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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-008335-00007-0000

Fecha: 2009-02-25 17:00:50 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 9

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 06-008335
Asunto : Solicitud de patente para: USO DE
ANTAGONISTAS DEL RECEPTOR DE ANGIOTENSINA II
Solicitante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Clase : A61K 031/416, A61P 003/010, A61P 005/050, A61P 009/012
Opositor : PROCAPS S.A.
Fecha solicitud: Enero 30 de 2006

1. ALEGATOS CONTESTACIÓN OPOSICIÓN

Yo, Emilio FERRERO, en mi condición de apoderado de la sociedad solicitante de la patente de la referencia, por el presente escrito doy respuesta a la oposición formulada por la sociedad PROCAPS S.A., opositora en el asunto de referencia.

2. CONTESTACIÓN DENTRO DEL TÉRMINO LEGAL

El oficio No. 11280, en el cual su Despacho dispuso otorgar a mi representada término para presentar sus argumentaciones a favor de la patentabilidad del invento de que trata el asunto en referencia, me fue notificado por fijación en lista el 05 de septiembre de 2008. Mediante memorial radicado el día 25 de noviembre de 2008, solicité plazo de sesenta (60) días para atender el oficio No. 11280. Por lo tanto, la presente defensa es presentada en tiempo oportuno.

3. RESPUESTA A LAS PETICIONES

Me opongo a las peticiones de la sociedad opositora y en consecuencia, solicito a ese Despacho que con fundamento en las

consideraciones de hecho y de derecho que se presentan en este escrito se declare sin fundamento la oposición presentada por la sociedad **PROCAPS S.A.**

En consecuencia, se declare que el invento titulado **USO DE ANTAGONISTAS DEL RECEPTOR DE ANGIOTENSINA II** cumple con los requisitos exigidos en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina y demás normas concordantes.

4. FUNDAMENTO FÁCTICO DE LA OPOSICIÓN

A continuación procederé a enumerar de manera resumida los argumentos que la opositora **PROCAPS S.A.** considera pertinentes para presentar oposición a la presente solicitud:

En el escrito de oposición se señala que la presente invención, carece de aplicación industrial y novedad con fundamento en dos anterioridades citadas: D1: ES 2175098 y D2: WO 0130353.

De acuerdo con los argumentos expuestos, la presente solicitud carece de aplicación industrial por cuanto las reivindicaciones hacen referencia al uso y al método de tratamiento.

De otra parte se señala que D1 revela una combinación que comprende una cantidad eficaz, sustancialmente no diurética del antagonista del receptor de aldosterona espironolactona y una cantidad terapéuticamente eficaz de un antagonista del receptor de angiotensina II seleccionado de un grupo de compuestos. De acuerdo con el escrito de oposición, es posible observar cómo D1 anticipa las características técnicas de la asociación reivindicada.

Asimismo se indica que D2 revela un método de tratamiento para tratar trastornos de microcirculación fibro-dependientes, el cual comprende la administración de una cantidad eficaz de una composición farmacéutica que contiene una pirimidina en combinación con otros activos, particularmente dipiridamol o mopidamol juntos con un antagonista de angiotensina II conocido. La opositora afirma que dicha combinación revela la misma solución que la presente solicitud.

Por último se afirma que a la luz de los documentos D1 y D2, la presente solicitud carece evidentemente de novedad.

5. RESPUESTA A LOS HECHOS Y ALEGATOS

A continuación presento a su Despacho las razones que demuestran que contrario a lo señalado por el apoderado de la sociedad opositora, el invento para el cual se solicita la protección a través de la concesión de la patente en el expediente de la referencia, cumple cabalmente con los requisitos del artículo 14 y demás normas concordantes de la Decisión 486 de la Comisión de la Comunidad Andina.

Además, los argumentos que aquí se presentan demuestran que los fundamentos de la opositora carecen de fundamento válido y por tanto, no pueden ni deben ser tomados en cuenta para negar la patente solicitada.

5.1 Modificación de una solicitud en trámite: con el objeto de diferenciar mejor el objeto de la presente solicitud frente a los argumentos de oposición y en virtud de lo establecido por el artículo 34 de la Decisión 486, se ha modificado el pliego reivindicatorio para presentar 15 reivindicaciones.

Las modificaciones realizadas son las siguientes:

Teniendo en cuenta los lineamientos vigentes, se han eliminado las reivindicaciones dirigidas al uso de la composición farmacéutica y a los métodos de tratamiento. De esta manera, se reivindica solamente el producto, que es una composición farmacéutica. De acuerdo con esto, los argumentos expuestos por la opositora en relación con la carencia de aplicación industrial y los usos no son válidos.

5.2 Argumentos a favor de la novedad de la presente solicitud: de acuerdo con los argumentos expuestos por la opositora, la presente solicitud carece de novedad frente a la materia revelada por los documentos D1: ES 2175098 y D2: WO 0130353. Es entonces relevante poner de presente lo que indica el Manual para el Examen de Solicitudes de Patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina, con respecto al análisis de la novedad:

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"Para determinar la novedad de la invención, se debe comprobar si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la invención".

Ahora bien, el mismo Manual establece que no podrá utilizarse más de un documento para atacar la novedad de una solicitud. No es claro entonces por qué la opositora ha citado dos documentos, sin establecer con argumentos válidos porque cada uno de estos documentos revela explícitamente todas las características técnicas esenciales de la invención.

A este respecto y a pesar de que la opositora a pasado por alto los lineamientos del Manual Andino de Patentes para la evaluación de la novedad de la presente solicitud, deseamos poner de presente que el documento D1 no es una anterioridad válida por cuanto no revela todas las características de la reivindicación 1 tal como está definida, es decir, una composición farmacéutica que contiene telmisartano en combinación con amlodipina o nifedipina, eplerenona, clopidogrel opcionalmente combinado con ácido acetilsalicílico, ó un inhibidor de DPP4.

De otro lado, es relevante poner de presente que el documento D2 está dirigido a un método de tratamiento y por lo tanto no debería ser considerado un documento válido. Adicionalmente, este documento tampoco revela una composición farmacéutica de acuerdo con lo que se expuso anteriormente.

Así las cosas, dado que los documentos D1 y D2 no revelan todas las características técnicas esenciales de la presente solicitud, no puede ser consideradas anterioridades válidas capaces de afectar su novedad.

6. MODIFICACIÓN DE LA SOLICITUD

Tal como lo indiqué en el capítulo anterior, junto con este escrito presento Formulario de Modificaciones y Correcciones, con nuevo capítulo reivindicatorio el cual solicito sea tenido en cuenta por ese Despacho.

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Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM INTERNATIONAL GMBH Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Binger Strasse 173, 55216 Ingelheim, Alemania Domicilio: Ingelheim, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 438.019 TP 31.929
4	Número de expediente: 06.008.335	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 15 reivindicaciones con el fin de superar las objeciones hechas por la Sociedad PROCAPS S.A., a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.	
6	Comprobante de pago No. 09-14.755 Fecha: 24 de febrero de 2009	
7	Anexos ☒ Comprobante de pago de la tasa por \$111.000, por concepto de modificaciones. ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

REIVINDICACIONES

1. Composición farmacéutica que comprende telmisartano en combinación con

- a) amlodipina ó nifedipina;
- b) eplerenona; \
- c) clopidogrel, opcionalmente combinado con ácido acetilsalicílico; o
- d) un inhibidor de DPP4

2. La composición de la reivindicación 1, para tratar personas en las que se diagnosticó diabetes mellitus de tipo 2 o existe sospecha de una prediabetes para la prevención de diabetes o para el tratamiento del síndrome metabólico y la resistencia a la insulina en pacientes con presión arterial normal.

3. La composición de la reivindicación 1, caracterizada porque en las personas por tratar, el valor de azúcar en la sangre en ayunas supera 125 mg de glucosa por dl de plasma.

4. La composición de la reivindicación 1, caracterizada porque en las personas por tratar, el valor de azúcar en la sangre en ayunas es de 110-125 mg de glucosa por dl de plasma.

5. La composición de la reivindicación 1, caracterizada porque en las personas por tratar se mide 2 horas después de la ingesta en ayunas de 75 g de glucosa un valor de azúcar en sangre superior a 200 mg de glucosa por dl de plasma.

6. La composición de la reivindicación 1, caracterizada porque en las personas por tratar se mide 2 horas después de la ingesta en ayunas de 75 g de glucosa un valor de azúcar en la sangre de 140-200 mg de glucosa por dl de plasma.

7. La composición de la reivindicación 1, caracterizada porque en las personas por tratar el valor de triglicéridos en sangre supera 150 mg/dl.

8. La composición de la reivindicación 7, caracterizada porque en las personas por tratar el valor de HDL en la sangre en mujeres es inferior a 40 mg por dl de plasma, en los hombres inferior a 50 mg por dl de plasma.

9. La composición de las reivindicaciones 7 y 8, caracterizada porque en las personas por tratar el valor de de azúcar en la sangre en ayunas supera 110 mg de glucosa por dl de plasma.

10. La composición de las reivindicaciones 2 a 9, caracterizada porque en las personas por tratar la presión arterial sistólica supera un valor de 140 mm Hg y la presión arterial diastólica supera un valor de 90 mm Hg.

11. la composición de las reivindicaciones 2, 3 y 5, caracterizada porque en las personas por tratar la presión arterial sistólica supera un valor de 130 mm Hg y la presión arterial diastólica supera un valor de 80 mm Hg.

12. La composición de las reivindicaciones 2 a 11, caracterizada porque en las personas por tratar la relación de medida de cintura a medida de cadera en las mujeres supera el valor 0,8 y en los hombres supera el valor 1.

13. La composición de la reivindicación 1, caracterizada porque contiene 20-200 mg de telmisartano.

14. La composición de la reivindicación 1, caracterizada porque el antagonista del receptor de la angiotensina II, telmisartano, se combina con un diurético.

15. La composición de la reivindicación 14, caracterizada porque contiene 10-50 mg de HCTZ o clortalidona.

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 14,755
FECHA : FEBRERO 24 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 444 RESPUESTAREQUE Folios: 9

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00024-9	19779034	23/02/2009	69,870,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
	12 MARCAS Y LENAS COMERCIALES	111,000.00
	TOTAL :	\$ 111,000.00
SON	CIENTO ONCE MIL PESOS	

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Cdo 09255-264005-1

(19)  Canadian
Intellectual Property
Office

An Agency of
Industry Canada

Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

(11) **CA 2 338 039**

(40) 27.01.2000

(43) 27.01.2000

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infected

(12)

(21) **2 338 039**

(22) 10.07.1999

(51) Int. Cl. 7:

**C07D 233/70, A61K 31/415,
C07D 233/54, C07D 233/68**

(85) 17.01.2001

(86) PCT/EP99/04886

(87) WO00/03994

(30) 198 32 429.4 DE 18.07.1998

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SCHWARK, JAN-ROBERT (DE).
WEICHERT, ANDREAS (DE).
PETRY, STEFAN (DE).**

(74)

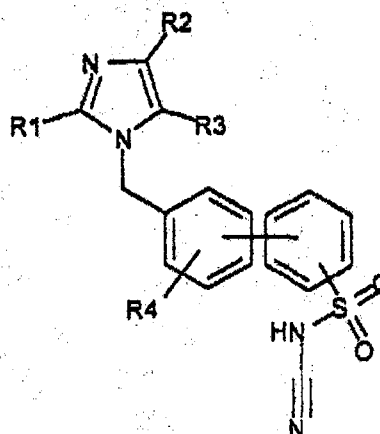
BERESKIN & PARR

(54) DERIVES D'IMIDAZOLE A SUBSTITUTION BIPHENYLSULFONYLE, LEUR PROCEDE DE PREPARATION, LEUR UTILISATION COMME MEDICAMENT OU AGENT DIAGNOSTIQUE, AINSI QUE MEDICAMENT LES CONTENANT

(54) BIPHENYLSULFONYL-SUBSTITUTED IMIDAZOLE DERIVATIVES, THEIR PREPARATION PROCESS, THEIR USE AS A DRUG OR DIAGNOSTIC AGENT AND DRUG CONTAINING THEM

(57)

The invention relates to compounds represented by formula (I), wherein the symbols have the meanings indicated in the description, which exhibit outstanding antiarrhythmic properties and comprise a cardioprotective component. The inventive compounds can preventively inhibit or strongly reduce pathophysiological processes upon occurrence of ischemic injuries, especially ischemic cardiac arrhythmia. Said compounds also exhibit a strong inhibiting effect on cellular proliferation.



WO 00/03994

PCT/EP99/04886

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radical in the 2-position, such as are described in EP-A 726254; cinnamoylguanidines, such as are described in JP 09059245; propenoylguanidines having a naphthalene substituent, such as are described in JP 9067332; propenoylguanidines having indole substituents, such as are described in JP 9067340; or heteroaryl-substituted acroylguanidines, such as are described in WO 9711055, and their physiologically tolerable salts.

Preferred NHE inhibitors are the compounds emphasized as preferred in the publications mentioned. Very particularly preferred compounds are cariporide (HOE642), HOE 694, EMD 96785, FR 168888, FR 183998, SM-20550, KBR-9032, and their physiologically tolerable salts. Most preferred is cariporide or another physiologically tolerable salt of N-(4-isopropyl-3-methanesulfonylbenzoyl)guanidine.

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Examples of classes of active compounds having cardiovascular activity which can therapeutically be combined advantageously with NCBE inhibitors or can additionally be combined with combinations of NCBE inhibitors and NHE inhibitors are beta-receptor blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, thiazide diuretics, potassium-sparing diuretics, aldosterone antagonists, such as are employed, for example, in lowering of the blood pressure, and also cardiac glycosides or other agents increasing the contractile force in the treatment of cardiac insufficiency and of congestive heart failures, and also antiarrhythmics of the classes I - IV, nitrates, KATP openers, KATP blockers, inhibitors of the veratridine-activatable sodium channel, etc. For example, the following are thus suitable: the beta-blockers propanolol, atenolol, metoprolol; the calcium antagonists diltiazem hydrochloride, verapamil hydrochloride, nifedipine; the ACE inhibitors captopril, enalapril, ramipril; trandolapril, quinapril, spirapril, preferably ramipril or trandolapril; the angiotensin II receptor antagonists losartan, valsartan, telmisartan, eprosartan, tasosartan, candesartan, irbesartan; the loop diuretics furosemide, piretanide, torasemide; the thiazide diuretics hydrochlorothiazide, metolazone, indapamide; the potassium-sparing diuretics amiloride, triamterene, spironolactone; the cardiac glycosides digoxin, digitoxin, strophanthin; the antiarrhythmics amiodarone, sotalol, bretylium, flecainide; the nitrate glycerol trinitrate; the K⁺(ATP) openers cromakalim, lemakalim, nocorandil,

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b) nifedipinea) telmisartan



US 20030077229A1

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74(19) **United States**(12) **Patent Application Publication**
Dugger, III(10) **Pub. No.: US 2003/0077229 A1**(43) **Pub. Date: Apr. 24, 2003**(54) **BUCCAL, POLAR AND NON-POLAR SPRAY
OR CAPSULE CONTAINING
CARDIOVASCULAR OR RENAL DRUGS**of application No. PCT/US97/17899, filed on Oct. 1,
1997.(76) **Inventor: Harry A. Dugger III, Flemington, NJ
(US)****Correspondence Address:**
PENNIE & EDMONDS LLP
1667 K STREET NW
SUITE 1000
WASHINGTON, DC 20006**Publication Classification**(51) **Int. Cl.⁷ A61K 9/00; A61L 9/04**
(52) **U.S. Cl. 424/43**(57) **ABSTRACT**

Buccal aerosol sprays or capsules using polar and non-polar solvent have now been developed which provide biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal polar compositions of the invention comprise formulation I: aqueous polar solvent, active compound, and optional flavoring agent; formulation II: aqueous polar solvent, active compound, optionally flavoring agent, and propellant; formulation III: non-polar solvent, active compound, and optional flavoring agent; and formulation IV: non-polar solvent, active compound, optional flavoring agent, and propellant.

(21) **Appl. No.: 10/230,075**(22) **Filed: Aug. 29, 2002****Related U.S. Application Data**(63) **Continuation-in-part of application No. 09/537,118,
filed on Mar. 29, 2000, which is a continuation-in-part***afternoon*

herein are by weight unless otherwise indicated. It is also preferable that the propellant be synthetically produced to minimize the presence of contaminants which are harmful to the active compounds. These contaminants include oxidizing agents, reducing agents, Lewis acids or bases, and water. The concentration of each of these should be less than 0.1%, except that water may be as high as 0.2%.

[0027] Suitable non-polar solvents for the capsules and the non-polar sprays include (C₂-C₂₄) fatty acid (C₂-C₆) esters, C₇-C₁₈ hydrocarbon, C₂-C₆ alkanoyl esters, and the triglycerides of the corresponding acids. When the capsule fill is a paste, other liquid components may be used instead of the above low molecular weight solvents. These include soya oil, corn oil, other vegetable oils.

[0028] As solvents for the polar capsules or sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600), low molecular weight (C₂-C₆) mono and polyols and alcohols of C₇-C₁₈ linear or branch chain hydrocarbons, glycerin may also be present and water may also be used in the sprays, but only in limited amount in the capsules.

[0029] It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the shell during curing and even throughout the shelf-life of the capsule.

[0030] Therefore, the values given herein are for the compositions as prepared, it being within the scope of the invention that minor variations will occur.

[0031] The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners (sugars, aspartame, saccharin, etc.), and combinations thereof.

[0032] The active substances include the active compounds selected from the group consisting of cyclosporine, sennoside, octreotide acetate, calcitonin-salmon, insulin lispro, sumatriptan succinate, clozapine, cyclobenzaprine, dexfenfluramine hydrochloride, glyburide, zidovudine, erythromycin, ciprofloxacin, ondansetron hydrochloride, dimenhydrinate, cimetidine hydrochloride, famotidine, phenytoin sodium, phenytoin, carboprost thrombectamine, carboprost, diphenhydramine hydrochloride, isoproterenol hydrochloride, terbutaline sulfate, terbutaline, theophylline, albuterol sulfate and neutraceuticals, that is to say nutrients with pharmacological action such as but not limited to carnitine, valerian, echinacea, and the like.

[0033] In another embodiment, the active compound is an anti-arrhythmic, anti-hypertensive, heart regulator, cardiovascular agent, plaque stabilization agent, vasodilator, anti-anginal, anti-coagulant, anti-hypotensive, anti-thrombotic, drug for treating congestive heart failure, p-FOX (fatty acid oxidation) inhibitor, or a mixture thereof.

[0034] In one embodiment the active compound is an anti-arrhythmic. Suitable anti-arrhythmics for use in the buccal sprays of the invention include, but are not limited to, adenosine, amiodarone, bepridil, bretylium, digitoxin, digoxin, diltiazem, disopyramide, dofetilide, D-sotalol, flecainide, lidocaine, mexiletine, milrinone, phenytoin, pilsicainide, procainamide, propafenone, propranolol, quinidine, tocainide, dofetilide, and mixtures thereof.

[0035] In one embodiment the active compound is an anti-hypertensive. Suitable anti-hypertensives for use in the buccal sprays of the invention include, but are not limited to, acebutolol, alfuzosin, amlodipine, atenolol, amlodipine/benazepril, bamidipine benazepril, bepridil, betaxolol, bisoprolol, bosentan, candesartan, captopril, cariporide, carvedilol, celiprolol, cilazapril, clonidine, diltiazem, doxazosin, enalapril, epirenone, eprosartan, esmolol, felodipine, fenoldopam, fosinopril, guanfacine, imidapril, irbesartan, isradipine, labetalol, lercanidipine, lisinopril, losartan, manidipine, methyldopa, metoprolol, moxonidine, nadolol, nicardipine, nicorandil, nifedipine, nitrendipine, nosoldipine, omapatrilat, perindopril erbumine, pindolol, prazosin, propranolol, quinapril, ramipril, sotalol, spirapril, tamsulosin, telmisartan, terazosin, torsemide, trandolapril, valsartan, vatanidipine, midodrine, and mixtures thereof.

[0036] In one embodiment the active compound is a heart regulator. Suitable heart regulators for use in the buccal sprays of the invention include, but are not limited to, digoxin, digitoxin, dobutamine, and mixtures thereof.

[0037] In one embodiment the active compound is a cardiovascular agent. Suitable cardiovascular agents for use in the buccal sprays of the invention include, but are not limited to, edaravone, iloprost, levosimendan, molsidomine, tezosentan, tirilazad, YM087, adenosine, avasimibe, fenofibrate, and mixtures thereof.

[0038] In one embodiment the active compound is a plaque stabilization agent. A suitable plaque stabilization agent for use in the buccal sprays of the invention includes, but is not limited to, avasimibe.

[0039] In one embodiment the active compound is a vasodilator. Suitable vasodilators for use in the buccal sprays of the invention include, but are not limited to, buflomedil, cilostazol, dipyridamole, diazoxide, hydralazine, minoxidil, naftidrofuryl, nicorandil, nitroprusside, alprostadil, apomorphine, phentolamine mesylate, sildenafil, tadalafil, vardenafil, and mixtures thereof.

[0040] In one embodiment the active compound is an anti-anginal. Suitable anti-anginals for use in the buccal sprays of the invention include, but are not limited to, amlodipine, amyl nitrite, atenolol, bepridil, diltiazem, erythritol tetranitrate, felodipine, isosorbide dinitrate, isradipine, metoprolol, nadolol, nicardipine, nifedipine, nimodipine, pentaerythritol tetranitrate, propranolol, and mixtures thereof.

[0041] In one embodiment the active compound is an anti-coagulant. Suitable anti-coagulants for use in the buccal sprays of the invention include, but are not limited to, abciximab, ardeparin, argatroban, bivalirudin, clopidogrel, dalteparin, danaparoid, desirudin, dipyridamole, enoxaparin, eptifibatide, fondaparinux, H376/95, lepirudin, melagatran, nadroparin, nafamostat mesilate, pentosan, pentoxifylline, reviparin, sarpogrelate, SNAC/SNAD-heparin, ticlopidine, tinzaparin, tirofiban, warfarin, and mixtures thereof.

[0042] In one embodiment the active compound is an anti-hypotensive. Suitable anti-hypotensives for use in the buccal sprays of the invention include, but are not limited to, midodrine, dobutamine, fludrocortisone, and mixtures thereof.

[0043] In one embodiment the active compound is an anti-thrombotic. Suitable anti-thrombotics for use in the

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US006248729B1

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

(10) Patent No.: **US 6,248,729 B1**
(45) Date of Patent: **Jun. 19, 2001**

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Deposited

(54) **COMBINATION OF AN ADP-RECEPTOR BLOCKING ANTIPLATELET DRUG AND ANTIHYPERTENSIVE DRUG AND A METHOD FOR PREVENTING A CEREBRAL INFARCTION EMPLOYING SUCH COMBINATION**

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(52) U.S. Cl. **514/85; 514/214.02; 514/301; 514/381; 514/397; 514/423**

(58) Field of Search **514/301, 214.02, 514/423, 85, 381, 397**

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,529,596	7/1985	Aubert et al.	
4,591,592	5/1986	Chowhan	514/301
4,847,265	7/1989	Badore et al.	
5,225,420	7/1993	Cazenave et al.	
5,270,317	12/1993	Bernhart et al.	
5,362,727	11/1994	Robl	514/214
5,366,973	11/1994	Flynn et al.	514/221

5,508,272	4/1996	Robl	514/80
5,525,723	6/1996	Robl	540/521
5,576,328	11/1996	Herbert et al.	
5,661,150	8/1997	Shirasaki	514/252

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(57)

ABSTRACT

A method is provided for preventing a cerebral infarction by administering to a patient a combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with an antihypertensive agent such as an angiotensin AII antagonist (for example, irbesartan), an ACE inhibitor (for example, fosinopril) or a NEP/ACE inhibitor such as omapatrilat.

25 Claims, No Drawings

COMBINATION OF AN ADP-RECEPTOR BLOCKING ANTIPLATELET DRUG AND AN ANTIHYPERTENSIVE DRUG AND A METHOD FOR PREVENTING A CEREBRAL INFARCTION EMPLOYING SUCH COMBINATION

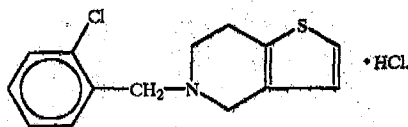
Priority is claimed from U.S. application Ser. No. 60/089,650 filed Jun. 17, 1998.

FIELD OF THE INVENTION

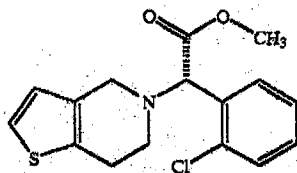
The present invention relates to a novel combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, and an antihypertensive drug, for example, an angiotensin II antagonist such as irbesartan, or an ACE inhibitor such as fosinopril, or a NEP/ACE inhibitor such as omapatrilat, and to a method for preventing or inhibiting onset of a cerebral infarction employing such combination.

BACKGROUND OF THE INVENTION

Ticlopidine hydrochloride is disclosed in U.S. Pat. No. 4,591,592 as a platelet aggregation inhibitor, is marketed in the U.S. under the name Ticlid® by Roche Laboratories, and has the chemical name 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and the structure



Clopidogrel is a thieno-[3,2-c]pyridine derivative which has the chemical name methyl (4)-(S)-α-(o-chloro-phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5-acetate and the formula



including pharmaceutically acceptable acid addition salts thereof, preferably the hydrogen sulfate salt, and is disclosed in U.S. Pat. Nos. 4,529,596 to Aubert et al and U.S. Pat. No. 4,847,265 to Badore et al as having blood platelet aggregation inhibiting activity and anti-thrombotic activity and thus useful in inhibiting or preventing arterial and venous thrombosis.

U.S. Pat. No. 5,576,328 to Herbert et al discloses that clopidogrel may be employed in secondary prevention of ischemic events such as myocardial infarction, unstable or stable angina, acute reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis after PTCA, thrombotic stroke, transient ischemic attack, reversible ischemic neurological deficit, and intermittent claudication.

The above Aubert et al, Badore et al and Herbert et al patents are incorporated herein by reference.

WO 97/29753 published Aug. 21, 1997, discloses a pharmaceutical composition containing clopidogrel and aspirin.

Bernhart et al in U.S. Pat. No. 5,270,317 disclose a series of N-substituted heterocyclic derivatives which possess

angiotensin II antagonist activity. Bernhart et al disclose that such compounds can be used in the treatment of various cardiovascular complaints, especially hypertension, heart failure, and venous insufficiency, as well as in the treatment of glaucoma, diabetic retinopathy and various complaints of the central nervous system. It is also disclosed that such compound can be used in combination with other active agents such as tranquilizers, beta-blocking compounds, a calcium antagonist, or a diuretic.

Selective neutral endopeptidase inhibitors are taught by Delaney et al in U.S. Pat. Nos. 4,722,810 and 5,223,516 and the use of selective neutral endopeptidase inhibitors alone or in combination with angiotensin converting enzyme inhibitors to treat hypertension are disclosed by Delaney et al U.K. Patent Application 2,207,351 and by Haslanger et al in U.S. Pat. No. 4,749,688. The treatment of congestive heart failure by administration of a combination of a selective neutral endopeptidase inhibitor and an angiotensin converting enzyme inhibitor is disclosed by Seymour in U.S. Pat. No. 5,225,401.

Compounds possessing both neutral endopeptidase and angiotensin converting enzyme inhibition activity are disclosed by Flynn et al in U.S. Pat. No. 5,366,973, European Patent Application 481,522 and PCT Patent Applications WO 93/16103, and WO 94/10193, Warshawsky et al European Patent Applications 534,363, 534,396 and 534,492, Fournie-Zaluski European Patent Application 524,553, Barish et al European Patent Application 599,444, Karanewsky European Patent Application 595,610, Robl et al, European Patent Application 629,627, Robl U.S. Pat. No. 5,362,727 and U.S. patent application Ser. No. 153,854 filed Nov. 18, 1993, now U.S. Pat. No. 5,525,723.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, a method for preventing or inhibiting onset of a cerebral infarction in mammals is provided wherein an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with an antihypertensive drug is administered in therapeutically effective amounts to inhibit onset of a cerebral infarction (also known as a thrombotic stroke).

In addition, in accordance with the present invention, a novel combination is provided which includes an ADP-receptor blocking antiplatelet drug, such as clopidogrel, and an antihypertensive drug.

ADP-receptor blocking drugs which may be used in the combination and method of the invention include clopidogrel, ticlopidine and the like.

Antihypertensive drugs, which may be used in the combination and method of the invention in combination with the ADP-receptor blocking antiplatelet drug include angiotensin II antagonists, angiotensin converting enzyme (ACE) inhibitors or NEP/ACE inhibitors.

It is believed that the combination of an ADP-receptor blocking antiplatelet drug and the antihypertensive drug, which works by a mechanism other than inhibition of ADP-induced platelet aggregation, is a surprising and unique concept in treating diseases involved with platelet aggregation, thrombus formation and ischemic events, in that the combination may provide additional antiplatelet aggregation, antiischemic and anti-thrombus effects over that which may be obtained using each of the components of the combination alone. It may be expected that reduced levels of each of the ADP-receptor blocking antiplatelet drug and antihypertensive drug may be employed to achieve desired results, albeit with reduced side effects and at reduced cost of goods.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "ADP-receptor blocking antiplatelet drug" refers to drugs which inhibit ADP-induced platelet aggregation via platelet ADP-receptor blocking including clopidogrel and/or ticlopidine and do not include drugs such as aspirin which inhibit platelet aggregation by other mechanisms.

The term "clopidogrel" as employed herein includes clopidogrel in its free acid form, esters thereof including the acetate and/or all pharmaceutically acceptable salts thereof, including the hydrogen sulfate salt.

The term "ticlopidine" as employed herein includes all pharmaceutically acceptable salts of ticlopidine, including the hydrochloride salt thereof.

The term "cerebral infarction" as employed herein refers to primary or secondary thrombotic stroke.

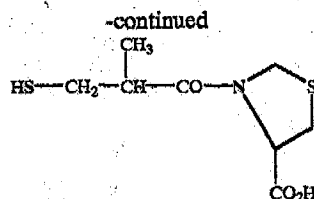
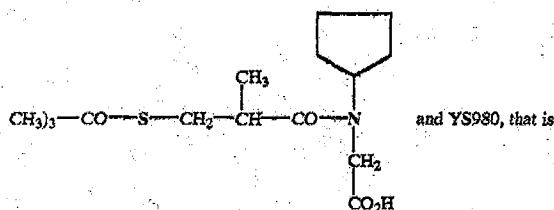
It is to be understood that the term "antihypertensive drug" refers to various classes of antihypertensive agents including angiotensin II antagonists, ACE inhibitors and NEP/ACE inhibitors which contribute, with the antiplatelet drug, to inhibit onset of primary or secondary cerebral infarction.

The combination of the ADP-receptor blocking antiplatelet drug, such as clopidogrel or ticlopidine, and the antihypertensive drug will be employed in a weight ratio to each other of within the range of from about 1000:1 to about 0.001:1, and preferably from about 0.05:1 to about 100:1.

The angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not limited to, irbesartan, including salts thereof such as the K and Na salts thereof (disclosed in U.S. Pat. No. 5,270,317 to Bernhart et al), losartan, valsartan, telmisartan, candesartan, tasosartan or eprosartan, with irbesartan or losartan being preferred.

The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril, that is



Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)-phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred, phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamides disclosed in U.S. Pat. No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Nos. 80822 and 60668; Chugai's MC-838 disclosed in CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-[[1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[1(S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Eur. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R_o 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck), indalopril (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983), spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and CI 925 (Warner-Lambert) [(3S)-[2[R(*)R(*)]] 3R(*)]-2-[2-[[1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred ACE inhibitors are fosinopril, as well as captopril, enalapril, lisinopril, quinapril, benazapril, trandolapril, fentiapril, ramipril, and moexipril.

NEP/ACE inhibitors may also be employed herein in that they possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein include those disclosed in U.S. Pat. Nos. 5,508,272, 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 5,552,397, 4,749,688, 5,504,080, 5,612,359, and 5,525,723 and European Patent Applications 0481,522, 0534363A2, 534,396 and 534,492,

Preferred are those NEP/ACE inhibitors which are designated as preferred in the above U.S. patents which are

incorporated herein by reference. Especially preferred is the angiotensin II antagonist losartan or irbesartan, or EP/ACE inhibitor omapatrilat (disclosed in U.S. Pat. No. 5,508,272), in combination with clopidogrel.

The ADP-receptor blocking antiplatelet drug will be employed in combination with an ACE inhibitor or AII antagonist, or NEP/ACE inhibitor, in a weight ratio to ACE inhibitor or AII antagonist or NEP/ACE inhibitor of within the range from about 0.1:1 to about 50:1, and preferably from about 0.2:1 to about 20:1.

It will also be appreciated that the drugs or compounds employed herein in accordance with the present invention may be employed in conjunction or combination with one or more known therapeutic agents for preventing or treating cerebral infarction, such as, for example, but not limited to cholesterol lowering drugs such as including HMG CoA reductase inhibitors preferably pravastatin, lovastatin, simvastatin, atovastatin, fluvastatin and cerivastatin.

Other cholesterol lowering drugs suitable for use herein include, but are not limited to, antihyperlipoproteinemic agents such as fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clonofibrate and the like, probucol, and related compounds as disclosed in U.S. Pat. No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Polidexide®), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Pat. No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Pat. No. 4,027,009, and other known serum cholesterol lowering agents.

Aspirin may optionally be included in the combination of the invention.

In carrying out the method of the present invention, the ADP-receptor blocking antiplatelet drug in combination with the antihypertensive drug may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., and, as such, may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), antioxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Clopidogrel will be employed in an oral daily dosage within the range from about 10 to about 1000 mg, and preferably from about 25 to about 600 mg, and most preferably, from about 50 to 100 mg.

Ticlopidine may be employed in a daily dosage as set out in the 1997 PDR (250 mg bid) although daily dosages from about 10 to about 1000 mg, preferably 25 to about 800 mg may be employed in accordance with the present invention.

The or dual acting neutral endopeptidase and angiotensin converting enzyme inhibitor can be administered at a dosage

range from about 0.03 to about 1000 mg per kg of body weight per day with a dosage range of from about 0.3 to about 300 mg per kg of body weight per day being preferred. The angiotensin II antagonist or ACE inhibitor can be administered at a dosage range from about 0.001 to about 75 mg per kg of body weight with a dosage range of from about 0.1 to about 15 mg per kg of body weight being preferred or as directed in the Physicians Desk Reference 1998 (52 Ed.).

For oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in dosages employed, for example, for lovastatin, pravastatin, simvastatin, fluvastatin, lovastatin, atorvastatin or cerivastatin, as indicated in the Physician's Desk Reference 1998 (52 Ed.), such as in an amount within the range of from about 0.1 to 2000 mg, and preferably from about 0.2 to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain clopidogrel or ticlopidine in an amount from about 10 to about 500 mg, and the antihypertensive agent in an amount of from about 0.1 to about 1000 mg.

The other serum cholesterol lowering drugs when present will be employed in dosages normally employed as indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range from about 0.1 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

Where present, the aspirin (employed with the ADP-receptor blocking antiplatelet drug and antihypertensive agent) will be employed in daily dosages within the range from about 1 mg to about 500 mg, preferably from about 20 mg to about 100 mg, and in a weight ratio to the ADP receptor blocking antiplatelet drug within the range from about 0.02:1 to about 1000:1, preferably from about 0.04:1 to about 20:1.

The ADP-receptor blocking antiplatelet drug and the antihypertensive agent, and optionally drugs for preventing or treating cerebral infarction may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of the ADP-receptor blocking antiplatelet drug and the antihypertensive drug and optionally components are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for cerebral infarction continues. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least three days are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

Formulations suitable for oral administration for inhibiting platelet aggregation and thrombus formation are prepared as described below.

EXAMPLE 1

Capsules are prepared each containing 75 mg clopidogrel (as described below) and 150 mg irbesartan (as described in the 1998 PDR)

Ingredient	Example 1 Amount (mg/Capsule)
Clopidogrel hydrogen sulfate	75
Lactose, Hydrous, NF ca.	108
Microcrystalline Cellulose, ca. NF	13
Pregelatinized Starch, NF	10.5
Polyethylene glycol 6000 NF	7.5
Hydrogenated castor oil, NF	3.3

The above clopidogrel tablet is prepared by blending anhydrous lactose, clopidogrel hydrogen sulfate, pregelati-

nized starch, and polyethylene glycol 6000 in a bin-type blender for about 15 minutes at 7 rpm.

The blended mix is then screened (1.25 mm screen) and blended for about 30 minutes at 7 rpm in a bin-type blender. The blend is compacted using a roller compactor fitted with milling equipment. The milled granulation which contains particles ranging from 1 mm to less than 20 mm is blended with microcrystalline cellulose (screen through 1.25 mm screen) and hydrogenated castor oil in a bin-type blender for about 30 minutes at 7 rpm. The blend is compressed into 240 mg tablets.

The clopidogrel tablets and 150 mg irbesartan tablets are ground into powders and filled into a single capsule.

EXAMPLE 2

Capsules each containing 75 mg clopidogrel hydrogen sulfate (tablets as described in Example 1) and 20 mg fosinopril (tablets as described in 1998 PDR) are prepared by grinding up the clopidogrel tablet and fosinopril tablet and filling the resulting powders into a single capsule.

EXAMPLES 3 and 4

Formulations suitable for oral administration for inhibiting platelet aggregation and thrombus formation are prepared as described below.

Capsules each containing 75 mg clopidogrel hydrogen sulfate (prepared as per Example 1) and about 10 mg omapatrilat (Example 3), and about 20 mg omapatrilat (Example 4) are produced from the following ingredients.

Ingredient	Example 3 Amount (mg/ Capsule)	Example 4 Amount (mg/ Capsule)
Clopidogrel (Example 1 formulation)	75	75
Omapatrilat	10	20
Lactose, Hydrous, NF	ca. 151.1	ca. 99.9
Microcrystalline Cellulose, NF	50.0	50.0
Pregelatinized Starch, NF	25.0	25.0
Sodium Starch Glycolate, NF	12.5	12.5
Colloidal Silicon Dioxide, NF	5.0	5.0
Magnesium Stearate, NF	0.6	0.6
Purified Water, USP or	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.
Gray, Opaque, Size #0 Capsule Shell	One Capsule	One Capsule

The omapatrilat, and colloidal silicon dioxide are blended in a suitable blender with lactose hydrous, microcrystalline cellulose, pregelatinized starch and a portion of sodium starch glycolate. The resulting blend is wet granulated with water. The wet granulation is dried in a suitable dryer. The remaining portion of sodium starch glycolate is added to the granulation and mixed therein. Magnesium stearate is added to the granulation and mixed therein. The resulting blend is filled into capsules together with ground up clopidogrel tablets.

What is claimed is:

1. A pharmaceutical composition comprising an ADP-receptor blocking antiplatelet drug and an angiotensin II antagonist.

2. A pharmaceutical composition comprising an ADP-receptor blocking antiplatelet drug and an ACE inhibitor.

3. A pharmaceutical composition comprising an ADP-receptor blocking antiplatelet drug and a dual NEP/ACE inhibitor.

4. The composition as defined in claim 1 wherein the antiplatelet drug is clopidogrel which is present in a weight ratio to the angiotensin II antagonist which is irbesartan within the range from about 0.001:1 to about 1000:1.

5. The composition as defined in claim 2 wherein the antiplatelet drug is clopidogrel or ticlopidine.

6. The composition as defined in claim 3 wherein the antiplatelet drug is clopidogrel or ticlopidine.

7. The composition as defined in claim 1 wherein the antiplatelet drug is clopidogrel or ticlopidine.

8. The composition as defined in claim 2 wherein the antiplatelet drug is clopidogrel which is present in a weight ratio to the ACE inhibitor which is fosinopril within the range from about 0.001:1 to about 1000:1.

9. The composition as defined in claim 3 wherein the antiplatelet drug is present in a weight ratio to the dual NEP/ACE inhibitor of within the range of from about 0.001:1 to about 1000:1.

10. The composition as defined in claim 1 wherein the angiotensin II antagonist is irbesartan, losartan, telmisartan, valsartan, candesartan, tasosartan or eprosartan and the antiplatelet drug is clopidogrel or ticlopidine.

11. The composition as defined in claim 2 wherein the antiplatelet drug is clopidogrel which is present in a weight ratio to the ACE inhibitor which is ramipril within the range from about 0.001 to 1 to about 1000:1.

12. The composition as defined in claim 3 wherein the antiplatelet drug is clopidogrel which is present in a weight ratio to the dual NEP/ACE inhibitor which is omapatrilat within the range from about 0.001:1 to about 1000:1.

13. The composition as defined in claim 1 wherein the antiplatelet drug is present in a weight ratio to the angiotensin II antagonist of within the range of from about 0.001:1 to about 1000:1.

14. The composition as defined in claim 2 wherein the ACE inhibitor is fosinopril, enalapril, lisinopril, captopril, quinapril, trandolapril, ramipril or benazapril, and the antiplatelet drug is clopidogrel or ticlopidine.

15. The composition as defined in claim 3 wherein the NEP/ACE inhibitor is omapatrilat and the anti-platelet drug is clopidogrel or ticlopidine.

16. A method for preventing or inhibiting or treating a cerebral infarction in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical composition as defined in claim 1.

17. The method as defined in claim 16 wherein the cerebral infarction is a primary or secondary ischemic event.

18. The method as defined in claim 16 wherein the pharmaceutical composition comprises an angiotensin II antagonist which is irbesartan, losartan, valsartan, candesartan, telmisartan, tasosartan or eprosartan and clopidogrel.

19. A method for preventing or inhibiting or treating a cerebral infarction in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical composition as defined in claim 2.

20. The method as defined in claim 5 wherein the cerebral infarction is a primary or secondary ischemic event.

21. A method for preventing or inhibiting or treating a cerebral infarction in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical composition as defined in claim 3.

22. The method as defined in claim 20 wherein the cerebral infarction is a primary or secondary ischemic event.

23. The method as defined in claim 21 wherein the pharmaceutical composition comprises an ACE inhibitor which is fosinopril, enalapril, lisinopril, captopril, quinapril, trandolapril, ramipril or benazapril and clopidogrel.

24. The method as defined in claim 21 wherein the pharmaceutical composition comprises a NEP/ACE inhibitor which is omapatrilat and clopidogrel.

25. The composition as defined in claim 2 wherein the antiplatelet drug is present in a weight ratio to the ACE inhibitor of within the range of from about 0.001:1 to about 1000:1.

* * * * *



US 20030114469A1

341 DC.
342
Inh. de
DPP4-(19) **United States**(12) **Patent Application Publication**
Cohen(10) **Pub. No.: US 2003/0114469 A1**(43) **Pub. Date: Jun. 19, 2003**(54) **COMBINATIONS**(76) **Inventor: David Saul Cohen, New Providence,
NJ (US)****Correspondence Address:****THOMAS HOXIE
NOVARTIS, PATENT AND TRADEMARK
DEPARTMENT
ONE HEALTH PLAZA 430/2
EAST HANOVER, NJ 07936-1080 (US)**(21) **Appl. No.: 10/231,427**(22) **Filed: Aug. 28, 2002****Related U.S. Application Data**(60) **Provisional application No. 60/325,485, filed on Sep.
27, 2001.****Publication Classification**(51) **Int. Cl.⁷ A61K 31/522**(52) **U.S. Cl. 514/263.22**(57) **ABSTRACT****The present invention relates to a pharmaceutical composition, comprising**

(a) a phosphodiesterase 5 inhibitor or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) an anti-diabetic agent;

(ii) HMG-Co-A reductase inhibitors;

(iii) an anti-hypertensive agent; and

(iv) a serotonin reuptake inhibitor (SSRI)

or, in each case, or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier. The pharmaceutical composition may be employed for the treatment of sexual dysfunction, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridemia, diabetes, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, syndrome X, erectile dysfunction, coronary heart disease, hypertension, especially ISH, angina pectoris, myocardial infarction, stroke, vascular restenosis, endothelial dysfunction, impaired vascular compliance, congestive heart failure.

COMBINATIONS

[0001] The present invention relates to a combination, especially a pharmaceutical composition, comprising

[0002] (a) a DPP-4 inhibitor or a pharmaceutically acceptable salt thereof and

[0003] (b) at least one active ingredient selected from the group consisting of

[0004] (i) an anti-diabetic agent; DPP-4 inh.

[0005] (ii) HMG-Co-A reductase inhibitors;

[0006] (iii) an anti-hypertensive agent; and Fe/mis

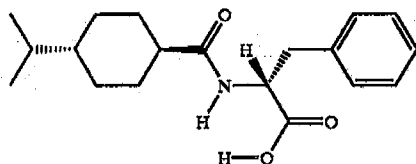
[0007] (iv) a serotonin reuptake inhibitor (SSRI)

[0008] or, in each case, a pharmaceutically acceptable salt thereof; and

[0009] a pharmaceutically acceptable carrier.

[0010] Anti-diabetic agents include insulin secretion enhancers which are active ingredients that have the property to promote the secretion of insulin from pancreatic β -cells. Examples of insulin secretion enhancers are a biguanide derivative, for example, metformin or, if appropriate, a pharmaceutically acceptable salt thereof, especially the hydrochloride thereof. Other insulin secretion enhancers include sulfonylureas (SU), especially those which promote the secretion of insulin from pancreatic β -cells by transmitting signals of insulin secretion via SU receptors in the cell membrane including, but are not limited to, tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide); glibenclamide (glyburide); gliclazide; 1-butyl-3-metanyllurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; and tolylcyclamide, or pharmaceutically acceptable salts thereof.

[0011] Insulin secretion enhancers furthermore include short-acting insulin secretion enhancers, such as the phenylalanine derivative nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] (cf. EP 196222 and EP 526171) of the formula



[0012] and repaglinide [(S)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid]. Repaglinide is disclosed in EP 589874, EP 147850 A2, in particular Example 11 on page 61, and EP 207331 A1. It can be administered in the form as it is marketed, e.g., under the trademark NovoNorm™; calcium (2S)-2-benzyl-3-(cishexahydro-2-isoinidolincarbonyl)-propionate dihydrate (mitiglinide—cf. EP 507534); furthermore representatives of the new generation of SUs such as glimepiride (cf. EP 31058); in free or pharmaceutically acceptable salt form.

The term nateglinide likewise comprises crystal modifications such as disclosed in EP 0526171 B1 or U.S. Pat. No. 5,488,510, respectively, the subject matter of which, especially with respect to the identification, manufacture and characterization of crystal modifications, is herewith incorporated by reference to this application, especially the subject matter of claims 8-10 of said U.S. patent (referring to H-form crystal modification) as well as the corresponding references to the B-type crystal modification in EP 196222 B1 the subject matter of which, especially with respect to the identification, manufacture and characterization of the B-form crystal modification. Preferably, in the present invention, the B- or H-type, more preferably the H-type, is used. Nateglinide can be administered in the form as it is marketed, e.g., under the trademark STARLIX™.

[0013] Insulin secretion enhancers likewise include the long-acting insulin secretion enhancer DPP-IV inhibitors, glucagon-like peptide-1 (GLP-1) and GLP-1 agonists.

[0014] DPP-IV is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

[0015] The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. DPP-IV inhibitors are in each case generically and specifically disclosed, e.g., in WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications. Preferred are those compounds that are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively.

[0016] GLP-1 is a insulinotropic protein which was described, e.g., by W. E. Schmidt et al., Diabetologia, 1985, 28:704-707 and in U.S. Pat. No. 5,705,483.

[0017] The term "GLP-1 agonists" used herein means variants and analogs of GLP-1(7-36)NH₂ which are disclosed in particular in U.S. Pat. Nos. 5,120,712, 5,118,666, 5,512,549, WO 91/11457 and by C. Orskov et al., J. Biol. Chem., 1989, 264:12826. The term "GLP-1 agonists" comprises especially compounds like GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg is displaced with Gly at the 37th position of the GLP-1(7-36)NH₂ molecule and variants and analogs thereof including GLN⁹-GLP-1(7-37), D-GLN⁹-GLP-1(7-37), acetyl LYS⁹-GLP-1(7-37), LYS¹⁸-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL⁸-GLP-1(7-37), GLY⁸-GLP-1(7-37), THR⁸-GLP-1(7-37), MET⁸-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig et al., Diabetologia, 1999, 42:45-50.

[0018] An insulin sensitivity enhancer restores impaired insulin receptor function to reduce insulin resistance and consequently enhance the insulin sensitivity.

[0019] An appropriate insulin sensitivity enhancer is, for example, an appropriate hypoglycemic thiazolidinedione derivative (glitazone).

claims are hereby incorporated into the present application by reference to these publications. Comprised are likewise the corresponding stereoisomers as well as the corresponding crystal modifications, e.g., solvates and polymorphs, which are disclosed therein and, where applicable, all pharmaceutically acceptable salts thereof.

[0047] Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

[0048] HMG-Co-A reductase inhibitors (also called β -hydroxy- β -methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol, especially LDL-cholesterol, in blood.

[0049] The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin (cf. EP 680320), cerivastatin (cf. EP 491226), fluvastatin (cf. U.S. Pat. No. 5,354,772), pitavastatin (cf. EP 304063), lovastatin (cf. EP 22478), pravastatin (cf. UK 2077264), rosuvastatin (S 4522) (Wantanabe, Bioorg. Med. Chem., 1997, 5(2):437-444) and simvastatin (cf. EP 33538), or, in each case, a pharmaceutically acceptable salt thereof.

[0050] Preferred HMG-Co-A reductase inhibitors are those agents that have been marketed, most preferred is fluvastatin, atorvastatin, pravastatin or simvastatin or, in each case, a pharmaceutically acceptable salt thereof.

(b) (i) [0051] Anti-hypertensive agents include angiotensin converting enzyme inhibitors (ACE-inhibitors) and AT_1 receptor antagonists. The interruption of the enzymatic degradation of angiotensin I to angiotensin II with ACE-inhibitors is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

[0052] The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of alacepril (cf. EP 7477), benazepril (cf. EP 72352), benazeprilat (cf. EP 72352), captopril (cf. U.S. Pat. No. 4,105,776), ceronapril (cf. EP 229520), cilazapril (cf. EP 94095), delapril (cf. EP 51391), enalapril (cf. EP 12401), enalaprilat (cf. EP 12401), fosinopril (cf. EP 53902), imidapril (cf. EP 95163), lisinopril (cf. EP 12401), moveltipril (cf. ZA 82/3779), perindopril (cf. EP 49658), quinapril (cf. EP 49605), ramipril (cf. EP 79022), spirapril (cf. EP 50800), temocapril (cf. EP 161801), andtrandolapril (cf. EP 551927), or, in each case, a pharmaceutically acceptable salt thereof.

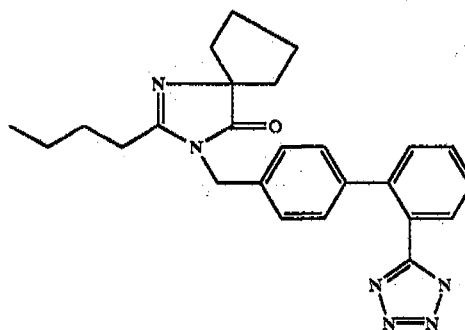
[0053] Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

[0054] The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

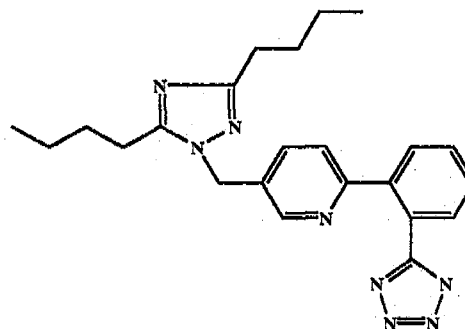
[0055] The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid

addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example, COOH) can also form salts with bases.

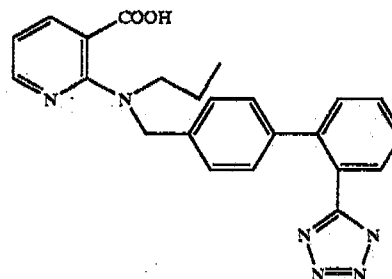
[0056] The class of AT_1 receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds which are selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula



[0057] the compound with the designation SC-52458 of the following formula



[0058] and the compound with the designation the compound ZD-8731 of the following formula



[0059] or, in each case, a pharmaceutically acceptable salt thereof.

344 D47
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Performing your original search, *telmisartan hydrochlorothiazide*, in PubMed will retrieve 27 records.

1: Am J Ther. 2002 Mar-Apr;9(2):111-7.

Related Articles, Links

Wolters Kluwer | Lippincott
Williams & Wilkins

Comparison of a fixed-dose combination of 40 mg telmisartan plus 12.5 mg hydrochlorothiazide with 40 mg telmisartan in the control of mild to moderate hypertension.

Lacourcière Y, Martin K.

Hypertension Research Unit, Center Hospitalier Universitaire de Québec, Québec. yves.lacourciere@crchul.ulaval.ca

This study investigated whether a fixed-dose combination of 40 mg of the angiotensin II antagonist telmisartan plus 12.5 mg of the diuretic hydrochlorothiazide (HCTZ) was superior to 40 mg telmisartan in patients with mild to moderate hypertension who failed to respond adequately to 40 mg telmisartan monotherapy. One hundred forty-six patients were withdrawn before randomization. Nonresponders (n = 327) were double blind and randomized to 40 mg telmisartan + 12.5 mg HCTZ (n = 160) or 40 mg telmisartan (n = 167). After 8 weeks of treatment, 40 mg telmisartan + 12.5 mg HCTZ lowered diastolic blood pressure (DBP) by an additional 3.5 mm Hg (P <.01) and systolic blood pressure (SBP) by 7.4 mm Hg (P <.01) compared with 40 mg telmisartan. Most of the additional effect of the combination was seen after 4 weeks of treatment. At week 8, blood pressure was normalized (SBP <140 mm Hg and DBP <90 mm Hg) in 51.6% of patients on 40 mg telmisartan + 12.5 mg HCTZ compared with 23.5% on 40 mg telmisartan (P <.05). The combination of 40 mg telmisartan + 12.5 mg HCTZ normalized DBP in 64.8% of patients, whereas 40 mg telmisartan normalized DBP in 40.1% (P <.05). SBP decreased by > or =10 mm Hg from baseline in 63.5% of patients receiving the fixed-dose combination compared with 42.6% of those receiving 40 mg telmisartan (P <.05). Both treatments were well tolerated. Adverse events were predominantly mild, transient, and considered unrelated to therapy. These findings indicate that a fixed-dose combination of 40 mg telmisartan + 12.5 mg HCTZ is clinically and statistically superior to 40 mg telmisartan in patients with mild to moderate hypertension failing to respond to 40 mg telmisartan alone.

✓

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335 345

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
EMILIO FERRERO

ASUNTO	Radicación	06008335
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	6836
	Folios	019

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☐

No. Sol. Internacional PCT/EP2004/008326

Fecha de Presentación Internal. Julio 24 de 2004.

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 42 a 65 como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios: 66 a 68 como se radicó inicialmente.
Folios: 328 a 329
(15 reivindicaciones) modificado: 25/02/ 2009.
- 1.3. Oposiciones: 1- Folios 112 a 318 de 25/10/ 2007.
Laura Catalina Silva (Procaps S.A)
- 1.4. Prioridad: Julio 31 de 2003, DE, 10335027.6
Octubre 6 de 2003, DE, 10346260.0
Diciembre 5 de 2003, DE, 10356815.8

2. Objeto de la invención

Título de la invención: USO DE ANTAGONISTAS DEL RECEPTOR DE ANGIOTENSINA II

Problema Técnico Planteado: La necesidad de una composición que incluya un antagonista del receptor de angiotensina II, para tratar la hipertensión y al mismo

tiempo la diabetes.

Solución: Proporciona una composición farmacéutica que comprende telmisartano en combinación con: a) amlodipina ó nifedipina; b) eplerenona; clopidogrel, opcionalmente combinado con ácido acetil salicílico; ó d) un inhibidor de DPP4.

IPC: A61K31/416, A61p3/10.

3. De la solicitud de Patente

3.2 Reivindicaciones (artículo 30 D 486)

La reivindicación 1, presenta combinaciones de telmisartan con: amlodipina o nifedipina, eplerenona, clopidogrel opcionalmente combinado con ácido acetilsalicílico, ó un inhibidor de DPP4", mediante lo cual se obtienen varias composiciones; pero en la descripción solo existe sustento, con ejemplos, para las composiciones: de telmisartan combinado con metformina y telmisartan combinado con hidroclorotiazida.

La reivindicación 13, tampoco tiene sustento en la descripción.

Las reivindicaciones 2-12, no están caracterizadas por sus componentes sino por un uso cuando se menciona que están "caracterizadas porque en las personas por tratar..."

Las reivindicaciones 14 y 15 muestran una falsa dependencia con la reivindicación 1, dado que esta combinación (telmisartan y un diurético) no esta comprendida en la reivindicación 1; sin embargo se realiza análisis de patentabilidad a las reivindicaciones 14 y 15.

4. Unidad de invención (artículo 25 D 486)

El hecho de que en la reivindicación 1, se reclamen diferentes combinaciones de telmisartan con cualquiera de los otros principios activos mencionados en a, b, c ó d; es evidencia de que existe mas de un grupo inventivo.

5. Análisis de la(s) Oposición(es): (artículo 43 D. 486):

5.1 OPOSICION DE PROCAPS S.A:

Laura Catalina Silva, actuando en calidad de apoderada de PROCAPS S.A, argumenta que la presente solicitud carece de Novedad y de aplicación industrial, a la luz de los documentos D1(ES2175098) y D2 (WO0130353).

5.2 RESPUESTA DEL SOLICITANTE BOEHRINGER INGELLHEIM INTERNACIONAL(folios 322-330; de 25/02/ 2009):

El interesado antes de entrar a discutir los argumentos que realzan la novedad de la presente invención frente a las enseñanzas de los documentos citados por PROCAPS S.A, decide cambiar el capítulo reivindicatorio desistiendo de las reivindicaciones 1-19 (de uso) y radicando un nuevo capítulo reivindicatorio (1-15

reivindicaciones, folios 328-329).

5.2.1 El solicitante en su respuesta frente a lo argumentado por el opositor, PROCAPS S.A dice que:

1-La afirmación de la falta de novedad soportada en los documentos **D1 y D2** mencionados anteriormente, resulta equivocada dado que ninguno de estos documentos, enseñan una composición: "tal como esta definida, es decir, una composición farmacéutica que contiene telmisartano en combinación con amlodipina o nifedipina, eplerenona, clopidogrel opcionalmnete combinado con acido acetilsalicílico, ó un inhibidor de DPP4".

5.3 RESPUESTA DEL EXAMINADOR TECNICO A LA OPOSICION DE PROCAPS S.A Y AL SOLICITANTE BOEHRINGER INGELLHEIM INTERNACIONAL.

Esta oficina considera que, aunque el solicitante presenta un nuevo capítulo reivindicatorio y que los documentos **D1 y D2** presentados por el opositor, no afecten la novedad de la presente solicitud; no obstante, existen documentos que ya divulgaban las combinaciones reclamadas en la reivindicación 1; tal como se demuestra en el análisis de patentabilidad.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: Julio 31 de 2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D3	CA 2338039	Biphenylsulfonyl-substituted imidazole derivatives, their preparation process, their use as drug or diagnostic agent and drug containing them	Enero 27 de 2000
D4	US20030077229	Buccal, polar and no polar spray or capsule containing cardiovascular or renal drugs	Abril 24 de 2003
D5	US6248729	Combination of an ADP-receptor blocking antiplatelet drug and antihypertensive drug and a method for preventing a cerebral infarction employing such combination	Junio 19 de 2001
D6	US2003/0114469	Combinations	Junio 19 de 2003
D7	*articulo	Comparison of a fixed-dose combination of 40 mg telmisartan plus 12.5 mg hydrochlorothiazide with 40 mg telmisartan in the control of mild to moderate hypertension.	Marzo de 2002

D3(folios 331-332); D4 (folios 333-334); D5 (folios 335-340); D6 (folios 341-343); D7 (folio 344).

7. Análisis de patentabilidad (según requisito) (artículo 14 D486)

7.1 Novedad (artículo 16 D486)

Respecto a la solicitud en estudio:

Las reivindicación 1, reclama: Una composición farmacéutica que comprende, Telmisartano en combinación con: Amlodipina ó nifedipina; Eplerenona; clopidogrel, opcionalmente combinado con Acido acetil salicílico; ó un inhibidor de DPP4.

Respecto al estado de la Técnica:

D3, divulga: Combinación de telmisartano con nifedipina (folio 331, pg 25, párrafo 35)

D4, divulga: Combinación de telmisartano con eplerenona (folio 334, pag 9, renglones 29 y 32)

D5, divulga: Combinación de telmisartano con clopidogrel (folio 336, columna 2, renglones 51-51; folio 337, columna 3, renglones 32-41).

D6, divulga: Combinación de telmisartano con un inhibidor de DPP4 (folio 342, pag 1 párrafo 14; folio 337, columna 3, renglones 32-41).

La reivindicación 14, reclama: Una composición farmacéutica que comprende, Telmisartano en combinación con: Un diurético.

Respecto al estado de la Técnica:

D7, describe: Combinación de telmisartano con hidroclorotiazida (diurético), (folio 334).

Al realizar la comparación anterior se puede evidenciar que las características esenciales de la formulación farmacéutica que se pretende reclamar en la reivindicación 1 y sus dependientes 2-13, están divulgadas en D3, D4, D5, D6; lo mismo que las características esenciales de las reivindicaciones 14 y 15, se encuentran divulgadas en D7 ; por lo anterior, las reivindicaciones mencionadas anteriormente no se consideran nuevas.

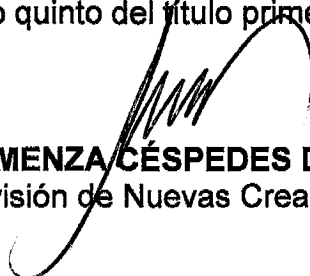
8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D3	CA 2338039	1-13	Novedad
D4	US20030077229	1-13	Novedad
D5	US6248729	1-13	Novedad
D6	US2003/0114469	1-13	Novedad
D7	*artículo	14-15	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
12 JUN. 2003

orig

CONCEPTO TÉCNICO No.1412	EXAMINADOR TÉCNICO Código No.202078
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