61P 9/12 (2006.01)

(72) Inventeur/Inventor:
EISENREICH, WOLFRAM, DE

(73) Propriétaire/Owner:
BOEHRINGER INGELHEIM INTERNATIONAL GMBH, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : COMPRIME BICOUCHE CONTENANT DU TELMISARTAN ET DE L'AMLODIPINE
(54) Title: BILAYER TABLET COMPRISING TELMISARTAN AND AMLODIPINE

(57) Abrégé/Abstract:
A bilayer tablet comprises a first layer formulated for instant release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix and a second layer formulated for instant release of the calcium channel blocker amlodipine from a disintegrating or eroding tablet matrix.

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

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2582049 C 2010/08/24

(11)(21) 2 582 049

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2005/10/29
(87) Date publication PCT/PCT Publication Date: 2006/05/11
(45) Date de délivrance/Issue Date: 2010/08/24
(85) Entrée phase nationale/National Entry: 2007/03/26
(86) N° demande PCT/PCT Application No.: EP 2005/011596
(87) N° publication PCT/PCT Publication No.: 2006/048208
(30) Priorité/Priority: 2004/11/05 (EP04026234.7)

(51) Cl.Int./Int.Cl. *A61K 9/20* (2006.01), *A61K 31/4184* (2006.01), *A61K 31/4422* (2006.01), *A61P 25/28* (2006.01), *A61P 3/10* (2006.01), *A61P 9/00* (2006.01), *A61P 9/04* (2006.01), *A61P 9/08* (2006.01), *A61P 9/10* (2006.01), *A61P 9/12* (2006.01)

(72) Inventeur/Inventor:
EISENREICH, WOLFRAM, DE

(73) Propriétaire/Owner:
BOEHRINGER INGELHEIM INTERNATIONAL GMBH, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : COMPRIME BICOUCHE CONTENANT DU TELMISARTAN ET DE L'AMLODIPINE
(54) Title: BILAYER TABLET COMPRISING TELMISARTAN AND AMLODIPINE

(57) Abrégé/Abstract:
A bilayer tablet comprises a first layer formulated for instant release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix and a second layer formulated for instant release of the calcium channel blocker amlodipine from a disintegrating or eroding tablet matrix.

CLAIMS:

1. A pharmaceutical tablet having instant release characteristics comprising a first layer of substantially amorphous telmisartan or a pharmaceutically acceptable salt thereof in a dissolving tablet matrix comprising a basic agent and a water-soluble diluent and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. The tablet of claim 1, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

3. The tablet of claim 1, wherein the basic agent is one or both of sodium hydroxide and meglumine.

4. The tablet of any one of claims 1 to 3, wherein the water-soluble diluent is selected from a monosaccharide; an oligosaccharide; and a sugar alcohol.

5. The tablet of claim 4, wherein the monosaccharide is glucose.

6. The tablet of claim 4, wherein the oligosaccharide is sucrose or lactose.

7. The tablet of claim 4, wherein the sugar alcohol is sorbitol, mannitol, or xylitol.

8. The tablet of any one of claims 1 to 7, wherein the first layer is produced by spray-drying an aqueous solution comprising the telmisartan or the salt thereof and the basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with the water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.

9. The tablet of any one of claims 1 to 8, wherein the dissolving tablet matrix further comprises excipients and adjuvants beyond the basic agent and the water-soluble diluent.

10. The tablet of claim 8, wherein the excipients and adjuvants beyond the basic agent and the water-soluble diluent are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

11. The tablet of claim 10, wherein the binders are selected from one or more of microcrystalline cellulose, pregelatinized starch and povidone.

12. The tablet of claim 10, wherein the fillers are selected from one or more of pregelatinized starch, microcrystalline cellulose, sorbitol and microcrystalline cellulose.

13. The tablet of claim 10, wherein the lubricant is magnesium stearate.

14. The tablet of any one of claims 1 to 13, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant and a lubricant.

15. The tablet of claim 14, wherein the disintegrating or eroding tablet matrix of the second layer further comprises a binder, a flow control agent or excipients and adjuvants beyond the one or more fillers, the disintegrant and the lubricant.

16. The tablet of claim 14 or 15, wherein the second layer is produced by direct compression, wet granulation or a roller compaction process.

17. The tablet of any one of claims 1 to 16, wherein the first layer comprises 10 to 160 mg of the telmisartan, or of the salt thereof.

18. The tablet of any one of claims 1 to 16, wherein the first layer comprises 20 to 80 mg of the telmisartan, or of the salt thereof.

19. The tablet of any one of claims 1 to 16, wherein the first layer comprises 40 to 80 mg of the telmisartan, or of the salt thereof.

20. The tablet of any one of claims 1 to 15, wherein the second layer comprises 1 to 20 mg of the amlodipine.

21. The tablet of any one of claims 1 to 15, wherein the second layer comprises 2.5 to 10 mg of the amlodipine.

22. The tablet of any one of claims 1 to 16, wherein the first layer comprises 40 mg of the telmisartan or of the salt thereof and the second layer comprises 5 mg of the amlodipine.

23. The tablet of any one of claims 1 to 16, wherein the first layer comprises 40 mg of the telmisartan or of the salt thereof and the second layer comprises 10 mg of the amlodipine.

24. The tablet of any one of claims 1 to 16, wherein the first layer comprises 80 mg of the telmisartan or of the salt thereof and the second layer comprises 5 mg of the amlodipine.

25. The tablet of any one of claims 1 to 16, wherein the first layer comprises 80 mg of the telmisartan or of the salt thereof and the second layer comprises 10 mg of the amlodipine.

26. The tablet of any one of claims 1 to 25, wherein the telmisartan is in the form of the telmisartan sodium salt thereof.

27. The tablet of any one of claims 1 to 26, packaged in a moisture proof packaging material.

28. The tablet of claim 27, wherein the moisture proof packaging material is an aluminium foil blister pack, a polypropylene tube or a high density polyethylene (HDPE) bottle.

29. The tablet of any one of claims 1 to 28 for treatment of hypertension in a patient.

30. The tablet of claim 29, wherein the patient is also being treated for or is being treated for prevention of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum

concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline or dementia.

31. The tablet of claim 29, wherein the patient is also being treated for or is being treated for prevention of chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

32. Use of the tablet of any one of claims 1 to 28 for treatment of hypertension in a patient.

33. The use of claim 32, wherein the patient is also being treated for or is being treated for prevention of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline or dementia.

34. The use of claim 32, wherein the patient is also being treated for or is being treated for prevention of chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

95029

ЕВРАЗИЙСКАЯ ПАТЕНТНАЯ ОРГАНИЗАЦИЯ
ЕВРАЗИЙСКОЕ ПАТЕНТНОЕ ВЕДОМСТВО

1-1800-EA

ЕВРАЗИЙСКИЙ ПАТЕНТ

ЕВРАЗИЙСКИЙ ПАТЕНТ

№ 013053

Название изобретения:

«ДВУСЛОЙНАЯ ТАБЛЕТКА, СОДЕРЖАЩАЯ ТЕЛМИСАРТАН И АМЛОДИПИН»

Патентовладелец (льцы):

БЁРИНГЕР ИНГЕЛЬХАЙМ ИНТЕРНАЦИОНАЛЬ ГМБХ (DE)

Изобретатель (и):

Айзенрайх Вольфрам (DE)

Заявка №:	**200700977**
Приоритет изобретения:	**05 ноября 2004 г.**
Дата подачи заявки:	**29 октября 2005 г.**
Дата выдачи патента:	**26 февраля 2010 г.**

Настоящим удостоверяется, что евразийский патент выдан на изобретение, изложенное в прилагаемом описании и формуле изобретения.

При уплате установленных годовых пошлин патент действует на территории государств участников Евразийской патентной конвенции – Азербайджанской Республики, Кыргызской Республики, Республики Армения, Республики Беларусь, Республики Казахстан, Республики Молдова, Республики Таджикистан, Российской Федерации, Туркменистана

ГРИГОРЬЕВ Александр Николаевич
Президент Евразийского патентного ведомства

(19) Евразийское патентное ведомство

(11) 013053 (13) B1

(12) ОПИСАНИЕ ИЗОБРЕТЕНИЯ К ЕВРАЗИЙСКОМУ ПАТЕНТУ

(45) Дата публикации и выдачи патента: 2010.02.26

(21) Номер заявки: 200700977

(22) Дата подачи: 2005.10.29

(51) Int. Cl. *A61K 9/20* (2006.01)
A61K 31/4184 (2006.01)
A61K 31/4422 (2006.01)
A61P 9/00 (2006.01)
A61P 9/04 (2006.01)
A61P 9/08 (2006.01)
A61P 9/10 (2006.01)
A61P 9/12 (2006.01)
A61P 3/10 (2006.01)
A61P 25/28 (2006.01)

(54) ДВУСЛОЙНАЯ ТАБЛЕТКА, СОДЕРЖАЩАЯ ТЕЛМИСАРТАН И АМЛОДИПИН

(31) 04026234.7
(32) 2004.11.05
(33) EP
(43) 2007.10.26
(86) PCT/EP2005/011596
(87) WO 2006/048208 2006.05.11

(71)(73) Заявитель и патентовладелец:
БЕРИНГЕР ИНГЕЛЬХАЙМ ИНТЕРНАЦИОНАЛЬ ГМБХ (DE)

(72) Изобретатель:
Айзенрайх Вольфрам (DE)

(74) Представитель:
Веселицкая И.А., Пивницкая Н.Н., Кузенкова Н.В., Веселицкий М.Б., Каксис Р.А., Комарова О.М., Белоусов Ю.В. (RU)

(56) WO-A-03059327

STANGIER, J. ET AL.: "PHARMACOKINETICS OF REPEATED ORAL DOSES OF AMLODIPINE AND AMLODIPINE PLUS TELMISARTAN IN HEALTHY VOLUNTEERS", JOURNAL OF CLINICAL PHARMACOLOGY, LIPPINCOTT CO, HAGERSTOWN, MD, US, vol. 40, no. 12, PART 1, December, 2000 (2000-12), pages 1347-1354, XP008058908, ISSN: 0091-2700, abstract, page 1348, right-hand column, paragraph 2, page 1349, left-hand column, lines 10-13, page 1353, left-hand column, paragraph 2, right-hand column, last paragraph

NEUTEL J.M. ET AL.: "The efficacy and safety of telmisartan compared to enalapril in patients with severe hypertension", INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, vol. 53, no. 3, 1999, pages 175-178, XP008060086, abstract, page 175, left-hand column, paragraph 1 - right-hand column, paragraph 2, page 177, left-hand column, paragraph 6 - right-hand column, paragraph 4, page 178, left-hand column, paragraph 4 - right-hand column, paragraph 2

WO-A-03097045

WO-A-2005070462

(57) В изобретении описана двуслойная таблетка, включающая первый слой, приготовленный для немедленного выделения антагониста рецептора ангиотензина II телмисартана из растворяющейся матрицы таблетки, и второй слой, приготовленный для немедленного выделения блокатора кальциевых каналов амлодипина из распадающейся или разрушающейся матрицы таблетки.

013053 B1

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix comprising a basic agent, a water-soluble diluent and a second layer of amlodipine in a disintegrating or eroding tablet matrix comprising one or more fillers, a disintegrant and a lubricant.

2. *The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.*

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix further comprises other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer further comprises a binder, a flow control agent or other excipients and adjuvants.

9. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

10. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

11. The tablet of any one of claims 1-12, wherein the first layer comprises telmisartan in the form of a pharmaceutically acceptable salt.

12. A method for the manufacture of a tablet of claim 1 by compressing a first and a second tablet layer composition on a tablet press to form a bilayer tablet, characterized in that
the first tablet layer composition is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend; and
the second tablet layer composition is manufactures by direct compression, wet granulation or a roller compaction process.

13. Use of the tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-

cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

14. The use of claim 15 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

26

NI00135

1-1800-1D

REPUBLIK INDONESIA
KEMENTERIAN HUKUM DAN HAK ASASI MANUSIA

SERTIFIKAT PATEN

Menteri Hukum dan Hak Asasi Manusia atas nama Negara Republik Indonesia berdasarkan Undang-Undang Nomor 14 Tahun 2001 tentang Paten, memberikan Paten kepada:

Nama dan Alamat Pemegang Paten	:	BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173, 55216 Ingelheim am Rhein GERMANY
untuk Invensi dengan Judul	:	TABLET BERLAPIS DUA YANG MENGANDUNG TELMISARTAN DAN AMLODIPIN
Inventor	:	Wolfram EISENREICH
Tanggal Penerimaan	:	29 Oktober 2005
Nomor Paten	:	ID P0029185
Tanggal Pemberian	:	23 September 2011

Perlindungan Paten untuk invensi tersebut diberikan untuk selama 20 tahun terhitung sejak Tanggal Penerimaan (Pasal 8).

Sertifikat Paten ini dilampiri dengan deskripsi, klaim, abstrak dan gambar (jika ada) dari invensi yang tidak terpisahkan dari sertifikat ini.

a.n. MENTERI HUKUM DAN HAK ASASI MANUSIA
DIREKTUR JENDERAL HAK KEKAYAAN INTELEKTUAL
u.b.
Direktur Paten

Corrie Naryati, SH
NIP. 195501231984032001

REPUBLIC OF INDONESIA
MINISTRY OF LAW AND HUMAN RIGHTS

PATENT CERTIFICATE

The Minister of Law and Human rights, in the name of the Republic of Indonesia, in accordance to the Law Number 14 of 2001 concerning Patents, has granted a Patent to :

Name and Address of The Patent Holder	: BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173, 55216 Ingelheim am Rhein, GERMANY

for the Invention :

Entitled	: BILAYER TABLET COMPRISING TELMISARTAN AMLODIPINE
The Inventors	: Wolfram EISENREICH
Date of receipt of the application	: October 29, 2005
Patent Number	: ID P0029185
Date of Grant	: September 23, 2011

Patent Protection for the Invention shall be granted for a period of 20 years as of the date of receipt of this patent application (art 8).

This Patent Certificate is enclosed with the description, claims, abstract and drawing(s) (if any) that are inseparable parts of this Patent Certificate.

For : THE MINISTER OF LAW AND HUMAN RIGHTS
Director General of Intellectual Property Rights
Director of Patent
(Signed)

Ir. Razilu, M. Si.
NIP. 196511281991031002

(12) PATEN INDONESIA

(19) DIREKTORAT JENDERAL
HAK KEKAYAAN INTELEKTUAL

(11) **ID P0029185 B**

(45) 23 September 2011

(51) Klasifikasi, IPC: A61K 9/20(2006.01), 31/4184(2006.01), 31/4422(2006.01); A61P 9/00(2006.01), 9/04(2006.01), 9/08(2006.01), 9/10(2006.01), 9/12(2006.01), 3/10(2006.01), 25/28(2006.01)

(21) Nomor Permohonan: W00200701371

(22) Tanggal Penerimaan: 29 Oktober 2005

(30) Data Prioritas:
(31) 04026234.7
(32) 05 Nopember 2004
(33) EP

(43) Tanggal Pengumuman: 16 Mei 2007

(56) Dokumen Pembanding:
WO-A-03059327
WO-A-03097045
WO-A-2005070462

(71) Nama dan Alamat Pemohon:
BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Binger Strasse 173, 55216 Ingelheim am Rhein
GERMANY

(72) Nama Inventor:
Wolfram EISENREICH, DE

(74) Nama dan Alamat Konsultan HKI:
Prof. Dr. T. HERATY N. ROOSSENO
228/2006
BIRO OKTROI ROOSSENO
Kantor Taman A-9, Unit C1 & C2,
Jl. Mega Kuningan, Kuningan, Jakarta 12950

Pemeriksa Paten: Ir. A. Fauzi Tanjung

Jumlah Klaim: 14 Klaim

(54) Judul Invensi: TABLET BERLAPIS DUA YANG MENGANDUNG TELMISARTAN DAN AMLODIPIN

Abstrak:

Tablet berlapis dua yang terdiri dari lapisan pertama yang diformulasikan untuk pelepasan segera antagonis reseptor angiotensin II telmisartan dari matriks melarut dan lapisan kedua yang diformulasikan untuk pelepasan segera amlodipin pemblokade kanal kalsium dari matriks tablet yang hancur atau mengikis.

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix comprising a basic agent, a water-soluble diluent and a second layer of amlodipine in a disintegrating or eroding tablet matrix comprising one or more fillers, a disintegrant and a lubricant.

2. The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix further comprises other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer further comprises a binder, a flow control agent or other excipients and adjuvants.

9. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

10. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

11. The tablet of any one of claims 1-12, wherein the first layer comprises telmisartan in the form of a pharmaceutically acceptable salt.

12. A method for the manufacture of a tablet of claim 1 by compressing a first and a second tablet layer composition on a tablet press to form a bilayer tablet, characterized in that
the first tablet layer composition is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend; and
the second tablet layer composition is manufactures by direct compression, wet granulation or a roller compaction process.

13. Use of the tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-

cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

14. The use of claim 13 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

Ministry of Economic Development
Manatū Ōhanga
Intellectual Property Office of New Zealand

1-1800-NZ

LETTERS PATENT

Number **555284**

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith; To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for

Bilayer tablet comprising telmisartan and amlodipine

(more particularly described in the complete specification relating to the application)

AND WHEREAS

BOEHRINGER INGELHEIM INTERNATIONAL GMBH, D-55216 Ingelheim am Rhein, Germany

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

Address for service: BALDWINS INTELLECTUAL PROPERTY, Level 14, Baldwins Centre, 342 Lambton Quay, Wellington 6011, New Zealand

NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise and vend the said invention within New Zealand and its dependencies during a term of twenty years from 29 October 2005 and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

(1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:

(2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:

(3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted:

(4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed on 12 February 2009 with effect from 29 October 2005.

COMMISSIONER OF PATENTS, TRADEMARKS & DESIGNS
NEW ZEALAND

Neville Harris
Commissioner of Patents, Trade Marks and Designs

205 Victoria Street, Wellington
PO Box 9241, Marion Square, Wellington 6141, New Zealand or DX SX 11129, Wellington
Freephone: 0508 4 IPONZ (0508 447 669), International callers dial: +64 3 962 2607, Fax: +64 4 978 3691, www.iponz.govt.nz

What is claimed is

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.

3. The tablet of claim 1 or claim 2, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of any one of claims 1 to 3, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4 or claim 5, wherein the water-soluble diluent is selected from monosaccharides; oligosaccharides and sugar alcohols.

7. The tablet of claim 6, wherein the monosaccharides is glucose.

8. The tablet of claim 6, wherein the oligosaccharide is sucrose or lactose.

9. The tablet of claim 6, wherein the sugar alcohols is selected from the group consisitng of sorbitol, mannitol, and xylitol.

10. The tablet of any one of claim 4 to 9, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

11. The tablet of any one of claims 1 to 10, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.

12 The tablet of any one of claims 1 to 11, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

13. The tablet of claim 12, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

14. The tablet of any one of claims 1-13, wherein the first layer comprises telmisartan in the form of a pharmaceutically acceptable salt.

15. The tablet of any one of claims 1 to 14, wherein the first layer contains 10-160 mg.

16. The tablet of claim 15, wherein the first layer contains 20-80 mg telmisartan.

17. The tablet of claim 15, wherein the first layer contains 40-80 mg telmisartan.

18. The tablet of any one of claims 1-17 , wherein the second layer contains 1-20 mg amlodipine.

19. The tablet of claim 18, wherein the second layer contains 2.5-10 mg amlodipine.

20. The tablet of claim 18 or 19, wherein the second layer comprises amlodipine in the form of a maleate, besylate or mesylate.

21. The tablet of any one of claims 1 to 20 packaged in a moisture proof packaging material.

22. The tablet of claim 21, wherein the moisture proof packaging material is selected from the group consisting of aluminium foil blister packs, polypropylene tubes and HDPE bottles.

23. A method for the manufacture of a tablet of claim 1 which comprises:

(i) providing a first tablet layer composition by

a) preparing an aqueous solution of telmisartan, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;

b) spray-drying said aqueous solution to obtain a spray-dried granulate;

c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;

d) mixing said premix with a lubricant to obtain a final blend for the first layer;

e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

a) a direct compression process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof, one or more fillers, flow control agents and disintegrants and/or other excipients in a mixer;
- optionally dry screening the mixture through a screen in order to segregate cohesive particles and to improve content uniformity;
- blending the mixture with remaining excipients such as a lubricant in a mixer in order to obtain the final composition;

b) a wet granulation process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof, one or more fillers, binders, disintegrants and optionally other excipients in a mixer;
- granulating the mixture by adding granulation liquid, -wet screening of the granules through a screen in order to segregate bigger agglomerates;
- drying of the granules in a fluidized bed dryer or a vacuum tray dryer;
- optionally dry screening of the granules through a screen in order to segregate cohesive particles and to improve content uniformity;
- blending the granules with remaining excipients in a mixer in order to obtain the final composition.

c) a dry granulation process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof with either a portion of filler(s), disintegrant(s), binder(s), flow control agent(s) and lubricant(s) or all the excipients in a mixer;
- compaction of the mixture on a suitable roller compactor;
- reducing the ribbons obtained in the previous step to small granules by suitable milling or sieving steps;
- optionally blending the granules with remaining excipients in a mixer in order to obtain the final composition;

(iii) compressing the first and second tablet layer composition from step (i) and (ii) on a suitable tablet press to form a bilayer tablet.

24. The method of claim 23, wherein the granulation liquid in step (ii)(b) is water.

25. The method of claim 23 and 24, wherein the remaining excipients in step (ii)(b) are one or more lubricants.

26. Use of telmisartan and amlodipine in the manufacture of a medicament in the form of a tablet as defined in any one of claims 1 to 22 for the treatment of hypertension either alone or in combination with the treatment or prevention of a

condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

27. The use of claim 26 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

28. A tablet as claimed in any one of claims 1 to 22, substantially as hereinbefore described and with reference to the Examples.

29. A method as claimed in any one of claims 23 to 25, substantially as hereinbefore described and with reference to the Examples.

30. A use as claimed in claim 26 or claim 27, substantially as hereinbefore described and with reference to the Examples.

1-1800-SG

THE REGISTRY OF PATENTS
SINGAPORE

THE PATENTS ACT
(CHAPTER 221)

CERTIFICATE OF GRANT OF PATENT No.: 132165

In accordance with section 35 of the Patents Act, it is hereby certified that a patent having the P-No. 132165 [WO 2006/048208] has been granted in respect of an invention having the following particulars:

Title	:	BILAYER TABLET COMPRISING TELMISARTAN AND AMLODIPINE
Application Number	:	200703252-7
Date of Filing	:	29 October 2005
Priority Data	:	5 November 2004 - PATENT APPLICATION NO. 04026234.7 (EUROPEAN PATENT OFFICE)
Name of Inventor(s)	:	EISENREICH, WOLFRAM
Name(s) and Address(es) of Proprietor(s) of Patent	:	BOEHRINGER INGELHEIM INTERNATIONAL GMBH BINGER STRASSE 173, 55216 INGELHEIM/RHEIN GERMANY
Date of Grant	:	31 May 2010

Dated this 31st day of May 2010.

Liew Woon Yin (Ms)
Registrar of Patents
Singapore

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. *The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.*

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. *The tablet of claim 1, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.*

9. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

10. The tablet of claim 9, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

11. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

12. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

13. The tablet of claim 1 packaged in a moisture proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles.

14. A method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

15. The method of claim 14 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

5

1-1800-TW

中華民國專利證書

發明第 I 355268 號

發明名稱：雙層錠劑

專利權人：百靈佳殷格翰國際股份有限公司

發明人：沃夫嵐 艾森雷齊

專利權期間：自2012年 1 月 1 日至2025年11月 3 日止

上開發明業經專利權人依專利法之規定取得專利權

經濟部智慧財產局

局長 王美花

中華民國 101 年 1 月 1 日

注意：專利權人未依法繳納年費者，其專利

理律法律事務所
LEE AND LI
ATTORNEYS-AT-LAW

(TRANSLATION)

THE REPUBLIC OF CHINA PATENT CERTIFICATE
INVENTION PATENT NO. I355268

Title of Invention: BILAYER TABLET

Patentee(s): BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Inventor(s): (Omitted in translation)

Patent Duration: from 1 January 2012 to 3 November 2025

The Patentee has obtained the patent right in accordance with the Patent Law.

Intellectual Property Office
Commissioner: Wang, Mei-Hua

Date: 1 January 2012

(Official Seal of the
Intellectual Property Office
Ministry of Economic Affairs)

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. *The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.*

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. *The tablet of claim 1, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.*

9. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

10. The tablet of claim 9, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

11. The tablet of claim 1, wherein the first layer contains 10-160 mg telmisartan.

12. The tablet of claim 11, wherein the first layer contains 20-80 mg telmisartan.

13. The tablet of claim 11, wherein the first layer contains 40-80 mg telmisartan.

14. The tablet of claim 1, wherein the second layer contains 1-20 mg amlodipine.

15. The tablet of claim 14, wherein the second layer contains 2.5-10 mg amlodipine.

16. The tablet of claim 1 packaged in a moisture proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles.

17. A method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

18. The method of claim 17 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

A-1600-U

УКРАЇНА UKRAINE

ПАТЕНТ

НА ВИНАХІД

№ 89065

ДВОШАРОВА ТАБЛЕТКА, ЯКА МІСТИТЬ ТЕЛМІСАРТАН І АМЛОДИПІН

Видано відповідно до Закону України "Про охорону прав на винаходи і корисні моделі".

Зареєстровано в Державному реєстрі патентів України на винаходи **25.12.2009.**

Голова Державного департаменту інтелектуальної власності М.В. Паладій

Міністерство освіти і науки України * Державний департамент інтелектуальної власності * № 1

(11) **89065**

(19) **UA**

(51) **МПК** (2009)
A61K 9/20
A61K 31/4184 (2006.01)
A61K 31/4422
A61P 9/00
A61P 3/10 (2006.01)
A61P 25/28 (2006.01)

(21) Номер заявки: **a 2007 05853**

(22) Дата подання заявки: **29.10.2005**

(24) Дата, з якої є чинними права на винахід: **25.12.2009**

(31) Номер попередньої заявки відповідно до Паризької конвенції: **04026234.7**

(32) Дата подання попередньої заявки відповідно до Паризької конвенції: **05.11.2004**

(33) Код держави-учасниці Паризької конвенції, до якої подано попередню заявку: **EP**

(41) Дата публікації відомостей про заявку та номер бюлетеня: **27.08.2007, Бюл.№ 13**

(46) Дата публікації відомостей про видачу патенту та номер бюлетеня: **25.12.2009, Бюл. № 24**

(86) Номер та дата подання міжнародної заявки, поданої відповідно до Договору про патентну кооперацію: **PCT/EP2005/011596, 29.10.2005**

(72) Винахідник:
Айзенрайх Вольфрам, DE

(73) Власник:
БЬОРІНГЕР ІНГЕЛЬХАЙМ ІНТЕРНАЦІОНАЛЬ ГМБХ,
Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany, DE

(54) Назва винаходу:

ДВОШАРОВА ТАБЛЕТКА, ЯКА МІСТИТЬ ТЕЛМІСАРТАН І АМЛОДИПІН

(57) Формула винаходу:

1. Фармацевтична таблетка, що включає перший шар, який містить телмісартан у матриці таблетки, яка розчиняється, що включає основний агент, розчинний у воді розріджувач і необов'язково інші інертні наповнювачі й допоміжні речовини, і другий шар, який містить амлодипін у матриці таблетки, яка розпадається або руйнується, що включає один або більшу кількість наповнювачів, речовину, що забезпечує розпад, змащувальну речовину й, необов'язково, сполучне, агент, що регулює сипкість, або інші інертні наповнювачі й допоміжні речовини.

2. Таблетка за п. 1, у якій телмісартан знаходиться в основному в аморфній формі.

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix comprising a basic agent, a water-soluble diluent and, optionally, other inert excipients and adjuvants and a second layer of amlodipine in a disintegrating or eroding tablet matrix comprising one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

2. The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.

3. The tablet of claim 1, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

4. The tablet of claim 1, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

5. The tablet of claim 1, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

6. The tablet of claim 1, wherein the first tablet layer composition comprises amorpheous telmisartan produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.

7. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

8. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

9. The tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

10. The tablet of claim 9 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

50

1-1800-VN

BỘ KHOA HỌC VÀ CÔNG NGHỆ
CỤC SỞ HỮU TRÍ TUỆ

CỘNG HOÀ XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

BẰNG ĐỘC QUYỀN
SÁNG CHẾ
Số: 9157

Tên sáng chế: VIÊN NÉN HAI LỚP CHỨA TELMISARTAN VÀ AMLODIPIN
Chủ Bằng độc quyền: BOEHRINGER INGELHEIM INTERNATIONAL GMBH (DE)
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
Tác giả: EISENREICH, Wolfram (DE)
Số đơn: 1-2007-01120
Ngày nộp đơn: 29.10.2005
Số điểm yêu cầu bảo hộ: 15 **Số trang mô tả:** 31
Cấp theo **Quyết định số:** 4265/QĐ-SHTT, **ngày:** 15.03.2011
Có hiệu lực từ ngày cấp đến hết 20 năm tính từ ngày nộp đơn.

CỤC SỞ HỮU TRÍ TUỆ
NATIONAL OFFICE OF INTELLECTUAL PROPERTY OF VIETNAM
BỘ KHOA HỌC VÀ CÔNG NGHỆ

VN 1-000915

KT. CỤC TRƯỞNG
PHÓ CỤC TRƯỞNG

CỤC SỞ HỮU TRÍ TUỆ

Phạm Phi Anh

(12) **BẢN MÔ TẢ SÁNG CHẾ THUỘC BẰNG ĐỘC QUYỀN SÁNG CHẾ**

(19) **Cộng hòa xã hội chủ nghĩa Việt nam (VN)**
CỤC SỞ HỮU TRÍ TUỆ

(11) **1-0009157**

(51)[7] **A61K 9/20**, 31/4184, 31/4422, A61P 9/00, 9/04, 9/08, 9/10, 9/12, 3/10, 25/28

(13) **B**

(21) 1-2007-01120
(22) 29.10.2005
(86) PCT/EP05/011596 29.10.2005
(87) WO06/048208 11.05.2006
(30) 04026234.7 05.11.2004 EP
(45) 25.04.2011 277
(43) 25.12.2007 237

(73) BOEHRINGER INGELHEIM INTERNATIONAL GMBH (DE)
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
(72) EISENREICH, Wolfram (DE)
(74) Công ty TNHH Sở hữu trí tuệ Thảo Thọ Quyến (INVENCO)

(54) VIÊN NÉN HAI LỚP CHỨA TELMISARTAN VÀ AMLODIPIN

(57) Sáng chế đề cập đến viên nén hai lớp bao gồm lớp thứ nhất chứa kháng thụ thể angiotensin II telmisartan có tính giải phóng nhanh trong hệ chất nền dễ tan và lớp thứ hai chứa chất chẹn kênh canxi amlodipin có tính giải phóng nhanh trong chất nền gây rã hoặc chất nền ăn mòn của viên nén.

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. *The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.*

3. The tablet of claim 1, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of claim 1, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4, wherein the water-soluble diluent is selected from mono-saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.

7. The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

8. *The tablet of claim 1, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.*

9. The tablet of claim 1, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

10. The tablet of claim 9, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

11. The tablet of claim 1, wherein the first layer contains 10-160 mg, preferably 20-80 mg or 40-80 mg telmisartan.

12. The tablet of claim 1, wherein the second layer contains 1-20 mg, preferably 2.5-10 mg amlodipine.

13. The tablet of claim 1 packaged in a moisture proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles.

14. A method for the manufacture of a tablet of claim 1 comprising the steps of

(i) providing a first tablet layer composition comprising a spray-dried granulate of telmisartan, at least one basic agent, a lubricant and, optionally, a solubilizer and/or a crystallization retarder;

(ii) providing a second tablet layer composition comprising the active ingredient amlodipine or a pharmaceutically acceptable salt thereof; and

(iii) compressing the first and second tablet layer composition from step (i) and (ii) on a suitable tablet press to form a bilayer tablet

wherein said tablet is used to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum

concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

15. The method of claim 14 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

1-1800-ZA

REPUBLIC OF SOUTH AFRICA

REPUBLIEK VAN SUID AFRIKA

PATENTS ACT, 1978

CERTIFICATE

In accordance with section 44 (1) of the Patents Act, No. 57 of 1978, it is hereby certified that

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

has been granted a patent in respect of an invention described and claimed in complete specification deposited at the Patent Office under the number

2007/2119

A copy of the complete specification is annexed, together with the relevant Form P2.

In testimony thereof, the seal of the Patent Office has been affixed at Pretoria with effect from the **30th** day of **July 2008**

.....

Registrar of Patents

Form P.2

REPUBLIC OF SOUTH AFRICA — PATENTS ACT, 1978

REGISTER OF PATENTS

OFFICIAL APPLICATION NO.	LODGING DATE : PROVISIONAL	ACCEPTANCE DATE
21 01 2007/02119	22	43 02/06/08.
INTERNATIONAL CLASSIFICATION	**LODGING DATE : COMPLETE**	**GRANTED DATE**
1 A61K, A61P	23 13 March 2007	30/07/08.

FULL NAME(S) OF APPLICANT(S)/PATENTEE(S)

71 BOEHRINGER INGELHEIM INTERNATIONAL GMBH

APPLICANTS SUBSTITUTED :	DATE REGISTERED

ASSIGNEE(S) :	DATE REGISTERED

FULL NAME(S) OF INVENTORS

72 EISENREICH, Wolfram

PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
Earliest priority claimed by PCT international application PCT/EP2005/011596 filed 29 October 2005	33 European Patent Application	31 04026234.7	32 05 November 2004
NB. Use international Abbreviations for country. (See Schedule 4)			

TITLE OF INVENTION

54 BILAYER TABLET COMPRISING TELMISARTAN AND AMLODIPINE

ADDRESS OF APPLICANT(S) / PATENTEE(S)

71 Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

ADDRESS FOR SERVICE	REF
74 DM Kisch Inc, 54 Wierda Road West, Inanda Greens Business Park, Sandton	P34753ZA00

PATENT OF ADDITION NO.	DATE OF ANY CHANGE
61	

FRESH APPLICATION BASED ON	DATE OF ANY CHANGE

Claims

1. A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.

2. The tablet of claim 1, wherein telmisartan is in a substantially amorphous form.

3. The tablet of claim 1 or claim 2, wherein the dissolving tablet matrix has instant release characteristics.

4. The tablet of any one of claims 1 to 3, wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

5. The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.

6. The tablet of claim 4 or claim 5, wherein the water-soluble diluent is selected from monosaccharides; oligosaccharides and sugar alcohols.

7. The tablet of claim 6, wherein the monosaccharides is glucose.

8. The tablet of claim 6, wherein the oligosaccharide is sucrose or lactose.

9. The tablet of claim 6, wherein the sugar alcohols is selected from the group consisitng of sorbitol, mannitol, and xylitol.

10. The tablet of any one of claim 4 to 9, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.

11. The tablet of any one of claims 1 to 10, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.

12 The tablet of any one of claims 1 to 11, wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.

13. The tablet of claim 12, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.

14. The tablet of any one of claims 1-13, wherein the first layer comprises telmisartan in the form of a pharmaceutically acceptable salt.

15. The tablet of any one of claims 1 to 14, wherein the first layer contains 10-160 mg.

16. The tablet of claim 15, wherein the first layer contains 20-80 mg telmisartan.

17. The tablet of claim 15, wherein the first layer contains 40-80 mg telmisartan.

18. The tablet of claim 1, wherein the second layer contains 1-20 mg amlodipine.

19. The tablet of claim 18, wherein the second layer contains 2.5-10 mg amlodipine.

20. The tablet of claim 18 or 19, wherein the second layer comprises amlodipine in the form of a maleate, besylate or mesylate.

21. The tablet of any one of claims 1 to 20 packaged in a moisture proof packaging material.

22. The tablet of claim 21, wherein the moisture proof packaging material is selected from the group consisting of aluminium foil blister packs, polypropylene tubes and HDPE bottles.

23. A method for the manufacture of a tablet of claim 1 which comprises:

(i) providing a first tablet layer composition by

a) preparing an aqueous solution of telmisartan, at least one basic agent and, optionally, a solubilizer and/or a crystallization retarder;

b) spray-drying said aqueous solution to obtain a spray-dried granulate;

c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;

d) mixing said premix with a lubricant to obtain a final blend for the first layer;

e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

a) a direct compression process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof, one or more fillers, flow control agents and disintegrants and/or other excipients in a mixer;
- optionally dry screening the mixture through a screen in order to segregate cohesive particles and to improve content uniformity;
- blending the mixture with remaining excipients such as a lubricant in a mixer in order to obtain the final composition;

b) a wet granulation process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof, one or more fillers, binders, disintegrants and optionally other excipients in a mixer;
- granulating the mixture by adding granulation liquid, preferably water;

- wet screening of the granules through a screen in order to segregate bigger agglomerates;
- drying of the granules in a fluidized bed dryer or a vacuum tray dryer;
- optionally dry screening of the granules through a screen in order to segregate cohesive particles and to improve content uniformity;
- blending the granules with remaining excipients such as lubricant(s) in a mixer in order to obtain the final composition.

c) a dry granulation process comprising the steps of

- blending the active ingredient amlodipine or a pharmaceutically acceptable salt thereof with either a portion of the filler(s), disintegrant(s), binder(s), flow control agent(s) and lubricant(s) or all the excipients in a mixer;
- compaction of the mixture on a suitable roller compactor;
- reducing the ribbons obtained in the previous step to small granules by suitable milling or sieving steps;
- optionally blending the granules with remaining excipients in a mixer in order to obtain the final composition.

(iii) compressing the first and second tablet layer composition from step (i) and (ii) on a suitable tablet press to form a bilayer tablet.

24. Use of telmisartan and amlodipine in the manufacture of a medicament in the form of a tablet as defined in any one of claims 1 to 22 for the treatment of hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, hypertriglyceridemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated

phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL(2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.

25. The use of claim 24 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

26. A method of treating or preventing a condition as defined in claim 24 or claim 23 which comprises administering to an individual a tablet as claimed in any one of claims 1 to 20.

27. A tablet as claimed in any one of claims 1 to 20;
a method as claimed in claim 23;
a use as claimed in claim 24 or claim 25;.
or a method as claimed in claim 26, substantially as hereinbefore described and with reference to the Examples.