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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-120205- -00007-0000

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Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

Referencia: Expediente No. 06.120.205

Solicitud de Patente de Invención titulada: "Formulación de tableta
revestida y método"

Solicitante: Bristol-Myers Squibb Company

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO.90
DEL 12 DE MARZO DE 2010, OFICIO NO. 3583 (EXAMEN DE FONDO)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

1. Objeciones del Examinador

1.1 Novedad

El Examinador plantea que, después de realizada la búsqueda de anterioridades, encontró el documento **D1** (WO03059330) afecta la novedad de las reivindicaciones 1 a 16 de la presente solicitud.

Particularmente, el Examinador considera que el documento **D1** afecta la novedad de la presente solicitud por cuanto:

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“D1 revela núcleos comprimidos de una composición farmacéutica estable que contiene un inhibidor de ACE y comprende un núcleo recubierto con una capa de inhibidor de ACE y el proceso para su preparación..

Revela que la cubierta puede contener de 2 a 90% en peso de inhibidor de ACE (página 3), que la dispersión, solución o dispersión inhibidor puede ser preparado por adición de los ingredientes activos en un solvente con agitación o cualquier otro método de mezclado y aditivos como polímeros formadores de película pueden ser adicionados a la mezcla (página 4) .

En el ejemplo 1, revela la secuencia de pasos que se realizaron para obtener las tabletas de la invención, y en base a dicho método presenta ejemplos específicos de las tabletas de la referencia que contiene un núcleo, una cubierta sellante, una capa de medicamento y una cubierta externa (página 7) tal y como se reclama en la presente solicitud.

Se concluye que la reivindicación 1 reclama materia que podría carecer de novedad dado que el estado del arte ya anticipaba la tableta que se reclama y los métodos que se presentan”.

2. Argumentos a favor de la patentabilidad de la solicitud

2.1 Modificación a una solicitud en trámite:

De conformidad con el artículo 34 de la Decisión 486 que establece que el solicitante en cualquier momento del trámite puede presentar modificaciones a su solicitud siempre y cuando no se presente una ampliación de la invención originalmente presentada, me permito presentar un nuevo capítulo reivindicatorio conformado por 13 reivindicaciones.

En particular se presentan las siguientes modificaciones:

Se cancelaron las reivindicaciones 2, 6, 7 y 9 del capítulo reivindicatorio anteriormente presentado.

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Las reivindicaciones 1, 15 y 11 se han modificado de tal forma que incorpora la limitación “polímero basado en alcohol polivinílico” (en parte) como la capa de revestimiento de sello interno, la segunda capa de revestimiento y la capa exterior de revestimiento protector. Esta modificación efectuada en dichas reivindicaciones 1, 15 y 11 están totalmente sustentadas en las anteriores reivindicaciones 2,6 y 7.

El término PVA se reemplazó por alcohol polivinílico en la reivindicación 8, que ahora corresponde a la reivindicación 5. El sustento para esta modificación puede encontrarse en la descripción página 6 línea 24 a la página 16 línea 8.

Se agregó la reivindicación 13. El sustento para esta reivindicación puede encontrarse en el ejemplo de la página 21 de la descripción.

2.2 Novedad

La novedad de una solicitud está legalmente definida en el Artículo 16 de la Decisión 486 así: *“una invención se considerará nueva, cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso de la prioridad reconocida...”*

En virtud de la anterior definición, consideramos que el documento WO 03/059330 (D1) no afecta la novedad de la presente invención ya que con la modificación efectuada al capítulo reivindicatorio se supera dicha observación.

La reivindicación 1 se lee de la siguiente forma:

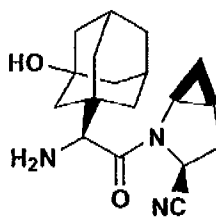
1. Una tableta recubierta que comprende un núcleo de tableta y:

a) una capa de sello interno de recubrimiento que comprende una formulación de recubrimiento de polímero que comprende un polímero a base de alcohol polivinílico que cubre el núcleo de la tableta;

b) una segunda capa de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico y un medicamento

que cubre la capa de sello interno de recubrimiento del núcleo de la tableta; y

c) opcionalmente una capa protectora exterior de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico que cubre la segunda capa del núcleo de la tableta, en donde el medicamento en dicha segunda capa es saxagliptina

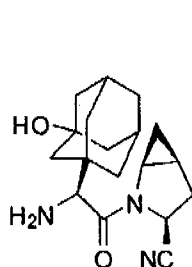


o una sal farmacéuticamente aceptable del mismo.

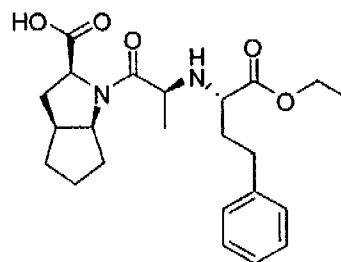
Por lo tanto, si se efectúa la comparación elemento por elemento entre la reivindicación 1 de la presente invención y **D1** se puede concluir que dicho documento no contiene todas las características específicas reclamadas por el nuevo pliego reivindicatorio de la presente invención.

Ahora bien, aunque su Despacho no objetó el nivel inventivo, mi representada presenta los siguientes argumentos con el fin de agilizar el trámite de la presente solicitud.

El nuevo pliego reivindicatorio se relaciona con una formulación de tableta revestida que comprende Saxagliptina la cual es un inhibidor de la DPP-IV. Contrario a esto, las enseñanzas de **D1** se limitan a formulaciones de tableta revestidas que comprenden un inhibidor de ACE, tales como “ramipril, quinapril, enalapril, spirapril, lisinopril, benazepril, y medicamentos relacionados estructuralmente”. Por favor ver página 1, líneas 10-13. La Saxagliptina no es un inhibidor de ACE y estructuralmente no está relacionada con los inhibidores ACE revelados en **D1** (ramipril, quinapril, etc).

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Saxagliptina



Ramipril

Además, **D1** enseña que los inhibidores de ACE se degradan vía: ciclización intramolecular hasta formar dicetopiperazinas. Los inhibidores ACE también pueden degradar vía hidrólisis del grupo Ester de la cadena lateral y por oxidación. Como medio para reducir la degradación, **D1** enseña núcleos de tableta que son revestidos con tres capas donde una de las capas contiene el ingrediente activo. Ver tablas I-V en las páginas 7-10.

Específicamente, **D1** enseña:

(a) capa de sello

- (i) hidroxipropilmetilcelulosa; y/o
- (ii) hidroxipropilcelulosa

(b) capa de medicamento

- (i) Ramipril
- (ii) hidroxipropilmetilcelulosa; y/o
- (iii) hidroxipropilcelulosa.

(c) revestimiento exterior

- (i) hidroxipropilmetilcelulosa; y/o
- (ii) hidroxipropilcelulosa.

Las tablas VI, VII y VIII de las páginas 11-12, proporcionan datos de la degradación para el Ramipril para las formulaciones reveladas en las tablas I, IV, y V, respectivamente.

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La Saxagliptina se degrada hasta una amidina cíclica diferente del producto de degradación dicetopiperidina de los inhibidores de ACE. Las formulaciones de la presente invención inesperadamente reducen o inhiben la degradación de la Saxagliptina. Las presentes formulaciones se relacionan con:

- (a) Una cubierta de sello interior que comprende:
 - (i) polímero a base de alcohol polivinílico;
- (b) Un segundo recubrimiento que comprende
 - (i) Saxagliptina; y
 - (ii) polímero a base de alcohol polivinílico;
- (c) Un recubrimiento exterior que comprende
 - (i) polímero a base de alcohol polivinílico

Con relación a las capas/recubrimientos, todas las tres capas/recubrimientos reivindicados contienen un polímero a base de alcohol polivinílico y no contienen hidroxipropilmetilcelulosa ni tampoco hidroxipropilcelulosa tal como lo enseñado por **D1**.

Los solicitantes de la presente invención enfatizan que las formulaciones reivindicadas reducen la degradación de la Saxagliptina más efectivamente que la reducción de la degradación del Ramipril que hacen las formulaciones de **D1** bajo las mismas condiciones de tiempo, humedad, temperatura, tal como se muestra en la siguiente tabla No. 1:

Tabla No. 1

	1 mes o 4 semanas (%)	2 meses o 8 semanas (%)	3 meses o 12 semanas (%)	6 meses o 26 semanas (%)	41 semanas (%)
Saxagliptina ¹ a 40°C/ 75% HR	0.05	0.09	0.25	0.32	0.90
Ramipril ² a 40°C/ 75% HR	1.26	1.92	2.88	4.92	ND

¹ La tabla 1 original de la descripción, página 26.
² La tabla VII del documento WO 03/059330, página 11.

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Los solicitantes de la presente invención respetuosamente declaran que el área de actividad de las formulaciones es imprevisible. **D1** sustenta esta afirmación en la página 1, líneas 17-19. "La estabilidad de las composiciones farmacéuticas que contienen inhibidores de ACE pueden también ser influenciados negativamente por la escogencia de auxiliares en el tableteado".

Respetuosamente, mi representada afirma que la única manera de determinar la apropiada formulación para reducir degradación de cualquier medicamento es mediante experimentación.

Existen muchas diferencias entre las formulaciones de tableta reveladas en **D1** y la presente invención, se mencionan las siguientes:

- (1) La Saxagliptina es un inhibidor de DPP-IV, y no un inhibidor de ACE.
- (2) La Saxagliptina es estructuralmente diferente a los inhibidores de ACE de **D1**;
- (3) La Saxagliptina se degrada a una amidina cíclica, y no a una dicetopiperaina como se revela en **D1**.
- (4) Las formulaciones de tableta de las actuales reivindicaciones abarcan capas/recubrimientos conformados por polímeros a base de alcohol polivinílico, y no a base de hidroxipropilmetilcelulosa y/o hidroxipropilcelulosa tal como se revela en **D1**.
- (5) Las formulaciones de tableta de la presente invención reduce la degradación de la Saxagliptina más efectivamente que las formulaciones de tableta de **D1** que reducen la degradación de inhibidores de ACE tal como Ramipril.

Por lo anteriormente expuesto, mi representada respetuosamente afirma que las formulaciones reclamadas no habrían sido obvias para una persona medianamente experta en la materia basándose en **D1**, por las diferencias significantes entre las formulaciones reclamadas por la presente invención y las formulaciones de **D1**, y no se puede predecir de manera obvia el área de actividad de formulaciones farmacéuticas tal como se argumentó anteriormente.

En este orden de ideas, tenemos que la invención propuesta por el solicitante si cumple con

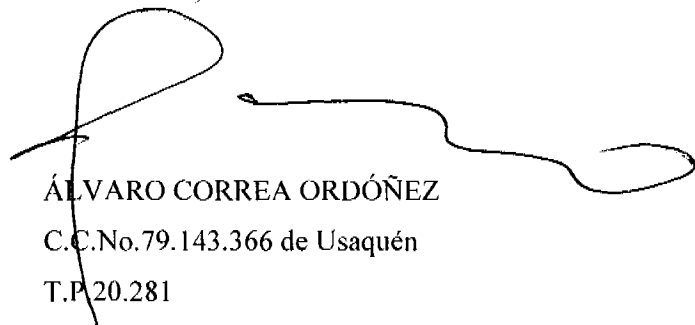
los requisitos de patentabilidad y de esta manera es susceptible de ostentar el título de patente de invención.

3. Solicitudes concedidas en otros países para esta misma invención.

A manera informativa, pongo en conocimiento del Examinador que la patente **Peruana No. 5275 (Anexo copia del título de patente y reivindicaciones otorgadas)**, equivalente a la presente solicitud colombiana ha sido otorgada. Aún cuando entiendo que esta decisión de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una patente que se decidió de acuerdo a lo establecido en la Decisión 486, la cual corresponde a la misma legislación que rige a Colombia en materia de propiedad intelectual, sí constituye una prueba de patentabilidad de la presente invención.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

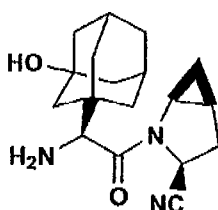
Anexos:

Capítulo reivindicatorio modificado
Copia de la Patente Peruana No. 5275 y capítulo reivindicatorio otorgado.

MGT/BOGDMS-#359930-V1-P2006_120205-0710 DOC

REIVINDICACIONES

1. Una tableta recubierta que comprende un núcleo de tableta y:
 - a) una capa de sello interno de recubrimiento que comprende una formulación de recubrimiento de polímero que comprende un polímero a base de alcohol polivinílico que cubre el núcleo de la tableta;
 - b) una segunda capa de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico y un medicamento que cubre la capa de sello interno de recubrimiento del núcleo de la tableta; y
 - c) opcionalmente una capa protectora exterior de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico que cubre la segunda capa del núcleo de la tableta, en donde el medicamento en dicha segunda capa es saxagliptina



o una sal farmacéuticamente aceptable del mismo.

2. La tableta recubierta como se define en la reivindicación 1, en donde dicha segunda capa de recubrimiento comprende desde 0,1 hasta 70% en peso de medicamento y de 30% a 99,5% en peso del polímero de recubrimiento, en base al peso de la segunda capa de recubrimiento.
3. La tableta recubierta como se define en la reivindicación 1, en donde la formulación de polímero de recubrimiento en la segunda capa de recubrimiento es al menos 2 mg con un núcleo de tableta de 200mg, y el medicamento es al menos 0,2 mg.
4. La tableta recubierta como se define en la reivindicación 1, que incluye además una tercera capa protectora exterior de recubrimiento dispuesta sobre dicha segunda capa de recubrimiento.
5. La tableta recubierta como se define en la reivindicación 1, en donde el polímero a base de alcohol polivinílico en la segunda capa de recubrimiento es sustancialmente el mismo polímero a base de alcohol polivinílico en las otras capas de recubrimiento.

6. La tableta recubierta como se define en la reivindicación 1, en donde en la segunda capa de recubrimiento el medicamento esta presente en una cantidad dentro del rango de 0,2 a 140 mg y el polímero de recubrimiento esta presente en una cantidad dentro del rango de 2 a 140 mg, y en cada una de la capa interna de sello de recubrimiento y la capa protectora de recubrimiento exterior opcional el polímero de recubrimiento esta presente en una cantidad dentro del rango de 1 a 100 mg.

7. La tableta recubierta como se define en la reivindicación 1, en donde el núcleo de la tableta comprende uno o más rellenos, opcionalmente uno o más aglutinantes, opcionalmente uno o más desintegrantes y opcionalmente uno o más lubricantes para formación de tabletas.

8. La tableta recubierta como se define en la reivindicación 1, en donde el núcleo de la tableta comprende celulosa microcristalina, monohidrato de lactosa, croscarmelosa de sodio, y estearato de magnesio.

9. La tableta recubierta como se define en la reivindicación 1, que tiene la siguiente composición:

Material de la tableta de placebo	Rango % en peso para una tableta de placebo de 200 mg
Lactosa	20 a 75% / 40 a 150 mg
Celulosa Microcristalina	20 a 75% / 40 a 150 mg
Croscarmelosa de sodio	2 a 10% / 4 a 20 mg
Estearato de magnesio	0,2 a 2% / 0,4 a 4 mg

Primera capa de recubrimiento de sello interno	% en peso para una tableta de placebo de núcleo de 200 mg
Polímero de recubrimiento y plastificante y deslizante opcionalmente	1 a 3% / 2 a 6 mg

Segunda capa de recubrimiento	% en peso para una tableta de placebo de núcleo de 200 mg
Inhibidor DPP4 (base libre o sal de HCl)	0.25 a 70% / 0.5 a 140 mg
Polímero de recubrimiento y plastificante y deslizante opcionalmente	1 a 50 % / 2 a 100 mg

Tercera capa protectora exterior de recubrimiento	% en peso para una tableta de placebo de núcleo de 200 mg
Polímero de recubrimiento y plastificante y deslizante y color opcionalmente	1 a 5% / 2 a 10 mg .

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10. La tableta recubierta como se define en la reivindicación 1 en donde para una potencia de 5 mg la segunda capa de recubrimiento comprende 5 mg de medicamento y 5 mg de polímero de recubrimiento a base de polímero y para una potencia de 2,5 mg la capa de recubrimiento comprende 2,5 mg de medicamento y 20 mg de recubrimiento a base de polímero.

11. Un método para preparar la tableta recubierta de acuerdo a la reivindicación 1 que comprende:

- a) proporcionar un núcleo de tableta;
- b) recubrir la tableta con una formulación de recubrimiento de sello interno la cual incluye al menos un polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico;
- c) secar la tableta recubierta para formar una capa de sello interno de recubrimiento sobre la misma;
- d) recubrir la tableta así cubierta con una segunda capa de formulación de recubrimiento la cual incluye un medicamento que es saxagliptina, y al menos un polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico.
- e) secar la tableta así cubierta para formar una segunda capa de recubrimiento sobre la misma; y
- f) opcionalmente recubrir la tableta así cubierta con una tercera formulación de capa de recubrimiento protectora la cual incluye al menos un polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico; y
- g) secar la tableta así cubierta para formar la tableta de la reivindicación 1.

12. El método como se define en la reivindicación 11 en donde las capas de recubrimiento se aplican como una suspensión del polímero de recubrimiento.

13. La tableta recubierta como se define en la reivindicación 8 en donde:

- (a) La capa de sello interior de recubrimiento que comprende alcohol polivinílico; polietilenglicol, talco, y dióxido de titanio;
- (b) La segunda capa de recubrimiento comprende saxagliptina; alcohol polivinílico; polietilenglicol, talco, y dióxido de titanio; y
- (c) La capa de recubrimiento protector exterior comprende alcohol polivinílico; polietilenglicol, talco, y dióxido de titanio.

Registro de la Propiedad Industrial

Dirección de Invenciones y Nuevas Tecnologías

TITULO N° 5275

La Dirección de Invenciones y Nuevas Tecnologías del Indecopi certifica que por mandato de la Resolución N° 000505-2009/DIN-INDECOPI de fecha 14 de abril de 2009, ha quedado inscrita en el Registro de Patentes de Invención, la siguiente invención:

Denominación : FORMULACION DE TABLETA REVESTIDA QUE
COMPRENDE SAXAGLIPTINA

Clasificación : A61K 9/24; A61K 31/403

Solicitud : 000601-2005

Fecha de Presentación : 30 de mayo de 2005

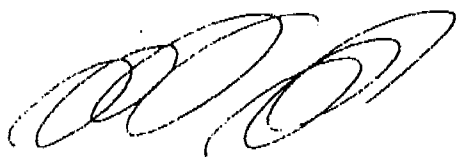
Fecha de Prioridad : 28 de mayo de 2004

Titular : BRISTOL-MYERS SQUIBB COMPANY

País : Estados Unidos de América

Inventores : DIVYAKANT S. DESAI; BING V. LI

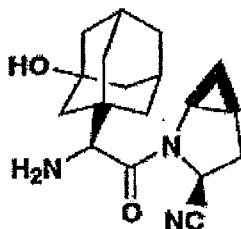
Vigencia : 30 de mayo de 2025



BRUNO MÉRCHOR VALDERRAMA
Director de Invenciones y
Nuevas Tecnologías
INDECOPI

CLAIMS

1. A coated tablet comprising a tablet core and
 - a) an inner seal coating layer comprising a coating polymer formulation comprising a polyvinyl alcohol (PVA) based polymer coated on the tablet core;
 - b) a second coating layer comprising a coating polymer formulation comprising a PVA based polymer and medicament coated on the inner seal coating of the tablet core; and
 - c) optionally an outer protective coating layer comprising a coating polymer formulation comprising a PVA based polymer coated on the second coating layer of the tablet core wherein the medicament in said second coating layer is saxagliptin,



or a pharmaceutically acceptable salt thereof.

2. The coated tablet as defined in Claim 1 wherein said second coating layer is comprised of from 0.1 to 70% by weight of medicament and from 30 to 99.5% by weight of coating polymer, based on the weight of the second coating layer.
3. The coated tablet as defined in Claim 1 wherein the coating polymer formulation in the second coating layer is at least 2 mg with a 200 mg tablet core, and the medicament is at least 0.2 mg.
4. The coated tablet as defined in Claim 1 further including a third outer protective coating layer disposed on said second coating layer.

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5. The coated tablet as defined in Claim 4 wherein said second coating layer comprises a PVA based polymer.
6. The coated tablet as defined in Claim 4 wherein each of the inner seal coating layer and the outer protective layer comprises a PVA based polymer.
7. The coated tablet as defined in Claim 6 wherein the PVA based polymer in the second coating layer is the same as the PVA based polymer in the other coating layers.
8. The coated tablet as defined in Claim 5 wherein the PVA based polymer is comprised of polyvinyl alcohol.
9. The coated tablet as defined in Claim 1 where in second coating layer the medicament is present in an amount within the range from 0.2 to 140 mg and the coating polymer is present in an amount within the range from 2 to 140 mg, and in each of the inner seal coating layer and optionally outer protective coating layer, the coating polymer is being present in an amount within the range from 1 to 100 mg.
10. The coated tablet as defined in Claim 1 wherein the tablet core is comprised of one or more fillers, optionally one or more binders, optionally one or more disintegrants and optionally one or more tableting lubricants.
11. The coated tablet as defined in Claim 10 wherein the tablet core is comprised of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate.
12. The coated tablet as defined in Claim 1 having the following composition:

Material	Range
Tablet Placebo	% by weight for 200 mg placebo

	tablet
Lactose	20 to 75%/40 to 150 mg
Microcrystalline cellulose	20 to 75%/40 to 150 mg
Croscarmellose sodium	2 to 10%/4 to 20 mg
Magnesium Stearate	0.2 to 2%/0.4 to 4 mg

First Inner Seal Coating Layer	% by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer and glidants	1 to 3%/2 to 6 mg

Second Coating Layer	% by weight of 200 mg placebo core tablet
Saxagliptin (free base or HCl salt)	0.25 to 70%/0.5 to 140 mg
Coating polymer, and optional plasticizer and glidants	1 to 50%/2 to 100 mg

Third Outer Protective Coating Layer	% by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer, glidants and color	1 to 5%/2 to 10 mg

13. The coated tablet as defined in Claim 1 where for a 5 mg potency the second coating layer is comprised of 5 mg medicament and 5 mg polymer based coating and for a 2.5 mg potency the coating layer is comprised of 2.5 mg medicament and 20 mg polymer based coating.
14. A method for preparing the coated tablet according to claim 1 comprising:
 - a) providing a tablet core;
 - b) coating the tablet with an inner seal coating layer formulation which includes at least one coating polymer comprising a polyvinyl alcohol (PVA) based polymer;
 - c) drying the coated tablet to form an inner seal coating thereon;
 - d) coating the so-coated tablet with a second coating layer formulation which includes medicament which is saxagliptin and at least

one coating polymer comprising a polyvinyl alcohol (PVA) based polymer;

e) drying the so-coated tablet to form a second coating layer thereon; and

f) optionally coating the so-coated tablet with a third outer protective coating layer formulation which includes at least one coating polymer comprising a polyvinyl alcohol (PVA) based polymer; and

g) drying the so-coated tablet to form the coated tablet of claim 1.

- 15 The method as defined in Claim 14 wherein the coating layers are applied as a suspension of the coating polymer.

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WO 2003/059330 A1 (patent application)**STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACE INHIBITOR(S)**

Front Page Full Text PDF Version Patent Family & Status

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Title

STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACE INHIBITOR(S)

Claims

1. A stable pharmaceutical composition for oral administration of ACE inhibitor(s) comprising a core coated with a layer of ACE inhibitor(s).
2. The composition of claim 1, wherein the said layer is without plasticizer.
3. The composition of claim 1, wherein the ACE inhibitor is selected from the group consisting of ramipril, quinapril, enalapril, spirapril, lisinopril, and benazepril.
4. The composition of claim 1, wherein the layer of ACE inhibitor(s) comprises film forming polymer.
5. The composition of claim 4, wherein the film forming polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, cellulose acetate, polyvinylpyrrolidone, gelatin, a combination of microcrystalline cellulose and carrageenan, and a combination of polyvinylalcohol and polyvinylacetate.
6. The composition of claim 4, wherein the layer of ACE inhibitor(s) further comprises other additives.
7. The composition of claim 1, wherein the core is a compressed tablet.
8. The composition of claim 1, wherein the core comprises a sugar sphere or nonpareil seeds.
9. The composition of claim 7 or 8, wherein compressed tablets, sugar spheres or nonpareil seeds are filled into hard gelatin capsules.
10. The composition of claim 1, wherein the core is inert.
11. The composition of claim 1, wherein the core has a pharmaceutically active substance other than the one which is susceptible to degradation by mechanical stress.
12. The composition of claim 11 wherein the pharmaceutically active substance is selected from the group consisting of hydrochlorothiazide, pirtanide, and dihydropyridines.
13. The composition of claim 12, wherein the dihydropyridines are selected from the group consisting of felodipine, nitrendipine, nifedipine and lacidipine.
14. A stable pharmaceutical composition for oral administration of pharmaceutically active substance, comprising a core coated with a layer of pharmaceutically active substance, wherein the pharmaceutically active substance is susceptible to degradation by mechanical stress.
15. The composition of claim 1, wherein a seal coat separates the core and the layer of ACE inhibitor(s).
16. The composition of claim 1, wherein the layer of ACE inhibitor(s) is further surrounded with an outer coat.
17. A process for the preparation of a stable pharmaceutical composition for oral administration of ACE inhibitor(s) comprising disposing a layer of an ACE inhibitor dispersion, suspension or solution onto a core.
18. The process of claim 17, wherein the layer is disposed as a coating dispersion.
19. The process of claim 18, wherein the coating dispersion is made in aqueous solvent.
20. The process of claim 17, wherein the dispersion is sprayed on the cores.
21. A method of treating a disorder selected from the group consisting of hypertension, congestive heart failure left ventricular dysfunction and diabetic nephropathy, the method comprising administration of a therapeutically effective amount of the pharmaceutical composition of claim 1 to a patient suffering from such disorder.

collapse claims

Abstract

The invention provides stable pharmaceutical compositions comprising ACE inhibitor(s) and other pharmaceutically active substances which are susceptible to degradation, as well as processes for the preparation thereof, and methods of treatment involving administration of such compositions.

States

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STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACE INHIBITOR(S)

Field of the invention The present invention relates to stable pharmaceutical compositions comprising ace inhibitor(s), which are susceptible to degradation, and processes for the preparation thereof.

Background Certain Angiotensin Converting Enzyme (ACE) inhibitors, which are useful as antihypertensives, are susceptible to certain types of degradation. ACE inhibitors such as ramipril, quinapril, enalapril, spirapril, lisinopril, benazepril and structurally related drugs can undergo cyclization via internal nucleophilic attack to form substituted diketopiperazines. These drugs can also degrade via hydrolysis (of the side-chain ester group) and oxidation, to form products having unwanted coloration. It has been found that a significant cause of such degradations can be the mechanical stress associated with the manufacturing process of pharmaceutical composition such as compression. The stability of pharmaceutical compositions containing ACE inhibitors can also be negatively influenced by the choice of tabletting auxiliaries. In view of the usefulness of ACE inhibitors in treating hypertension, a number of research endeavors have been directed towards overcoming the inherent instability problem associated with ACE inhibitor- containing compositions.

For example United States Patent Nos. 4,743,450, 4,830,853, 4,793,998, international patent application WO 99/62560, European patent EP 468929 disclose stabilization with various agents. United States Patent Nos. 5,151,433 and 5,442,008 disclose polymeric film-formers as protection against stress, as well as the use of buffers. Thus, either addition of a stabilizer or a polymeric coat on the active ingredient is believed necessary to stabilize the pharmaceutical composition of ACE inhibitors, which are susceptible to degradation. However, the addition of such stabilizers can produce unwanted pharmacological effects. Coating the active ingredient is quite cumbersome and low yielding moreover it requires specialized equipment. Summary The applicants of the present invention have discovered a process making the use of the above unnecessary. Active ingredient, for example, an ACE inhibitor, which is susceptible to degradation, is applied as a coat to the core, preferably to a compressed core, thereby avoiding degradation (such as cyclization to diketopiperazine) induced by mechanical stress, which builds up during compression. Such an arrangement also avoids the direct contact of the tabletting auxiliaries with the ACE inhibitor, thereby avoiding degradation by any incompatible tablet auxiliaries.

The present invention therefore allows greater flexibility in the choice of tabletting auxiliaries. Moreover, as stabilizers are not required, untoward pharmacological effects, which could occur with the addition of such additives, are nullified. The process can be easily scaled up using the conventional tabletting and coating equipment.

Therefore, the present invention can provide a stable pharmaceutical composition for oral administration of an ACE inhibitor comprising a core coated with a layer of ACE inhibitor(s) and process for preparation thereof.

Detailed Description The core of the present invention is preferably a compressed core, which could be inert or may contain a drug other than the ACE inhibitor susceptible to degradation, such as hydrochlorothiazide, piretanide; and dihydropyridines such as felodipine, nitrendipine, nifedipine, lacidipine or other similar drugs. Alternatively the core may be a sugar or starch particle such as non-pareil sugar seeds, or pregelatinized starch. The core can be of any convenient shape, such as an spheroidal shape. The cores can range from about 25 mg to about 1 gram. The compressed core may comprise diluent and other formulating agents such as binder, disintegrant, lubricant and glidant. The diluent may be, for example, any pharmaceutically acceptable, non-toxic diluent. Particular examples include lactose, dextrose, sucrose, maltose, microcrystalline cellulose, starch, calcium hydrogen phosphate, mannitol and the like. Binders may be, for example, starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose, hydroxypropylcellulose or the like. Disintegrant may be, for example, croscarmellose sodium, crospovidone, sodium starch glycolate, bentonite, sodium alginate, hydroxypropylmethylcellulose or the like. Lubricants may be, for example, talc, magnesium stearate, calcium stearate, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate, sodium benzoate or the like. Glidants may be, for example, colloidal silicon dioxide (aerosil), talc or the like.

The ACE inhibitor layer comprises ACE inhibitor(s), which are susceptible to degradation, including ramipril, spirapril, lisinopril, enalapril, quinapril, benazepril and other structurally related drugs. The process is applicable to other pharmaceutically active agents that are susceptible to mechanical stress-induced or mechanical stress-related degradation. The ACE inhibitor can be micronized, and suspended/dispersed in a solvent to which film forming polymer(s) is added. The film-forming polymer may be, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinylpyrrolidone, gelatin, LustreClear™ (combination of microcrystalline cellulose and carrageenan), combinations of polyvinylalcohol and polyvinylacetate, and the like. The amount of the film forming polymer(s) can be relatively low, to limit the tablet/pellet/beadlet size and the manufacturing effort, but should be sufficient to effectively coat the drug on to the core. The drug to polymer ratio may range from about 1 : 10 to about 10:1. For example, drug to polymer ratio can be from about 1:2 to about 2:1, or from about 1:1.2 to about 1.2:1, or, for example, about 1:1.

The polymer that is used for binding properties can also protect ACE inhibitors from atmospheric or chemical oxidation and degradation by agents such as atmospheric humidity through, for example, hydrolysis.

The ACE inhibitor layer may optionally contain plasticizers, and is desirably without plasticizers. Stability can be undesirably lessened through the use of plasticizers. Plasticizers which may be excluded from the compositions include polyethyleneglycol, propylene glycol, triethyl citrate, triacetin, dibutylphthalate, diethylphthalate, castor oil, tributyl citrate, glycerol, sorbitol, polysorbates, sorbitan esters and the like. The ACE inhibitor layer may also contain pigments, colorants, antifoaming agents, waxes, monoglycerides, emulsifiers, surfactants or other additives. The layer containing ACE inhibitor or other pharmaceutically active substance can contain such material from about 2% to about 90% by weight of the ACE inhibitor layer, and can also contain film-forming polymer from about 10% to about 98% by weight of the ACE inhibitor layer.

Drug coating solution can be prepared in water, non-aqueous solvents or mixtures thereof. However desirably in water as stability can be lessened through the use of non- aqueous solvents. Solvents that may be excluded are isopropyl alcohol, acetone and methylene chloride. A seal coat may optionally separate the core and the ace inhibitor layer to completely seal the tabletting auxiliaries to come in contact with the ACE inhibitor. Similarly, an outer coat may optionally be given on the ACE inhibitor layer to improve the aesthetic appeal of the tablet and to protect it from the atmospheric humidity. The seal coat and outer coat may have the same composition as the ACE inhibitor layer except the drug, or it may have a different composition. For example, the seal coat may contain other polymers, such as Povidone. The seal coat can be prepared from aqueous dispersion of from about 2% to about 30% by weight of film-forming polymer.

The process of the present invention may be carried out in the following manner. The compressed core can be prepared by conventional techniques such as direct compression, wet granulation and dry granulation.

The ACE inhibitor coating dispersion, suspension or solution can be prepared by

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✓ **WO 2001/052825 A2** (patent application)

✓ **COMBINATIONS COMPRISING DIPEPTIDYLPEPTIDASE - IV INHIBITOR**

Front Page Full Text PDF Version Patent Family & Status

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Title

COMBINATIONS COMPRISING DIPEPTIDYLPEPTIDASE - IV INHIBITOR

Claims

1. Combination which comprises a dipeptidylpeptidase - IV inhibitor (DPP-IV) inhibitor in free or pharmaceutically acceptable salt form, and at least one further antidiabetic compound or the pharmaceutically acceptable salt of such a compound and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.
2. Combination according to claim 1 wherein the further antidiabetic compound is selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α -adrenergic antagonists, or the pharmaceutically acceptable salt of such a compound.
3. Combination according to claim 1 or 2 which is a combined preparation or a pharmaceutical composition.
4. Combination according to claim 3 which is a combined preparation for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by DPP-IV.
5. Combination according to any one of claims 1 to 4 wherein the DPP-IV inhibitor is a N-(N'-substituted glycol)-2-cyanopyrrolidine of formula I
wherein R is: a) R1RiN(CH2)m- wherein R-i is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with lower alkyl, lower alkoxy or halogen; Ri is hydrogen or (C1-8)alkyl; and m is 2 or 3; b) (C3-12)cycloalkyl optionally monosubstituted in the 1-position with (d-3)hydroxyalkyl; c) R2(CH2)n- wherein either R2 is phenyl optionally mono- or independently di- or independently trisubstituted with lower alkyl, lower alkoxy, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is (C1-8)alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (d-8)alkyl; a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with lower alkyl, lower alkoxy or halogen; cyclohexene; or adamantyl; and n is 1 to 3; or R2 is phenoxy optionally mono- or independently disubstituted with lower alkyl, lower alkoxy or halogen; and n is 2 or 3; d) (3)2CH(CH2)2- wherein each R3 independently is phenyl optionally mono- or independently disubstituted with lower alkyl, lower alkoxy or halogen; e) R4(CH2)p- wherein R4 is 2-oxopyrrolidinyl or (C2-4)alkoxy and p is 2 to 4; f) isopropyl optionally monosubstituted in 1-position with (d-3)hydroxyalkyl; g) R5 wherein R5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (d-8)alkyl; adamantyl; or (C1-8)alkyl optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with lower alkyl, lower alkoxy or halogen; h) a substituted adamantyl; in free form or in acid addition salt form.
6. Combination according to claim 5 wherein the DPP-IV inhibitor a compound of formula I which is selected from
(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine and (S)-1-[2-[5-cyanopyridin-2-yl)amino]ethyl-aminoacetyl]-2-cyano-pyrrolidine, in free form or in acid addition salt form.
7. Combination according to any one of claims 2 to 4 wherein the insulin sensitivity enhancer is selected from the group consisting of antidiabetic thiazolidinediones and antidiabetic vanadium containing compounds.
8. Combination according to claim 2 wherein the insulin secretion enhancer is selected from the group consisting of sulphonyl urea derivatives, antidiabetic phenylacetic acid derivatives and antidiabetic D-phenylalanine derivatives.
9. Combination according to claim 8 wherein the antidiabetic D-phenylalanine derivative is a compound of formula X

Ry:

wherein Ph has the meaning of phenyl,

Ry-i is selected from hydrogen, d to C5 alkyl, C6 to C12aryl, C6 to C12 arylalkyl, -CH2CO2Ry3, -CH(CH3)-OCO-Ry3, and -CH2-OCO-C(CH3)3; Ry2 is selected from groups comprising C6 to d2aryl, a hetero six-membered ring, a hetero five-membered ring, cycloalkyl, or cycloalkenyl, any of which groups may have one or more substituents; and Ry3 is selected from hydrogen and d to C5 alkyl, with the proviso that when Ry1 and Ry3 are both hydrogen then Ry2 is other than substituted or unsubstituted phenyl or naphthyl; the pharmaceutically acceptable salts thereof and precursors which can be converted thereto in the human or animal body.

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0. Combination according to claim 1 wherein the DPP-IV inhibitor is selected from (S)-1-[(3-hydroxy-1-(adamantyl)amino)acetyl]-2-cyano-pyrrolidine and (S)-1-{2-[5-cyanopyridin-2-yl]amino}ethyl-aminoacetyl-2-cyano-pyrrolidine, and the further antidiabetic compound is selected from the group consisting of nateglinide, repaglinide, metformin, rosiglitazone, pioglitazone, troglitazone, glisoxepid, glyburide, glibenclamide, acetohexamide, chlorpropamide, glibomuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, glimepiride and glizalide, or the pharmaceutically acceptable salt of such a compound.
1. Method of treating a condition mediated by DPP-IV comprising administering to a warmblooded animal in need thereof jointly therapeutically effective amounts of a DPP-IV inhibitor in free or pharmaceutically acceptable salt form and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α -adrenergic antagonists, or the pharmaceutically acceptable salts of such compounds.
2. Method of improving the bodily appearance of a mammal which comprises orally administering to said mammal a dipeptidylpeptidase - IV inhibitor in free or pharmaceutically acceptable salt form, and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α -adrenergic antagonists, or the pharmaceutically acceptable salts of such compounds, in a dosage effective to influence the glucose metabolism, and to effect a cosmetically beneficial loss of body weight.
3. A pharmaceutical composition comprising a quantity which is jointly therapeutically effective against a condition mediated by DPP-IV of a combination according to any one of claims 1 to 10; and at least one pharmaceutically acceptable carrier.
4. Use of a combination according to any one of claims 1 to 10 for the preparation of a medicament for the prevention, delay of progression or treatment of a condition mediated by DPP-IV.
5. Use of a combination according to any one of claims 1 to 10 for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.
6. A commercial package comprising as active agents a combination according to any one of claims 1 to 10 together with instructions for simultaneous, separate or sequential use thereof in the prevention, delay of progression or treatment of a condition mediated by DPP-IV or in a method of improving the bodily appearance of a mammal.

collapse claims

Abstract

The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α -adrenergic antagonists, for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase - IV (DPP-IV). In particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

States

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GR GW HR HU IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU
LV MA MC MD ME MG MK ML MN MR MW MX MY NZ NO NZ PL PT RO RU
SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT TZ UA UG US VZ
VN YU ZA ZW ZY

Combinations Comprising a Dipeptidylpeptidase - IV Inhibitor

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises a dipeptidylpeptidase - IV (DPP-IV) inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α_2 -adrenergic antagonists, for simultaneous, separate or sequential use, especially in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase - IV (DPP-IV), in particular diabetes, more particular type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; the use of such combination for the preparation of a pharmaceutical preparation for the prevention, delay of progression or treatment of such conditions; the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; a method of prevention, delay of progression or treatment of conditions mediated by DPP-IV; a method of improving the bodily appearance of a warmblooded animal.

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.

Non-insulin dependent diabetes mellitus (type 2 diabetes mellitus) is characterized by both increased peripheral insulin resistance and abnormal insulin secretion. At least three abnormalities of insulin secretion are recognized: in the first phase, insulin secretion is lost and in the second phase insulin is both delayed and inadequate in the face of elevated circulating glucose levels. Several metabolic, hormonal, and pharmacological entities are known to stimulate insulin secretion including glucose, amino-acids and gastrointestinal peptides. The Diabetes Control and Complications Trial (DCCT) has established that lowering of blood glucose is associated with decreases in the onset and progression of diabetic microvascular complications (Diabetes Control and Complications Trial Research Group; N. Engl. J. Med. 1993, 329, 977-986). IGT is an impairment of glucose homeostasis closely related to type 2 diabetes mellitus. Both conditions convey a great risk of macrovascular disease. Therefore, one therapeutic focus is on optimizing and potentially normalizing glycemic control in subjects with type 2 diabetes mellitus, conditions of impaired fasting plasma glucose, or IGT. Presently available agents need to be improved in order to better meet this therapeutic challenge.

The present invention relates to a combination which comprises a DPP-IV inhibitor in free or pharmaceutically acceptable salt form, and at least one further antidiabetic compound or the pharmaceutically acceptable salt of such a compound and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

Preferably, the antidiabetic compound is selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α_2 -adrenergic antagonists, or the pharmaceutically acceptable salts of such a compound and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use, particularly in the prevention, delay of progression or treatment of conditions mediated by DPP-IV, in particular conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis, and preferably diabetes, especially type 2 diabetes mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition. The DPP-IV inhibitor can be peptidic or non-peptidic. Preferably, the DPP-IV inhibitor is non-peptidic.

Unless stated otherwise

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The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases. For example, the compounds to be combined can be present as a sodium salt, as a maleate or as a dihydrochloride. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

An antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α -glucosidase inhibitors, inhibitors of gastric emptying, insulin, and OC2- adrenergic antagonists, or a pharmaceutically acceptable salt of such a compound, will be referred to hereinafter as COMBINATION PARTNER OF THE INVENTION.

A combined preparation which comprises a DPP-IV inhibitor in free or pharmaceutically acceptable salt form and at least one further COMBINATION PARTNER OF THE INVENTION and optionally at least one, i.e., one or more, e.g. two, pharmaceutically acceptable carrier for simultaneous, separate or sequential use is especially a "kit of parts" in the sense that the components, a DPP-IV inhibitor in free or pharmaceutically acceptable salt form and at least one further COMBINATION PARTNER OF THE INVENTION, can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. at different time points or simultaneously. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the components. Preferably, there is at least one beneficial effect, e.g. a mutual enhancing of the effect of a DPP-IV inhibitor in free or pharmaceutically acceptable salt form, and at least one further COMBINATION PARTNER OF THE INVENTION, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or each of the components, and especially a synergism, e.g. a more than additive effect, between a DPP-IV inhibitor in free or pharmaceutically acceptable salt form, and at least one further COMBINATION PARTNER OF THE INVENTION.

The nature of conditions mediated by DPP-IV, especially diabetes, conditions of impaired fasting plasma glucose, and IGT, is multifactorial. Under certain circumstances, drugs with different mechanisms of action may be combined. However, just considering any combination of drugs having different mode of action but acting in the similar field does not necessarily lead to combinations with advantageous effects.

All the more surprising is the experimental finding that the combined administration of a DPP-IV inhibitor and at least one further COMBINATION PARTNER OF THE INVENTION results not only in a beneficial, especially a synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with diabetes, e.g. less gain of weight.

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

It can be shown by established test models and especially those test models described herein that the combination of a DPP-IV inhibitor, especially (S)-1-((2-[5-cyanopyridin-2-yl]amino)ethyl-aminoacetyl)-2-cyano-pyrrolidine (DPP728) or (S)-1-((3-hydroxy-1-adamantyl)amino)acetyl-2-cyano-pyrrolidine (LAF237), and at least one further COMBINATION PARTNER OF THE INVENTION results in a more effective prevention or preferably treatment of conditions mediated by DPP-IV, in particular diabetes, especially type 2 diabetes mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects. The pharmacological activity may, for example, be demonstrated following essentially an in-vivo test procedure in mice or in a clinical study as described hereinafter:

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The results of the studies show that the combination according to the present invention can be used for the prevention and preferably the treatment of conditions mediated by DPP-IV, in particular type 2 diabetes mellitus. The combination of the present invention can also be used for the prevention and preferably the treatment of other condition mediated by DPP- IV.

Furthermore, in a number of combinations as disclosed herein the side-effects observed with one of the components surprisingly do not accumulate on application of the combination.

Preferably, the jointly therapeutically effective amounts of a DPP-IV inhibitor in free or pharmaceutically acceptable salt form and at least one further pharmaceutically active compound are administered simultaneously or sequentially in any order, separately or in a fixed combination.

The condition mediated by DPP-IV is preferably selected from the group consisting of diabetes, impaired fasting plasma glucose, impaired glucose tolerance, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis. Very preferably, the condition mediated by DPP-IV is type 2 diabetes mellitus.

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against conditions mediated by DPP-IV, in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT, of a DPP-IV inhibitor (i) or a pharmaceutically acceptable salt thereof and (ii) at least one further COMBINATION PARTNER OF THE INVENTION and at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 100 %, e.g., 80% or 90 %, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

In this composition, components (i) and (ii) can be administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. In one preferred embodiment of the invention, the unit dose form is a fixed combination. In a fixed combination the components (i) and (ii) are administered in the form of a single galenic formulation, e.g. a single tablet or a single infusion. A further aspect of the present invention is the use of a pharmaceutical composition comprising a DPP-IV inhibitor and at least one further COMBINATION PARTNER OF THE INVENTION, in each case in free form or in form of a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical preparation for the prevention or treatment of conditions mediated by DPP-IV, in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

A therapeutically effective amount of each of the components of the combination of the present invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of treatment of the invention may comprise (i) administration of a DPP-IV inhibitor in free or pharmaceutically acceptable salt form and (ii) administration of at least one further COMBINATION PARTNER OF THE INVENTION simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the ratios described herein.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

Furthermore, the term administering also encompasses the use of prodrugs of any of the anti-diabetic drugs that convert in vivo to the selective anti-diabetic drug. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

If the combination comprises nateglinide, a composition, in particular a pharmaceutical composition, comprising solely nateglinide can be produced by a process that comprises granulating in the presence of water to form granules, drying the granules, and optionally screening the granules, for example, through a wire mesh screen. All of the ingredients of the composition may be added prior to or during the granulation. Alternatively, all or a portion of one or more of the ingredients may be added after the granulation step is complete. For example, all or a portion of anti-adherent (e.g., silica), all or a portion of lubricant (e.g., magnesium stearate) and/or all or a portion of disintegrant (e.g., croscarmellose or any salt thereof) may be added after the granulation. In one aspect of the invention, all ingredients except the magnesium stearate and the colloidal silica are loaded into the granulator, then they are added later. The process of producing this composition, in particular pharmaceutical composition, may be performed without the need for a pulverization step. As used herein, the terms "pulverization" and "pulverize" refer to any process that involves the grinding or smashing cutting of particles to reduce the particles' size. The composition, in particular pharmaceutical composition, is capable of being produced without pulverizing the granules between the granulation step and the drying and/or compression step used to form the granules into a tablet. In one preferred embodiment of the invention, nateglinide is used in the B-type or H-type crystal modification.

The invention relates in particular to a commercial package comprising jointly therapeutically effective amounts of a DPP-IV inhibitor, in free or pharmaceutically acceptable salt form, and at least one further COMBINATION PARTNER OF THE INVENTION together with instructions for use thereof in the treatment of conditions mediated by DPP-IV, in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired fasting plasma glucose, and conditions of IGT.

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

2020
Bogotá, D.C.,

Abogado:
ALVARO CORREA ORDOÑEZ

ASUNTO:	Radicación No.	06 120 205
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	21

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 comunica:

Documentos estudiados:

Descripción: Folios 30 a 56 como se radicó inicialmente.

Reivindicaciones: Folios 99 a 102 como se modificó en fase nacional.
Folios 121 a 123 como se modificó 10-06-2010

Prioridad: US 60/575.319 (2004-05-28)

Objeto de la Invención

Título de la invención: "Formulación de tableta revestida y método"

Problema Técnico Planteado: "Necesidad de formulaciones farmacéuticas estables que contienen medicamentos los cuales son sometidos a ciclización intra-molecular."

Solución: "Proporcionar una tableta revestida la cual puede incluir un medicamento el cual es sometido a ciclización intra-molecular, estable a condiciones e almacenamiento normal como 30°C y 60% de humedad relativa"

IPC: A61K 9/24 AC; A61K 31/403 AC; A61P 3/10

Se anota que se acepta el nuevo capítulo para su estudio.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad, concisión y Soporte en la descripción: La reivindicación 9 no menciona características técnicas relacionadas con la reivindicación 1, se observa que la reivindicación 9 presenta rangos de porcentaje de un grupo de componentes en general, de manera que la reivindicación 9 contiene materia mucho más amplia que

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la reclamada por la reivindicación 1.

Se requiere al solicitante para que ajuste el grupo de la composición presentada en la reivindicación 9, definiendo los términos: "Polímero de recubrimiento y plastificante y deslizante opcionalmente", "inhibidor DPP4", "Polímero de recubrimiento y plastificante y color opcionalmente", de acuerdo a lo reclamado por la reivindicación 1.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de prioridad 2004-05-28 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO03059330	Stable pharmaceutical compositions comprising ACE inhibitors(s)	24.07.2003
D2	WO01052825	Combinations comprising dipeptidylpeptidase - IV inhibitor	26.07.2001

Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La nueva reivindicación 1 dice: "Una tableta recubierta que comprende:

- un núcleo de tableta y:
- a) una capa sello interno de recubrimiento que comprende una formulación de recubrimiento de polímero que comprende un polímero a base de alcohol polivinílico que cubre el núcleo de la tableta;
- b) una segunda capa de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico y un medicamento que cubre la capa de sello interno de recubrimiento del núcleo de la tableta; y
- c) opcionalmente una capa protectora exterior de recubrimiento que comprende una formulación de polímero de recubrimiento que comprende un polímero a base de alcohol polivinílico que cubre la segunda capa del núcleo de la tableta, en donde el medicamento en dicha segunda capa es saxagliptina y una sal farmacéuticamente aceptable del mismo", folio 121.

D2 describe formulaciones farmacéuticas que esencialmente comprenden un inhibidor de dipeptidilpeptidasa IV (DPP-IV) (portada; pár.4, f. 134), que pueden ser preparadas como se conoce en el estado del arte, y que pueden tener diferentes formas galénicas para uso oral con una cantidad efectiva del activo, con vehículos adecuados, que pueden contener del 10 al 100% de activo, en donde las tabletas pueden ser recubiertas por azúcar (f.135).

La solicitud se diferencia de D2 en los polímeros formadores de película y las diferentes capas que recubren el núcleo.

El Efecto Técnico que logra la diferencia es reducir la degradación de la saxagliptina en una tableta para administración del mismo.

El Problema Técnico Objetivo de esta solicitud es la necesidad de formulaciones farmacéuticas que logren evitar la degradación de la saxagliptina.

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D1 revela núcleos comprimidos de una composición farmacéutica estable que contiene un activo (inhibidor ACE), con un núcleo recubierto con una capa de activo y su método de preparación (p.2), en donde: la cubierta contiene activo del 2 al 90% p/p (p.3); la dispersión, solución o dispersión inhibidor es preparada por adición de activos en un solvente – o cualquier otro método de mezcla - y polímeros formadores de película (p.4). En el ej.1, revela la secuencia de pasos que se realizaron para obtener las tabletas de la invención presenta ejemplos específicos de las tabletas con núcleo, una capa sellante, una capa de medicamento y una cubierta externa (p. 7). D1 revela que el polímero formador de película puede ser combinaciones de polivinilalcohol y polivinilacetato.

El experto en la materia habría sido motivado por D1 a administrar la saxagliptina – revelada en D2 - por medio de núcleos inertes recubiertos para superar los problemas de degradación del activo, por medio de una composición que consta de un núcleo inerte con una capa de revestimiento de sello interno, más una segunda capa de revestimiento con la saxagliptina en el revestimiento de sello interno y una capa de revestimiento protector exterior.

Por otro lado, D1 habría sugerido al experto el empleo de polímeros como el alcohol polivinílico en la formulación para la formación de sus capas.

Dado que el experto en la materia habría llegado a la materia acá revelada por medio de las enseñanzas de D1 y D2, se concluye que la reivindicación 1 y su dependientes reclaman materia que carece de nivel inventivo dado que el estado del arte ya anticipaba enseñanzas suficientes para que llegar a la tableta que se reclama y los métodos que se presentan.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03059330	1-13	Nivel inventivo
D2	WO01052825	1-13	Nivel inventivo

Respuesta a los argumentos del solicitante

Frente a las objeciones de claridad el solicitante dice que se cancelaron las reivindicaciones 2, 6, 7 y 9; y que el nuevo capítulo se ha modificado de tal forma que incorpora la limitación “polímero basado en alcohol polivinílico” (en parte) como la capa de revestimiento de sello interno, la Segunda capa de revestimiento y la capa exterior de revestimiento protector. El término PVA se reemplazo por alcohol polivinílico.

Se reitera que se ha aceptado el nuevo capítulo para su estudio.

Con relación a las objeciones relativas a la novedad de la presente solicitud el solicitante argumenta: “(...) D1 se puede concluir que dicho documento no contiene todas las características específicas reclamadas por el nuevo pliego reivindicatorio de la presente invención” y dice: “El nuevo pliego reivindicatorio se relaciona con una formulación de tableta revestida que comprende Saxagliptina la cual es un inhibidor de la DPP-IV. Contrario a esto, las enseñanzas de D1 se limitan a

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formulaciones de tableta revestidas que comprenden un inhibidor de ACE (...) D1 enseña que los inhibidores de ACE se degradan vía: ciclización intramolecular hasta formar dicetopiperazinas. (...) para reducir la degradación, D1 enseña núcleos de tableta que son revestidos con tres capas donde una de las capas contiene el ingrediente activo. (...)

Se considera que a la luz del nuevo capítulo reivindicatorio el documento D1 no afecta la novedad de la presente solicitud.

Adelantándose a las objeciones de nivel inventivo, el solicitante dice: "(...) la presente invención inesperadamente reducen o inhiben la degradación de la Saxagliptina. Las presentes formulaciones se relacionan con: (a) Una cubierta de sello interior que comprende: (i) polímero a base de alcohol polivinílico; (b) Un segundo recubrimiento que comprende (i) Saxagliptina; y (ii) polímero a base de alcohol polivinílico; (c) Un recubrimiento exterior que comprende (i) polímero a base de alcohol polivinílico. Con relación a las capas/recubrimientos, todas las tres capas/recubrimientos reivindicados contienen un polímero a base de alcohol polivinílico y no contienen hidroxipropilmetilcelulosa ni tampoco hidroxipropilcelulosa tal como lo enseñado por D1."

Frente a los comentarios del solicitante, este Despacho observa que D1 presenta una solución para reducir la degradación, D1 enseña núcleos de tableta que son revestidos con tres capas donde una de las capas contiene el ingrediente activo. De manera que D1 sugiere una posible solución para el problema planteado por el solicitante. Se anota que el nuevo capítulo reivindicatorio reclama un grupo más reducido de formulaciones que el inicial, por lo cual hay características estructurales que no son reveladas por D1.

Dice además: "... las formulaciones reivindicadas reducen la degradación de la Saxagliptina más efectivamente que la reducción de la degradación del Ramipril que hacen las formulaciones de D1 bajo las mismas condiciones de tiempo, humedad, temperatura, (...) y afirma que la única manera de determinar la apropiada formulación para reducir degradación de cualquier medicamento es mediante experimentación."

En el caso particular de la presente solicitud, D1 presenta una aproximación clara para la solución del problema que surge en los sistemas de entrega de fármacos cuando estos son altamente inestables, incluso en especialidades farmacéuticas orales, como es el caso del problema acá planteado.

Se considera que parte de la labor de rutina del formulador es el hallar la forma de evitar la degradación de los principios activos bajo condiciones de tiempo, humedad y temperatura determinados, por lo cual la persona versada había estado motivada por las sugerencias de D1, a intentar resolver el problema de inestabilidad por medio de: 1) un núcleo placebo, cubierto de una primera capa sellante de polímero, 2) una segunda capa de polímero mezclado con un principio activo y 3) una tercera capa sellante de polímero.

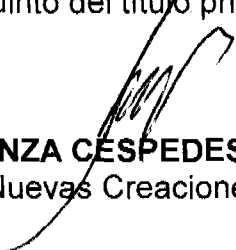
De manera que se ha mostrado que la forma de preservar un principio activo altamente inestable en formas farmacéuticas orales ya había sido divulgado en el estado del arte. En consecuencia, los resultados presentados por la presente solicitud no son inesperados en tanto ya el estado de la técnica sugería que una tableta con esas características técnicas esenciales lograría la disminución de la degradación de activo.

Y muestra diferencias entre las formulaciones de D1 y la presente invención: "(1) La Saxagliptina es un inhibidor de DPP-IV, y no un inhibidor de ACE. (2) La Saxagliptina es estructuralmente diferente a los inhibidores de ACE de D1; (3) La Saxagliptina se degrada a una amidina cíclica, y no a una dicetopiperaina como se revela en D1. (4) Las formulaciones de tableta de las actuales reivindicaciones abarcan capas/recubrimientos conformados por polímeros a base de alcohol polivinílico, y no a base de hidroxipropilmetilcelulosa y/o hidroxipropilcelulosa tal como se revela en D1. (5) Las formulaciones de tableta de la presente invención reduce la degradación de la Saxagliptina mas efectivamente que las formulaciones de tableta de D1 que reducen la degradación de inhibidores de ACE tal como Ramipril."

Con base en todo lo anterior se concluye que D1 no afecta la novedad de la presente solicitud, pues la materia reclamada por el nuevo capítulo reivindicatorio no muestra exactamente la misma materia, aunque si sugiere al técnico la forma de evitar la degradación de formulaciones que contengan otros activos, sin que esto indique que los estudios de estabilidad y de degradación sean extensivos entre formulaciones que contengan múltiples activos.

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 60 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
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

22 OCT 2010

CONCEPTO TECNICO NUMERO: 2809	EXAMINADOR TÉCNICO Código:202092
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