



No. 10-162245-00003-0000

Fecha: 2011-12-16 14:30:09 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 32

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

**SOLICITUD
PUBLICADA**

Número del expediente: 10-162.245
Solicitante: LABORATORIOS SILANES, S.A. DE C.V
Apoderado: DILIA MARIA RODRÍGUEZ D'ALEMAN
Título de la nueva creación o denominación del signo: “UNA NUEVA SAL DE GLICINATO DE METFORMINA PARA EL CONTROL DE GLUCOSA EN SANGRE”
Gaceta: 633

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 0815 E-mail:	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número 890.106.527-5	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 104 N°119-95 OF 104 Teléfono: 2131213 Fax: 6121979 E-mail: negocios@optimum-co.com	C.C. ☒ NT ☐ C.E. ☐ Otro ☐ Cual _____ Número 51.975.664 TP 83823	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo “Fundamento de Hechos”.

⑤ Comprobante de pago No.

11-122224

Fecha

16/12/2011

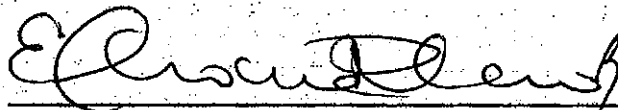
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51'975.664

TP. 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 11 - 122224

Bogotá D.C., Diciembre 16 de 2011 - 11:16:46

RECIBIDO DE : PROCAPS S.A. NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	144670142	13/12/2011	1.520.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable

Recibo de Caja Aplicado al Expediente No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-162245-00003-0000

Fecha: 2011-12-16 14:30:09 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 32

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Diciembre 16 de 2011 - 11:16:47

Señor Director,
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 10 162245
Asunto : Oposición a la solicitud de patente de Invención titulada
"UNA NUEVA SAL DE GLICINATO DE METFORMINA
PARA EL CONTROL DE GLUCOSA EN SANGRE"
Solicitante : LABORATORIOS SILANES, S.A. DE C.V.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 633 del 20 de octubre de 2011

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "UNA NUEVA SAL DE GLICINATO DE METFORMINA PARA EL CONTROL DE GLUCOSA EN SANGRE", cuyo titular es LABORATORIOS SILANES, S.A. DE C.V., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la

comercialización de algunos productos de mi representada, que contienen, en particular **metformina**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 24 de diciembre de 2010, reivindicando prioridad bajo la solicitud WO2008IB02665 del 2008-06-26; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 633 del 20 de octubre de 2011, cuya publicación internacional corresponde a la WO2009144527 del 2009-12-03.

2.2. La solicitud colombiana 10 162245 objeto de la presente oposición, se refiere a la síntesis de una nueva sal de Glicinato 1,1-dimetilbiguanid, llamada Glicinato de Metformina diseñada para el control de la glucosa en sangre. Esta sal exhibe ventajas sobre otras sales de metformina. Estas ventajas se refieren, en primer lugar, al hecho de que el contraión exhibe efectos hipoglucemientes por sí mismos, el efecto hipoglucemiente es más pronunciado. Además esta sal exhibe una mejor absorción, alcanzando una concentración plasmática más alta que aquella producida con clorhidrato de metformina. La síntesis se llevó a cabo a partir de clorhidrato de metformina liberando el contraión hidrocloreuro, usando una columna de intercambio iónico, la metformina liberada se disolvió en medio acuoso y subsecuentemente se adicionó glicina a temperatura ambiente y agitación constante, el producto resultante se calienta produciendo una solución concentrada del producto, se adiciona un solvente orgánico para crear insolubilidad y favorecer la cristalización en un medio saturado, el exceso de glicina precipita y se obtiene la sal glicinato de metformina después de filtrar y concentrar dicha sal. La sal Glicinato de Metformina presenta un efecto farmacológico más pronunciado en la reducción de los niveles de glucosa en sangre.

2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo

14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20.- "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US20080031964 publicada el 2 de julio de 2008.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una combinación farmacéutica para el tratamiento de la diabetes mellitus, donde dicha combinación comprende una cantidad terapéuticamente efectiva de metformina y una cantidad terapéuticamente eficaz de una betaina farmacéuticamente aceptable. Particularmente en los ejemplos se revela un sachet o bolsita que comprende una dosis en polvo de 500 mg de metformina y 2000 mg de glicina betaina. Como tal D1, revela una forma de dosificación en el que la metformina y la glicina se mezclan con un agente de granulación, extrusión y se convierten en esferas de aproximadamente 1 mm. A partir de esta divulgación en D1, se supone que en condiciones, la metformina y la glicina puede formar una sal de glicinato de metformina, por lo que lo revelado en la presente solicitud no es nuevo. D1 igualmente revela en los párrafos [0127] y [0128] que los compuestos combinados de la invención (glicina y metformina) aumentó el cuerpo de los pacientes de sensibilidad a la insulina y bajo los niveles de glucosa en ayunas. Los resultados indican la administración de una combinación de i) un compuesto de Fórmula I (siendo glicina) con ii) la metformina aumentado la eficacia de cada fármaco por

separado. Así las cosas, la materia revelada en la presente solicitud es conocida en el arte como lo demuestra esta anterioridad D1, de manera que carece de novedad.

2.6 Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente carece de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 162245 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los dos de los tres requisitos necesarios para su protección.

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

2.8.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 26 de junio de 2008 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, síntesis de una nueva sal de Glicinato 1,1-dimetilbiguanid, llamada Glicinato de Metformina diseñada para el control de la glucosa en sangre, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada ***“UNA NUEVA SAL DE GLICINATO DE METFORMINA PARA EL CONTROL DE GLUCOSA EN SANGRE”***, cuyo titular es LABORATORIOS SILANES, S.A. DE C.V, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 633 del 20 de octubre de 2011.

3. PRUEBAS

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

- D1: US20080031964 publicada el 2 de julio de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena
- 4.3. En las demás normas concordantes.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

5. ANEXOS

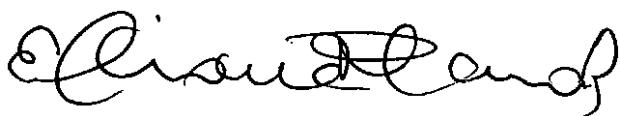
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US20080031964 publicada el 2 de julio de 2008.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 10 162.245, titulada **"UNA NUEVA SAL DE GLICINATO DE METFORMINA PARA EL CONTROL DE GLUCOSA EN SANGRE"**, cuyo titular es **LABORATORIOS SILANES, S.A. DE C.V.**, publicada en la gaceta No. 633 del 20 de octubre de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativamente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 9 días del mes de Diciembre de 2011.

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO

09 DIC. 2011

PROCAPS S.A.

NOTARIA
3^o
NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Ante el Notario Tercero de Barranquilla se presento:
Walter Parona Lalexawa
identificado con: C: 16251923 Palmira
Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo refrenda.
Barranquilla: 12 DIC. 2011





***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979, bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

***** C O N T I N U A *****

OFXPRE S.A.S. NIT. 900.106.527-1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla.	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

Correo electrónico:

mlozada@procaps.com.co

Pagina Web:

Telefono:

3719272

C E R T I F I C A

DURACION: Que la sociedad no se halla disuelta y su término de
duración se fijó hasta el
18 de Agosto de 2073.

C E R T I F I C A

DE

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion,

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costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,298,000,000	*****1,298,000	*****1,000
Pagado		
\$*****1,298,000,000	*****1,298,000	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representa-

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cion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos

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o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

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cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****

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3. Minski Sharon

PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente. Minski Gontovnik Ruben	CC.******7,463,982

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente. Tanaka Tatekawa Walter	CC.******16,251,923

C E R T I F I C A

Que según Acta No. 658 del 07 de Dic/bre de 2011 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Dic/bre de 2011 bajo el No. 176,066 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General. Otero Arteaga Javier	CC.******90,263,999
Vicepresidente Minski Gontovnik Jose	CC.******8,671,834
Suplente del Presidente Minski Gontovnik Meyer	CC.******7,461,324
Suplente del vicepresidente Carvajalino Pagano Marcela	CC.******22,579,748

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

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S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 158 del 17 de Junio de 2011 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 23 de Junio de 2011 bajo el No. 170,929 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Suplente Rodriguez Rey Jose Luis	CC.*****72,001,912

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condición de Presidente y ----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder ----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO ----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que - - -
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de ---
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar ----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo

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ante la DIAN, de tal forma que en ningun momento quede sin -----
 representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
 confiere poder especial amplio y suficiente a las personas que se ----
 determinan seguidamente, que conforman el grupo A y B, para, para
 que conjuntamente suscriban contratos de suministros de mercancías
 y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS
 MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
 liquidados a la tasa representativa del mercado vigente en el día
 que se realice la respectiva transaccion. Grupo A. WALTER NAKA
 TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
 CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
 VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
 DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
 CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
 FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
 amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
 CC.No.8.715.941, para que en nombre y representacion de PROCAPS ----
 S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a
 que este obligada la sociedad, en el giro normal de sus negocios y
 operaciones sociales, por tanto, quedan facultados para firmarlas,
 como tambien los demas documentos relacionados con ellas, -----
 notificarse, aportar y solicitar las pruebas que sean necesarias.
 c.- Otorgar poder especial amplio y suficiente al señor MARLON ----
 TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
 CERRA CC.No.8.715.941, para que en nombre y representacion de -----
 PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
 documento relacionado con los tramites o registros de Comercio ----
 Exterior y o cualquier entidad del Estado que haga sus veces: d)
 Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
 ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
 TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
 representacion de PROCAPS S.A.; endosen los titulos valores de la
 sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
 (1.000.000.000.00) M.L. CUARTO: El representante legal de la -----
 sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
 que la presente reforma fue aprobada por la Asamblea General -----
 Extraordinaria de Accionista de PROCAPS S.A., con observancia de
 las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008,
 otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente
 se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008
 bajo el No. 3,748 del libro respectivo,-----

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Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condicion de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ----- publico Poder especial Amplio y Suficiente a la doctora MILENA ----- ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y ----- representacion de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda ----- facultada para firmar, como tambien los demas documentos ----- relacionados con ellas, notificarse, aportar y solicitar las ----- pruebas que sean necesarias.-----

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de 2010 bajo el Nro 4,201 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ---- quien obra en el caracter de Presidente y/o Representante legal de la sociedad PROCAPS S.A., que por medio de este instrumento ----- publico, otorga Poder Especial Amplio y Suficiente a la Doctora ---- MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para que en nombre y representacion de la sociedad, Endose las Facturas Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa, queda facultada para realizar todo acto o tramite necesario para el cabal cumplimiento del presente mandato.-----

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de 2010 bajo el Nro 4,228 del libro respectivo,-----
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su condicion de Presidente y representante legal de PROCAPS S.A., ---- confiere poder especial, amplio y suficiente al señor RICARDO DORADO HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y ----- peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado para presentar, gestionar, tramitar y firmar las diferentes ----- solicitudes y peticiones de la empresa, segun la competencia de ---- estas entidades, como tambien presentar y firmar todo los ----- documentos relacionados con estas solicitudes, notificarse de ----- cualquier acto administrativo que expidan, aportar y solicitar las pruebas que sean necesarias, desistir, y en general a realizar todo tramite o acto necesario de tal forma que la sociedad en ningun ---- momento quede sin representacion legal ante estas entidades, en ---- cumplimiento fiel al mandato otorgado.-----

C E R T I F I C A

***** C O N T I N U A *****



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Que por Documento Privado del 03 de Agosto de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto de 2010 bajo el Nro 4,258 del libro respectivo,-----
consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las -----
facultades otorgadas por los Estatutos Sociales, todo lo cual -----
demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de -----
edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes -----
actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS -----
(\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones -----
Cambiarias, Aduaneras y Tributarias a las que esta obligada la -----
sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda -----
facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el -----
cabal cumplimiento del presente mandato.-----

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2011.

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

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre

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que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. Rayos

ANEXO



US 20080031964A1

19

(19) **United States**

(12) **Patent Application Publication**
Messadek

(10) **Pub. No.: US 2008/0031964 A1**

(43) **Pub. Date: Feb. 7, 2008**

(54) **COMBINATION THERAPEUTIC
COMPOSITIONS AND METHOD OF USE**

Publication Classification

(51) **Int. Cl.**

A61K 9/14 (2006.01)

A61K 31/14 (2006.01)

A61P 3/10 (2006.01)

(52) **U.S. CL.** *424/490; 514/556*

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ABSTRACT

The present invention provides pharmaceutical compositions and methods for the treatment of diabetes mellitus using combination therapy. The compositions relate to a compound of Formula 1 selected from one or more of betaines, lipidic betaines, betaine lipids and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of compound of Formula 1 with antidiabetic agent where the two components are delivered in a simultaneous manner, where the compound of Formula 1 is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound of Formula 1.

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(63) **Continuation-in-part of application No. PCT/BE06/00040, filed on Apr. 27, 2006.**

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COMBINATION THERAPEUTIC COMPOSITIONS AND METHOD OF USE

[0001] This application is a continuation-in-part application of: 1) PCT/BE2006/000049 filed on Apr. 27, 2006, published under WO2006/113978; 2) PCT/BE2005/000022 filed on Feb. 15, 2005, published under WO2006/086856; and 3) U.S. application Ser. No. 10/635,048 filed on Aug. 4, 2003, which is a continuation-in-part application of: (a) Ser. No. 09/945,391 filed on Aug. 31, 2001, which is a continuation-in-part application of PCT/BE2000/00021 filed on Mar. 1, 2000; and (b) PCT/BL2002/00013 filed on Feb. 4, 2001, all of which are incorporated by reference herein.

ABSTRACT OF THE DISCLOSURE

[0002] The present invention provides pharmaceutical compositions and methods for the treatment of diabetes mellitus using combination therapy. The compositions relate to a compound selected from one or more of betaines, lipidic betaines, betaine lipids and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of compound of Formula I with antidiabetic agent where the two components are delivered in a simultaneous manner, where the compound selected from one or more of betaines, lipidic betaines, betaine lipids is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound selected from one or more of betaines, lipidic betaines, betaine lipids. In the claims, betaine means pharmaceutically acceptable betaine, lipidic betaines, betaine lipids, pharmaceutically acceptable salts thereof and combinations thereof.

FIELD OF INVENTION

[0003] In general, the present invention relates to pharmaceutical compositions, and more particularly, to pharmaceutical compositions for the treatment of diabetes mellitus using combination therapy.

BACKGROUND OF THE INVENTION

[0004] Diabetes mellitus is a term generally used to refer to various pathological states characterized by hyperglycemia and altered metabolism of lipids, carbohydrates and proteins. These conditions are also often associated with other co-morbidities, such as obesity and an increased risk of cardiovascular disease. By some estimates, as many as 600,000 new individuals become clinically diabetic every year in the United States.

[0005] Diabetic conditions are generally classified as either insulin-dependent diabetes mellitus (IDDM, Type I diabetes) or non-insulin-dependent diabetes mellitus (NIDDM, Type II diabetes). There are also less common clinical pathologies that are associated with diabetic conditions, such as gestational maturity-onset diabetes of youth (MODY), tropical diabetes secondary to chronic pancreatitis, diabetes secondary to pancreatic disease or surgery, and diabetes secondary to endocrinopathies.

[0006] Virtually all forms of diabetes are due to a decrease in the circulating concentration of insulin (insulin defi-

ciency) and/or a decrease in the response of peripheral tissues to insulin (insulin resistance). These abnormalities lead to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids, and a hyperglycemic condition. IDDM appears to have an autoimmune etiology, which results in destruction of beta islet cells in the pancreas and the resulting inability to produce insulin. The etiology of NIDDM, the most prevalent form of diabetes, is more complex and possibly heterogeneous. Some loss of beta-cell volume is generally noted in these patients, as well as decreased circulating levels of insulin. NIDDM patients may also suffer commonly from insulin resistance.

[0007] The best-established therapy for all IDDM and many NIDDM patients is subcutaneous insulin treatment. Additionally, insulin is used as the treatment of choice for patients with post-pancreatectomy diabetes or gestational diabetes. While insulin is a key element in the control of these hyperglycemic conditions, there are a number of limitations associated with its use, including hypoglycemia, allergic reactions to insulin, lipodystrophy, lipohypertrophy, body weight gain, edema, and insulin resistance. There are a number of new forms of insulin on the market or in various stages of clinical evaluation, including new delivery systems, various recombinant forms, new routes of administration, and gene therapy. These novel forms of insulin treatments are believed to share some of the same limitations outlined above. A significant improvement in the treatment of diabetes can be achieved if insulin treatment is combined with agents that increase the insulin sensitivity of the peripheral tissues.

[0008] The concept of combination therapy is well exploited in current medical practice. Treatment of a pathology by combining two or more agents that target the same pathogen or biochemical pathway sometimes results in greater efficacy and diminished side effects relative to the use of the therapeutically relevant dose of each agent alone. In some cases, the efficacy of the drug combination is additive (the efficacy of the combination is approximately equal to the sum of the effects of each drug alone), but in other cases the effect can be synergistic (the efficacy of the combination is greater than the sum of the effects of each drug given alone). In real medical practice, it is often quite difficult to determine if drug combinations are additive or synergistic.

[0009] For most diabetic patients, treatment involves some form of insulin therapy. In addition, IDDM patients may receive a biguanide (e.g., metformin) to enhance the insulin utilization by peripheral tissues. NIDDM patients are often treated with a combination of insulin, a sulfonylurea (to enhance insulin production in the pancreas) and a biguanide or glitazone (to enhance insulin sensitivity by peripheral tissues). For example, the improved utility of a glitazone in combination with a sulfonylurea was recently demonstrated in human clinical trials (see, WO 98/36755). Recently, two glitazone compounds (rosiglitazone and pioglitazone) were approved in the United States for the treatment of NIDDM patients in combination with metformin.

[0010] A variety of antidiabetic compounds are known. For example, sulfonylureas are a group of drugs that induce hypoglycemia by stimulating insulin release from the pancreas. Generally, sulfonylureas have found wide utility in the treatment of NIDDM. Their efficacy is decreased in IDDM

because of the inherent inability of the patient to produce insulin. Adverse reactions to sulfonylureas occur in a fraction of patients, particularly the elderly. One of the most severe side effects is hypoglycemia and coma. Other side effects include nausea and vomiting, cholestatic jaundice, agranulocytosis, cardiovascular mortality, aplastic and hemolytic anemias, generalized hypersensitivity reactions and dermatological reactions.

[0011] Biguanides are another group of drugs, first introduced in the mid 1950's, that have shown efficacy in the treatment of hyperglycemia by mechanisms that are not well understood. The best known agents of this type include metformin, phenformin and buformin. Unlike the sulfonylureas, metformin does not induce release of insulin from the pancreas. It is thought that its effects are mediated by increasing insulin activity in peripheral tissues, reducing hepatic glucose output due to inhibition of gluconeogenesis and reducing the absorption of glucose from the intestine. Side effects associated with the use of biguanides include lactic acidosis, diarrhea, nausea, and anorexia. These agents are often given in combination with drugs that increase the output of insulin from the pancreas, such as the sulfonylureas, which sometimes results in greater efficacy and/or the ability to use lower doses of the drugs, with an improved side effect profile.

[0012] More recently, the glitazones have been introduced and are widely used in the treatment of NIDDM. These agents, also known generically as thiazolidinediones, such as troglitazone, rosiglitazone and pioglitazone, are thought to work by increasing the sensitivity of peripheral tissues, such as skeletal muscle, towards insulin. They are often used in combination with insulin or other agents, such as the sulfonylureas, that enhance the release of insulin from the pancreas. A number of side effects have been described during the clinical evaluation of these agents, including hepatotoxicity, organomegaly, edema, anemia and body weight gain. While hepatotoxicity may be the most acutely life-threatening of these conditions, it does not appear in a large percentage of the patient population. On the other hand, the increases in body weight gain associated with chronic glitazone treatment are generally perceived as worsening an already critical co-morbid condition in the majority of the diabetic patients, and may ultimately result in the loss of antidiabetic efficacy for this type of agent after chronic treatment.

[0013] Alpha-Glucosidase inhibitors, such as acarbose, reduce intestinal absorption of starch, dextrin and disaccharides by inhibiting the action of intestinal brush border alpha-glucosidase. Inhibition of this enzyme slows the absorption of carbohydrates and the rise in plasma glucose that normally follows after a meal is blunted. Acarbose has shown some benefit in IDDM and NIDDM patients, but is often associated with dose-related malabsorption, flatulence and abdominal bloating.

[0014] Other types of agents that have found limited utility in treating diabetes include potassium channel antagonists such as repaglinide, and aldose reductase inhibitors such as zopolrestat and tolrestat. Still in the experimental stage, glucagon antagonists, activators of the retinoid-X receptor (RXR), activators of PPAR.alpha., activators of PPAR.delta., and anti-obesity agents are also being evaluated as potential antidiabetic agents.

[0015] In view of the foregoing, there remains a need in the art to provide more efficacious treatment for diabetic conditions and diabetic complications. Combination therapy treatments are needed that will reduce the amount of drugs taken, thereby decreasing side effects. Surprisingly it was found that combining the betaines, i.e. one or more compounds selected from one or more of betaines, lipidic betaines, betaine lipids, of the invention with antidiabetic agents enhance their effectiveness while lessening their potential side effects. The concomitant uses of betaines with antidiabetic agents permit to lower the amounts of the latter. The present invention fulfills these and other needs.

SUMMARY OF THE INVENTION

[0016] The present invention provides pharmaceutical compositions for the treatment of a variety of diseases, including diabetes mellitus, such as IDDM, NIDDM, gestational diabetes, juvenile diabetes, and the like, using combination therapy. In certain aspects, the pharmaceutical compositions comprise a pharmaceutically acceptable carrier with a compound of Formula I and an antidiabetic agent. Advantageously, the compositions of the present invention provide clinical advantage over the use of a single agent alone. As such, the present advantageous invention provides a combination or association or composition comprising: (i) a compound of Formula I: $(\text{CH}_3)_3\text{N}^+ (\text{CH}_2)_n\text{COO}^-$ being an integer from 1 to 5 (preferably $n=1$) including pharmaceutically acceptable salts of compounds of Formula I, esters thereof, precursors thereof, and mixtures thereof; and (ii) one or more antidiabetic agents, including, but not limited to, sulfonylureas, biguanides, glitazones and other PPAR.gamma. agonists, PPAR.alpha. agonists, PPAR.delta. agonists, alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent (5), prodrugs thereof, or pharmaceutically acceptable salts of the antidiabetic agents, and a pharmaceutically acceptable carrier or diluent.

[0017] In certain aspects, the compositions of the present invention comprise a compound of Formula I formulated together with one or more antidiabetic agents. Alternatively, the compositions of the present invention comprise a compound of Formula I independently formulated with one or more antidiabetic agents i.e., separately formulated.

[0018] Suitable antidiabetic agents include, but are not limited to, sulfonylureas, biguanides, glitazones and other PPAR.gamma. agonists, alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, activators of PPAR.alpha., activators of PPAR.delta., insulin therapy or other anti-obesity agents. The administration of a composition or combination comprising: (i) one or more compound of Formula I, which increase insulin production and/or increase peripheral tissue sensitivity to insulin, with (ii) an antidiabetic agent such as insulin therapy, or a stimulator of insulin secretion, and the like, increases the efficacy of either agent alone. In addition to increased efficacy, the combination therapy of the present invention allows for a concomitant reduction in the dose of the agents. The combination therapy of a compound of Formula I and one or more of another antidiabetic agents (e.g., biguanides, glitazones, RXR ligands, PPAR.gamma. agonists, etc.) results in a reduction in the side effects normally associated with certain antidiabetic agents.

[0019] In certain aspects, compounds of Formula I are administered successively (for example prior to the administration of the antidiabetic agent) or substantially simultaneously in combination with antidiabetic agents that are ineffective for stimulation of insulin secretion or insulin sensitivity, such as α -glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, RXR ligands, PPAR α agonists, PPAR δ agonists, and anti-obesity agents. Surprisingly, these types of combination therapy result in enhanced efficacy relative to the use of the single agents alone.

[0020] In another embodiment, the present invention provides methods of treating metabolic or inflammatory disorders in a host by administering a composition of the present invention. In certain preferred aspects, the method includes the administration of a composition comprising a combination of a compound of Formula I with the antidiabetic agent delivered in a simultaneous manner, such as in a single formulation. In certain other aspects, the methods of the present invention include combination therapy wherein the compound of Formula I is administered at least partly first for example by means of a first formulation, followed by the antidiabetic agent administration for example by means of another or separate formulation. The methods also include an antidiabetic agent being delivered first in one formulation, followed by a compound of Formula I in a separate formulation. The present invention includes all such methods of administration. The combination therapy is especially efficacious on conditions associated with diabetes, such as obesity, cardiovascular diseases, cerebrovascular diseases, thrombosis, ischemia, hypoxia, hypertension, hypercholesterolemia, lipid disorders, peripheral neuropathies, Intermittent Claudication, metabolic syndrome . . . and other neurological disorders, and the like. The compound of formula I and the antidiabetic agent can be administered simultaneously, but preferably with a controlled release at least partly for the amount to be administered for the compound of formula I and/or for the amount of antidiabetic agent.

DEFINITIONS

[0021] Betaine or betaines as used in the claims means "Betaines" such as compound of formula I, "lipidic betaines" and "betaine lipids", as well as combinations thereof.

[0022] The term "Betaines" as employed herein refers advantageously to compounds of formula I: $(CH_2)_nN^+(CH_2)_3COO^-$ with n an integer from 1 to 5, (preferably glycine betaine n=1), pharmaceutically acceptable salts thereof, esters thereof, precursors thereof, and mixtures thereof.

[0023] The terms "lipidic betaines" and "betaine lipids" refer to betaine lipids which are structural components of membranes commonly found in ferns, mosses, fungi, amoeba, eukaryotes such as nonseed plants and algae. Betaine lipids are ether-linked, nonphosphorous glycerolipids that resemble the more commonly known phosphatidylcholine in overall structure. Most common glycerolipids are containing a diacyl-glycerol moiety to which a polar head group is attached. This head group can be a carbohydrate moiety as in the very abundant plant galactolipids or a phosphorylester as in the glycerophospholipids, the most common lipid class in animals. Betaine lipids represent a third class of glycerolipids in which a quaternary amine

alcohol is bound in an ether linkage to the diacylglycerol moiety. They can be obtained by extraction, by biosynthesis or by synthesis. The betaine lipid diacylglycerol-O-4'-(N,N,N-trimethylhomoserine and a closely related isoforn diacylglycerol-O-2'-(hydroxymethyl)(N,N,N-trimethyl)- β -alanine are the most common.

[0024] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include, but are not limited to, those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, diphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, malic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0025] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0026] In addition to salt forms, the present invention provides compounds that are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by in vivo, chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a reservoir such as transdermal patch and/or enteral reservoir and/or an implantable reservoir with a suitable enzyme or chemical reagent.

[0027] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, includ-

ing hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention can exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0028] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

[0029] The compounds of the present invention can also contain unnatural proportions of atomic isotopes, stable isotopes etc., at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0030] The term "prodrug" refers to compounds that are drug precursors, which, following administration, release the drug in vivo via a chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form).

[0031] "A combination amount sufficient," "an effective combination amount," "therapeutically effective combination amount" or "an effective amount of the combination of" all refer to a combined amount of both a compound of Formula I and the antidiabetic agent that is effective to ameliorate symptoms associated with diabetic diseases. As used herein, the term "combination" of compound of Formula I with an antidiabetic agent means the two compounds can be delivered in a simultaneous manner, in combination therapy wherein the compound of Formula I is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first, followed by a compound of Formula I. The desired result can be either a subjective relief of a symptom(s) or an objectively identifiable improvement in the recipient of the dosage.

[0032] The terms "synergistic effective amount" refers to a combined amount of both a compound of Formula I and an antidiabetic agent that is effective to cause a synergistic effect. Synergy is a biological phenomenon in which the effectiveness of two active components in a mixture is more than additive, i.e., the effectiveness is greater than the equivalent concentration of either component alone. In certain aspects, the effectiveness of the combination therapy of a compound of Formula I and an antidiabetic agent is synergistic. Thus, synergism is a result, or function, that is more than the sum of the results, or functions of individual elements.

[0033] The term "simultaneous manner" and "combination treatment" refer to an administration protocol wherein the compounds of the present invention and at least one antidiabetic agent are administered within a single 24-hour period.

[0034] In one embodiment the period can be longer such as a week, a month, 3 months, 6 months, etc. Such longer

periods are necessary when the compounds of the invention are administered with implanted mini-pumps and/or devices and/or dosages forms suitable for long period deliveries in the body.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Compositions

[0035] In one embodiment, the present invention provides a pharmaceutical composition comprising: (i) a compound of Formula I; and (ii) an antidiabetic agent. Advantageously, the compositions of the present invention provide clinical advantage over the use of a single agent alone.

[0036] Based on the unique features of the compounds of Formula I, the combination of one of these compounds with one or more antidiabetic agents described herein provides a significant clinical advantage over the use of a single agent alone. Thus, (1) the combination of a compound of Formula I (which is thought to increase peripheral tissue sensitivity to insulin) with either insulin therapy, or a stimulator of insulin secretion (e.g., a sulfonylurea) increases the efficacy of either agent alone, and moreover, allows for the reduction in dosage of all agents used in the combination therapy. In addition, (2) the combination therapy between a compound of Formula I and one or more other agents that increase insulin sensitivity (e.g., biguanides, glitazones, RXR ligands, PPAR gamma agonists, and the like.), results in an enhanced effect between the various agents, with reduction in the side effects normally associated with these other agents. Further, (3) compounds of Formula I can be administered in combination with antidiabetic agents whose mode of action is other than stimulation of insulin secretion or insulin sensitivity (e.g., alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, RXR ligands and anti-obesity agents). Importantly, these types of combinations result in enhanced efficacy relative to the use of a single agent alone. In addition, the present invention includes (4) a combination treatment comprising a compound of Formula I in combination with agents aimed at treating any one of the conditions often associated with diabetes, such as obesity, cardiovascular diseases, cerebrovascular diseases, thrombosis, ischemia, hypoxia, hypertension, hypercholesterolemia and other lipid disorders, peripheral neuropathies and other neurological disorders. Furthermore, (5) the combination therapy between a compound of Formula I and one or more other agents that increase insulin sensitivity (e.g., biguanides, glitazones, RXR ligands, PPAR gamma agonists, and the like.), results in a prevention of diabetic troubles or conditions or in a delaying of the appearance of diabetic troubles or conditions.

[0037] The compounds of Formula I, particularly glycine betaine, are known to possess antaggregant, anticoagulant, anti-adhesive, anti-inflammatory and fibrinolytic properties. The exact potency and intrinsic agonist activity of each compound of Formula I is a function of the compound's structure in a relatively predictable manner.

[0038] In an embodiment of the invention the compounds of Formula I, preferably glycine betaine (n=1) can be used for therapeutic and/or dietary supplementation as to manage diabetes.

[0039] According to the invention, therapeutic and/or dietary betaine supplementation may represent a potentially useful strategy for the management of diabetes. Betaine is a stable amino acid in an aqueous solution, and is not destroyed by sterilization conditions (e.g., high temperature and high pressure). In addition, betaine is nontoxic, and its administration is generally safe for both humans and animals. Betaine can be useful in the treatment of patients with type I diabetes, when been used along with insulin therapy to increase insulin secretion by the remaining pancreatic β -cells and improve insulin sensitivity in tissues via enhanced production of NO. This can help reduce the dosage and frequency of insulin therapy for patients with type I diabetes, while improving protein balance and endothelial function. In patients with type II diabetes, the pancreas is exhausted from the overproduction of insulin to overcome the insulin resistance of tissues, and most clinicians do not use drugs or agents that stimulate insulin secretion to treat this type of diabetes.

[0040] In one embodiment, betaine treatment can increase the plasma concentration of insulin in patients with type II diabetes. However, betaine supplementation may be a promising method of improving cardiovascular function in patients with type II diabetes by increasing endothelial NO synthesis. In support of this view, recent studies indicate that intravenous infusion of betaine (30 g over 30 min) reduces blood pressure and improves haemodynamic functions in patients with type II diabetes. Thus, dietary betaine supplementation may enhance insulin sensitivity and attenuate or even prevent insulin resistance, thereby eliminating the need for the additional insulin therapy that is often required with sulfonylurea.

[0041] In one embodiment, therapeutic and/or dietary betaine supplementation reduces body weight loss (in diabetic patients), improves glucose homeostasis, increases plasma and endothelial concentrations of betaine, enhances endothelial BIL, availability for NO synthesis, enhances endothelial NO synthesis, improves circulation and lessens hypertension in the diabetic subjects. These findings provide a biochemical basis for the beneficial effect of therapeutic and/or dietary betaine supplementation in preventing endothelial dysfunction in diabetic subjects.

[0042] In one embodiment, one or more compounds of Formula I can be partly or completely in slow, delayed, extended, sustained or controlled release dosage forms when associated to one or more of the anti-diabetic compounds.

[0043] In one embodiment, one or more of the anti-diabetic compounds can be partly or completely in slow, delayed, extended, sustained or controlled release dosage forms when associated to one or more compounds of Formula I.

[0044] In one embodiment, one or more compounds of Formula I can be partly or completely in slow, delayed, extended, sustained or controlled release dosage forms and are associated to one or more anti-diabetic compounds which are partly or completely in slow, delayed or controlled release dosage forms.

[0045] According to the invention, dietary betaine supplementation may represent a potentially useful strategy for the management of juvenile diabetes. To achieve this purpose, betaine and compounds of Formula I can be enclosed in

useful dietary products such as chocolate bars, cookies, drinks, meals, sweets, confectioneries and edible products which are usually ingested by young people. According to the invention, dietary and/or edible sweet products can contain one or more of cacao, cocoa, honey, cereals, marsh, nougat, caramel, seeds, kola, mint, fruits, fruit aromas, sugar, molasses and an efficient amount of one or more compound of Formula I. Such products might be particularly useful in the management of diabetes while allowing higher carbohydrates daily intake. In one particular embodiment, due to the cardiovascular properties of the compounds of Formula I, such dietary and/or edible sweet products can also be used in the management of cardiovascular risks in persons in need, i.e. at risk to develop cardiovascular events.

[0046] Diabetic chocolates are usually sweetened with a type of sugar as 'polyol'. Polyols are used as other sugar alternatives. In summary, polyols such as sorbitol and maltitol are still carbohydrates and the body will turn them, at least in part, into glucose. Polyols can also behave like a laxative, making feel gassy, bloated and giving you stomach ache. Betaine supplementation avoids these kinds of side effects.

[0047] In one embodiment, a chocolate composition containing cocoa and compounds of Formula I are claimed. Glycine betaine due to its sweet taste can be preferred. The betaine can be mixed with the chocolate paste at the end of the manufacturing process of the chocolate. A chocolate bar containing betaine for diabetics is claimed. Disclosed and claimed are cocoa extracts, compounds, combinations thereof and compositions containing the same and further containing one or more compound of Formula I, glycine betaine being preferred for its sweet taste. In one embodiment the chocolate bar will be sensibly free of sugar and carbohydrates, betaine fulfilling their sweetening effects while having its cardiovascular and antidiabetic effects.

[0048] In one embodiment, the chocolate composition can be, chocolate pasta such as spread pasta.

[0049] In one embodiment the chocolate composition containing cacao and one or more compound of formula I is sweetened by polyols such as sorbitol, tagatose and maltitol. Tagatose is derived from lactose can constitute an interesting alternative according to the present invention.

[0050] Although older studies found that, similarly to fructose, sugar alcohols (i.e., sorbitol, xylitol, maltitol, mannitol) induced low glycaemic responses, more recent studies have found that some sugar alcohols, notably maltitol, induce no less of a glucose surge than glucose itself when used in certain products, such as chocolate. Maltitol is used frequently in "sugar-free" chocolate and other candies, so this effect is clinically meaningful. Other sugar alcohols, such as sorbitol, lactitol, and xylitol appear to raise blood glucose and insulin levels substantially less than glucose and for this reason are being used with increasing frequency as sweeteners in the creation of "sugar-free" products. They are incompletely absorbed in the digestive tract, and as a result, have a lower caloric content than sugar (range, 1.5 to 3 kcal/g). Diet products, especially those aimed at low-carbohydrate dieters, seek to position themselves as lower caloric and lower carbohydrate, and thus, better for weight loss. Because sugar alcohols and fiber are not completely metabolized, there is a trend toward subtracting them from the carbohydrate count reported on the nutrient facts panel. This

results in the "net" carbohydrate count, which is substantially lower than the actual carbohydrate content. This is primarily a food marketing scheme to promote products as "dietetic" or "healthy" and "low carb." It is another goal of the present invention to provide chocolate formulations where one or more compounds of Formula I, preferably glycine betaine, is admixed with cocoa and one or more sugar such as glucose, succharose, sorbitol, lactitol, tagatose, xylitol, fructose, sugar alcohols, maltitol, mannitol and the sugars known by the skilled person, to serve to chocolate manufacture. Compounds of formula I supplementation in all known chocolate formulations will be suitable to obtain a "diabetic chocolate". Due to the numerous pharmacological properties previously described by the inventor, such chocolate with betaine can also claim "cardiovascular chocolate", "dietetic", "healthy" and "low carb." chocolate. The amounts of betaine per weight of chocolate can be adjusted depending of the type of dietetic claim, the type of pharmacological claim and/or the type of patient.

[0051] In one embodiment the chocolate composition can be sensibly free of sugars.

[0052] In one embodiment betaine and compounds of Formula I can be enclosed in useful dietary products such as chocolate bars, cookies, drinks, meals, sweets, confectioneries and edible products destined specifically to persons suffering or at risk to suffer of diabetes mellitus, hyperlipemia and impaired glucose tolerance.

Examples of Products:

[0053] Milk Bar Ingredients: Maltitol, Cocoa Butter, Milk Powder, Cocoa Mass, Butter Oil, Soya Lecithin, Natural Vanilla and sufficient amount of betaine

[0054] Dark Bar Ingredients: Maltitol, Cocoa Mass, Cocoa Butter, Soya Lecithin, Natural Vanilla and sufficient amount of betaine

[0055] White Bar Ingredients: Maltitol, Cocoa Butter, Milk Powder, Butter Oil, Soya Lecithin, Natural Vanilla and sufficient amount of betaine

[0056] Compounds of Formula I have been shown, in diabetic patients to normalize fasting blood glucose levels with the anti-diabetic efficacy of the glitazones, but with a decreased propensity to induce body weight gain. One of the major side effects of glitazones (e.g., troglitazone, rosiglitazone and pioglitazone) is their obesity-inducing potential. Advantageously, compounds of Formula I possess a diminished propensity towards inducing body weight gain and thus, avoiding one of the major side effects of known glitazones. In one embodiment, the use of the compounds of Formula I are claimed to normalize body weight in a mammal in need. Moreover, compounds of Formula I have also shown beneficial effects on plasma lipid profiles.

[0057] Moreover, in certain embodiments, additional compounds can be mixed with the compounds of Formula I and are described in WO 99/38845, published Aug. 5, 1999, to De La Brouse-Elwood et al., and incorporated herein by reference in its entirety for all purposes. Certain compounds as described therein, are potent, selective activators of PPAR-gamma and are useful for the treatment of NIDDM and other disorders related to lipid metabolism and energy homeostasis. In other aspects, and depending on the biological environment (e.g., cell type, pathological condition

of the host, and the like.), the compounds can activate or block the actions of PPAR gamma. By activating the PPAR-gamma receptor, the compounds will find use as therapeutic agents capable of modulating conditions mediated by the PPAR-gamma receptor. Additionally, the compounds are useful for the prevention and treatment of complications of diabetes (e.g., neuropathy, retinopathy, glomerulosclerosis, and cardiovascular disorders), and treating hyperlipidemia. The compounds are useful for the modulation of inflammatory conditions which most recently have been found to be controlled by PPAR-gamma. (see, Ricote, et al., Nature, 391:79-82 (1998) and Jiang, et al., Nature, 391:82-86 (1998). Examples of inflammatory conditions include rheumatoid arthritis and atherosclerosis. Compounds that act via antagonism of PPAR gamma are useful for treating obesity, hypertension, hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, and metabolic disorders.

[0058] Preferred compound of Formula I are those in which $n=1$ i.e. glycine betaine. But at least one or more of the betaines of Formula I can be used according to the invention alone to achieve the therapeutical purposes of the invention. One or more of the betaines of Formula I, can also be used in mixtures or in combinations with the antidiabetic compounds of the invention to achieve the therapeutical purposes of the invention.

[0059] The compositions of the present invention further comprises one or more (ii) antidiabetic compounds. A wide range of antidiabetic agents can be used in the compositions and methods of the present invention. Suitable agents include, but are not limited to, one or more antidiabetic agent such as sulfonylureas, biguanides, glitazones and other PPAR-gamma agonists, alpha-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent, prodrugs thereof, or pharmaceutically acceptable salts of the antidiabetic agents. In certain instances, the antidiabetic agents include, but are not limited to, one or more agents such as insulin and insulin analogs (e.g. LysPro insulin); GI P-1 (7-37) (insulinotriptin) and GI P-1 (7-36)-NH₂sub.2; sulfonylureas and analogs, including, but not limited to, chlorpropamide, glibencamide, tolbutamide, tolazamide, acetohexamide, glipizide, glimepiride, repaglinide and meglitinide; biguanides, including, but not limited to, metformin, phenformin and buformin. The methods of treatment combining the uses of one or more of the antidiabetic agents, as described in the present application, with the compounds of Formula I for treating the pathologies, as described in the present application, are also claimed.

[0060] In one embodiment, the combined compounds of the invention are claimed to treat, alleviate and/or provide method of treatment to diabetic associated conditions such as: diabetic retinopathy, heart disease, mouth conditions, proteinuria, retinal detachment, transient ischemic attack, hypertension, pulmonary hypertension, portal hypertension, obesity, high cholesterol, diabetic retinopathy, heart disease, etc.

[0061] In one embodiment, the compounds of Formula I can be associated to endothelin antagonist such as bosentan to treat endothelin related pathologies, among them pulmonary hypertension.

[0062] In one embodiment, the associations of the present application, namely one or more of the compounds of

Formula 1, and one or more antidiabetic agents, can be further associated and/or combined with one or more therapeutic agent selected from the group consisting in: aspirin, polyphenols, vitamins, dhca, statins, hi-aspirin, antioxidants, etc.

[0063] In one embodiment, the compounds of Formula 1, when used alone are claimed to treat, alleviate and/or provide method of treatment in diabetic associated conditions such as: diabetic retinopathy, heart disease, mouth conditions, proteinuria, retinal detachment, transient ischemic attack, hypertension, pulmonary hypertension, portal hypertension, obesity, high cholesterol, diabetic retinopathy, heart disease, etc.

[0064] In another embodiment, the antidiabetic agents include various forms of insulin, such as insulin in its various dosage forms, subcutaneous, oral, inhaled, and the like, molecular variations, and short-, medium- and long-acting versions. Suitable insulin sources include, but are not limited to, recombinant human insulin, natural pig insulin, natural ox insulin, natural bovine insulin, natural human insulin, recombinant human arginine-insulin, recombinant human aspartic-insulin, dalanated insulin, defalan insulin, glargine insulin, human insulin zinc, human insulin isophane, lispro insulin, neutral insulin, human proinsulin, their mixtures and the like.

[0065] In one embodiment, the antidiabetic agents used in the compositions of the present invention are sulfonylureas. Preferred sulfonylureas suitable for use in the present invention include, but are not limited to, acetohexamide, chlorpropamide, glyburide, glibipizide, gliclazide, glimepiride, glipizide, glisoxepid, glibenclamide, glimepiride, glibenclamide, gliclazide, glibenclamide, glymidine, glypamide, tolpyruramide, glythexamide, plicbutamide, tolazamide, tolbutamide, tolycyclamide and their mixtures. Those of skill in the art will know of other sulfonylureas suitable for use in the present invention.

[0066] Sulfonylureas are a group of drugs that induce hypoglycemia by stimulating insulin release from the pancreas. Generally, sulfonylureas have found wide utility in the treatment of NIDDM. Their efficacy is decreased in IDDM because of the inherent inability of the patient to produce insulin. Adverse reactions to sulfonylureas occur in a fraction of patients, particularly the elderly. One of the most severe side effects is hypoglycemia and coma. Other side effects include nausea and vomiting, cholestatic jaundice, agranulocytosis, cardiovascular mortality, aplastic and hemolytic anemias, generalized hypersensitivity reactions and dermatological reactions. The compounds of Formula 1 increase insulin sensitivity, and when used in combination with sulfonylureas, increase the efficacy and side effect profile of either type of agent alone. In certain instances, the combination therapy allows the use of lower doses of both agents.

[0067] In a preferred embodiment, the antidiabetic agents used in the compositions of the present invention are biguanides. Biguanides are a group of drugs that are efficacious in the treatment of hyperglycemia. Preferred biguanides suitable for use in the present invention include, but are not limited to, metformin, phenformin and buformin. Unlike the sulfonylureas, metformin does not induce release of insulin from the pancreas. Without being bound by any particular theory, it is thought that its effects are mediated by increas-

ing insulin activity in peripheral tissues, reducing hepatic glucose output due to inhibition of gluconeogenesis and reducing the absorption of glucose from the intestine. Side effects associated with the use of biguanides include lactic acidosis, diarrhea, nausea, and anorexia. Preferred biguanides include metformin, buformin, etoformin and phenformin.

[0068] In another embodiment, the antidiabetic agent is a glitazone. Glitazones, also known as thiazolidinediones, cigitazone, darglitazone, englitazone, AID-5075, and BM-131246. Preferably, the glitazone compounds used in the present invention include troglitazone, rosiglitazone, and pioglitazone.

[0069] As disclosed therein, oxyiminotetramic acid derivatives are disclosed that are useful for treating and/or preventing diabetes mellitus, hyperlipemia, impaired glucose tolerance, inflammatory disease and arteriosclerosis. Moreover, the compounds are useful for controlling retinoid-related receptors, enhancing insulin sensitivity and improving insulin resistance, and for treating and preventing diabetic complications. Other PPAR γ modulators are disclosed in WO 99/38850, published Aug. 5, 1999, to Lohray et al., and incorporated herein by reference in its entirety for all purposes.

[0070] In another embodiment, the present invention provides compositions comprising compounds of Formula 1 and α -glucosidase inhibitors. Preferred α -glucosidase inhibitors include acarbose, celastrol, camiglibase, voglibose and miglitol. Suitable α -glucosidase inhibitors are disclosed in WO 99/29327, to Odaka et al., published Jan. 17, 1999, entitled "Use of an α -glucosidase inhibitor to treat high-risk impaired glucose tolerance" and incorporated herein by reference in its entirety for all purposes. As described therein, the α -glucosidase inhibitor is particularly useful in the treatment of non-insulin-dependent diabetes mellitus. In addition, WO 99/26606, published Jan. 5, 1999, to Goldman et al., and entitled "Sustained-release formulations of α -glucosidase inhibitors," and incorporated herein by reference in its entirety for all purposes, discloses sustained released formulations of α -glucosidase inhibitors, (e.g. acarbose useful in the present invention).

[0071] Other types of agents that have found limited utility in treating diabetes include potassium channel antagonists such as repaglinide, and aldose reductase inhibitors such as zopolrestat, minirestat, ponarestat and tolrestat. Still in the experimental stage, glucagon antagonists, activators of the retinoid-X receptor (RXR), and anti-obesity agents are also being evaluated as potential antidiabetic agents. Others agents suitable for use in the present invention include, but are not limited to, glucagon, and miscellaneous agents such as methyl palmoxirate, palmoxirate sodium, piroglutide, pramlintide, amlinide, seglitide.

Methods, Uses, Dosages and Schedules

[0072] In another embodiment, the present invention provides a method for modulating conditions associated with diabetes or diabetes-related disorders in a host, comprising administering to the host an efficacious amount of compositions comprising (i) a compound of Formula 1 in combination with (ii) one or more antidiabetic agents. In certain aspects, the compositions of the present invention that are

administered comprise a compound of Formula I formulated together with one or more antidiabetic agents. Alternatively, the composition that is administered comprises a compound of Formula I independently formulated from one or more antidiabetic agents i.e., separately formulated.

[0073] The pharmaceutical compositions of the present invention are suitable for use in a variety of drug delivery systems. Examples of suitable formulations for use in the present invention are found in Remington's Pharmaceutical Sciences (Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985)), which is incorporated herein by reference. In addition, for a brief review of methods for drug delivery, see, Langer, Science 249:1527-1533 (1990), which is incorporated herein by reference. The pharmaceutical compositions of the present invention are intended for parenteral, topical, oral or local administration. In certain aspects, the pharmaceutical compositions are administered parenterally, (e.g., intravenously, subcutaneously, intradermally, or intramuscularly). In one embodiment, the invention provides compositions for parenteral administration which comprise a compound of Formula I, an antidiabetic agent as described above, dissolved or suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used including, for example, water, buffered water, 0.4% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well-known sterilization techniques or they may be sterile filtered. The resulting aqueous solutions may be packaged for use as is or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions including pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, such as, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

[0074] For solid formulations, compounds of Formula I can be admixed with conventional nontoxic solid carriers can be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10-95% of active ingredient and more preferably at a concentration of 25%-75%.

[0075] For aerosol administration, the compounds of Formula I and antidiabetic agents are preferably supplied in finely divided form along with a surfactant and propellant. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, oleosteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. A carrier can also be included, as desired, as with, (e.g., lecithin for intranasal delivery).

[0076] The compounds of the present invention can be prepared and administered in a wide variety of oral, enteral

and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and either a compound of Formula I or a pharmaceutically acceptable salt of a compound of Formula I.

[0077] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0078] In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0079] The powders and tablets preferably contain from 5% to 95% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0080] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0081] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0082] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0083] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These prepa-

rations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0084] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as blisters, packeted tablets, capsules, and powders and/or beads in vials, bags, sachets or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0085] The quantity of active components in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, preferably 1.0 mg to 5000 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0086] In therapeutic use especially for the treatment of obesity, NIDDM, or inflammatory conditions, the antidiabetic compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 500 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 150 mg/kg is preferred. Most preferably, the daily dose range is comprised between 1 mg/kg and 100 mg/kg, especially between 2 mg/kg and 25 mg/kg. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0087] In therapeutic applications, the compounds of Formula I and antidiabetic agents of the present invention are administered to a patient in a combination amount sufficient to elicit a response. An amount adequate to accomplish this is defined as "therapeutically effective combination dose." The methods include the administration of the combination of compound of Formula I with antidiabetic agent wherein the two components are delivered in a simultaneous manner; in combination therapy wherein the compound of Formula I is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the compound of Formula I.

[0088] The betaine of Formula I utilized in the pharmaceutical method of the invention is administered at the initial dosage of about 0.001 mg/kg to about 500 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 150 mg/kg is preferred. Most preferably, the daily dose range is comprised between 1 mg/kg and 100 mg/kg, especially between 25 mg/kg and 75 mg/kg.

[0089] Since the present invention has an aspect that relates to a combination of active ingredients which can be administered separately, the invention also relates to com-

bining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I, a prodrug thereof or a pharmaceutically acceptable salt and a second compound such as an antidiabetic agent as described above. The kit comprises a container for containing the separate components such as a divided bottle or a divided foil packet, however, the separate components can also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[0090] Effective combination amounts for various uses will depend on, for example, the particular antidiabetic agent, the compound of Formula I employed, the manner of administration, the weight and general state of health of the patient, and the judgment of the prescribing physician. In one embodiment, composition or formulation to be administered will contain a quantity of a compound(s) according to Formula I in an amount effective to treat the disease/condition of the subject being treated, (e.g., a glycogen phosphorylase dependent disease/condition). The amount of antidiabetic agent will depend in part to the chemical class.

[0091] In certain instances, administration of the compounds of Formula I can be via any method which provides systemic exposure to the compound of this invention, preferably to the muscle and fatty tissue. These methods include oral routes, enteral, parenteral, intraduodenal routes, etc. Generally, the compounds of the present invention are administered in single (e.g., once daily) or multiple doses. The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of Formula I together with a pharmaceutically acceptable carrier or diluent. Thus, the compounds of this invention can be administered individually or together in any conventional oral, parenteral or transdermal dosage form.

[0092] For oral administration, a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various binders such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules, preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0093] In one embodiment, the combined compounds in the form of a powder, granules, microgranules, microspheres, pellets and gels. The combined compounds can be in the form of a pharmaceutical unit dosage form said dosage form being selected from the group consisting of sachets, pouches, blisters and bags. Pharmaceutical unit dosage form of a composition containing at least a betaine, said dosage form being selected from the group consisting of sachets, pouches, blisters and bags, wherein the pharmaceutical unit dosage form is provided with moisture barrier property defined by an increase of weight of the composition of less than 1% after storage of the unit dosage form in sealed condition in an environment with a temperature of 38° C. and a relative humidity of 90% during 30 days.

[0094] Such individual sachet being possibly further submitted to an encrypting against counterfeiting and/or a notch to facilitate the tearing and/or the opening.

[0095] As MVTR stands for "Moisture Vapor Transmission Rate", a measure of the passage of gaseous H₂O through a barrier, the pharmaceutical oral unitary dose of betaine in a sealed dosage form from the group consisting of sachets, bags, blisters and pouches in which the dosage form is at least partly flexible, water impermeable and characterized by a protective barrier by a MVTR value inferior to 0.1 g/m² at 38° C. and 90% relative humidity during 24 hours.

[0096] In one embodiment, the sizes of the betaines particles can be selected so as to absorb minimally the water (for instance from micronized particles to an optimal size particles allowing a minimal water intake). Optionally the particles for the dosage form such as a sugar-coated pill could be further enveloped by a surfactant having good moisture barrier) can be sugar-coated and optionally such particles can be trapped in a gel or a polymer before being packaged in a selected MVTR container or pharmaceutical unit dosage form.

[0097] For example the coating or primary packaging material could be a laminate which is made up of 12 µm PET, 25 µm Alufoil and a 50 µm PE inner heat-seal layer. Further high quality and clarity of surface decoration might be realized by gravure reverse printing process.

[0098] The complete barrier requirement for this highly hygroscopic product (betaine after being dried, i.e. its liquid content partially or completely removed) could be provided by a laminate of PET, PE and Alufoil. The single 250 to 5000 mg doses are easy to tear open and safe for mouth contact. In this dosage form betaine can be taken directly by mouth without the need to dissolve in water. Some flavoring agents might be added to mask betaines taste by the way augmenting patients' compliance. Geometrical forms which augment the facility of use can be privileged.

[0099] In one embodiment a stick format of the sachet will be preferred as it uses a minimum amount of material in relation to the volume of its contents and further by reducing the bag surface it allows also to reduce the MVTR.

[0100] The dosage forms can be optimized according to selected combinations of MVTR, betaine doses, tensile strengths, sizes, forms, coefficients of friction. The initial rate of moisture of the betaines can also be selected and/or controlled so as to lower the other parameters (MVTR, etc) thus augmenting the compliance of the dosage form.

[0101] Betaine monohydrate and/or Betaine anhydrous and/or their mixtures solutions after being submitted to the processes of the invention can be dried and sachets as unit oral dosage forms of betaine(s) can be realized using as primary packaging material multilayer Alufoil material. The realized sachets will be weighted just after their manufacture and 1, 3, 6 and 12 months later, so as to determine the possible water intake of the betaine(s) inside the sealed dosage forms. The results could show that the weight variation is in accordance and in the limits allowed by the International Pharmacopoeia and come up to the FDA and/or BGA directives and the recommended and approved instructions given by EF for this kind (sachets/blister/pouches) of pharmaceutical dosage form. Due to the high hygroscopic properties of betaines, in one embodiment betaine monohydrate can be preferred. In effect the water intake of betaine monohydrate can be in a preliminary step controlled so as to avoid/control further moisture intake.

[0102] In one embodiment Betaine monohydrate and/or Betaine anhydrous and/or their mixtures are used "as is", i.e. as provided in pharmaceutical grade (suitable for oral use) by the manufacturers after the sugar beet molasses separation processes or the chemical or biological synthesis. These betaines can be packaged in such unit oral dosage form sachets having such moisture and/or oxygen and/or light barriers and/or tensile strength and/or coefficient of friction.

[0103] The coefficients of friction outside/outside and/or inside/inside will have to be carefully chosen so as to allow the maximum of the compound to be delivered at the administration. When absorbing moisture the betaine can start a process of higher size crystallization which can adhere inside the sachet making a part of the betaine unavailable upon administration. In the other side such medication being destined to a daily utilisation during years, it is necessary to carefully choose the physical properties of the primary packaging material so as to have at the same time a good moisture barrier while having an easy opening, i.e. a "friendly" tensile strength allowing for instance elderly people to take easily their daily or twice daily medication. The primary packaging material must be easy to tear while possessing good moisture and/or oxygen barriers, such barriers preventing betaines deliquescence. Moisture sorption could lead to betaine particles agglomeration which can then adhere inside the sachet leading to a partial delivery of the drug after tearing. When carefully choose, selected and combined these parameters will allow compliance with the International Pharmacopoeia and Pharmaceutical Industry standards as they (parameters) will allow a better compliance of the end user, i.e. the patient. All the combinations do not work and only a careful selection of specific materials with particular parameters can provide this double compliance of sachet oral unit dosage forms of betaines.

[0104] Thus it is claimed here the combinations of the above physical characteristics of betaines forms (salts, sizes, coatings, polymers, etc) and the physical characteristics of the packaging materials (MVTR, tensile strength, coefficient of friction, tear strength, etc) which (the combinations) allow to augment the compliance of the pharmaceutical dosage form while retaining and respecting correct (according to international regulations and directives) conservation properties.

[0105] In one embodiment, the compounds of Formula 1 and/or the antidiabetic compounds and/or the combined compounds of the invention can be manufactured in formulations, forms and dosages forms such as those claimed in WO0051596, US 20020065320, WO02062322, US 20040033223, WO2004049095, WO2004091601, JP 2004/0364, PCT/JP 2004/00110, PCT/JP 2004/000163 of the inventor.

[0106] According to the invention it will be appreciated that the actual preferred course of therapy will vary according to, inter alia, the mode of administration of the compound of Formula 1, the particular formulation of the antidiabetic agent being utilized, the mode of administration of the compounds, the particular disease being treated and the particular host being treated. The optimal course of therapy for a given set of conditions can be ascertained by those skilled in the art using conventional course of therapy determination tests and in view of the information set out herein.

Additional Uses for Compounds of Formula 1

[0107] The compounds of Formula 1 have been recently shown to enhance nitric oxide production in human and other species. As such, specific compounds of Formula 1 are well suited for the treatment of the various conditions and diseases established to be mediated by, or linked to nitric oxide levels. Thus the compounds of Formula 1 can be suitable to treat below outline other indications alone or in combinations with the antidiabetic compounds of the present invention.

[0108] Metabolic Conditions such as: Diabetes and Conditions Secondary to Diabetes, Hypertension, Angina pectoris, Dyslipidemia, Hypertriglyceridemia, Gout, Hyperlipoproteinemia, Hypercholesterolemia, Nephropathy and other renal diseases secondary to diabetes, Diabetic neuropathy, other insulin-resistance-related diseases, polycystic ovarian syndrome, glucocorticoid-induced insulin resistance.

[0109] Obesity, promote adipocyte differentiation and fat.

[0110] Hypertension, suppress or lower or cross endothelin-1 secretion by vascular endothelial cells and result in decreased blood pressure.

[0111] Lipid Disorders, been implicated in systemic glucose and lipid homeostasis.

[0112] Bone Disorders.

[0113] Female specific conditions where Formula 1 compounds can be used to inhibit excessive uterine bleeding in women and also to alleviate hormones disorders in menopausal women.

[0114] Male hormone disorders such as andropause related disorders.

[0115] Acne and other skin disorders associated with differentiation of epidermal cells as proliferative diseases of the skin.

[0116] CNS, Alzheimer's, Neuroinflammation, such as ischemic stroke, closed-head injury, and multiple sclerosis.

[0117] Chemotherapy, Cancer.

[0118] Inflammation/Immune disorders.

[0119] Ophthalmic, Macular Degeneration.

[0120] 3. Antiangiogenic

[0121] The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner.

EXAMPLES

Example 1

[0122] Dosage form with metformin and betaine anhydrous: Sachet comprising unit powder dosage form of 500 mg metformin and 2000 mg glycine betaine.

[0123] The dosage form of example 1 has been repeated excepted that metformin and glycine betaine are mixed together with a granulating agent, extruded and spheronized in beads of about 1 mm. The beads have been coated with eudragit, said eudragit being mixed in an organic solvent and sprayed on the beads, where after the beads are dried.

Example 2

[0124] This example illustrates combination therapy of a compound of Formula 1 and a metformin by oral administration.

[0125] Patients having NIDDM (Type II diabetes mellitus) are selected for therapy. The patients weigh between 70-100 kilograms. A compound of Formula 1 is orally administered in a dosage of 1 to 15 grams twice daily, more typically 100 mg/kg twice daily. For infants or children the doses suggested are lowered in a linear fashion based on body weight or surface area.

[0126] Half the patient population is administered metformin as well as a compound of Formula 1 using an effective dose of both agents. The other half of the patients are administered an effective dose of metformin. The patients are monitored for improvement in the manifestations of the disease and for side effects, such as body weight gain and signs of liver toxicity.

[0127] The combined compounds of the invention increased the patients' body's sensitivity to insulin and lowered glucose fasting levels.

[0128] The results indicate the administration of a combination of i) a compound of Formula 1 with ii) metformin increases the efficacy of either agent alone. The composition also provides concomitant decrease in the side effects of either agent alone.

Example 3

[0129] Capsule containing glyburide and betaine anhydrous: Sachet comprising unit powder dosage form of 1 mg glyburide and 1000 mg glycine betaine.

[0130] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily

apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

1. A pharmaceutical combination for treating diabetes mellitus, said combination comprising a therapeutically effective amount of metformin and a therapeutically effective amount of a pharmaceutically acceptable betaine.

2. (canceled)

3. The pharmaceutical combination of claim 1, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine and pharmaceutically acceptable salts thereof.

4. The pharmaceutical combination of claim 1, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine anhydrous, glycine betaine monohydrate and mixtures thereof.

5. The pharmaceutical combination of claim 2, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine and pharmaceutically acceptable salts thereof.

6. The pharmaceutical combination of claim 2, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine anhydrous, glycine betaine monohydrate and mixtures thereof.

7. The pharmaceutical combination of claim 1, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine is comprised between 1:10 and 10:1.

8. The pharmaceutical combination of claim 1, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine is comprised between 1:8 and 8:1.

9. The pharmaceutical combination of claim 1, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine is comprised between 1:5 and 5:1.

10. The pharmaceutical combination of claim 1, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine is greater than 1.

11. The pharmaceutical combination of claim 1, which comprises an oral controlled release form comprising the metformin.

12. The pharmaceutical combination of claim 11, in which the oral controlled release form comprises less than 3 g of metformin.

13. The pharmaceutical combination of claim 1, which comprises an oral controlled release form comprising less than 2.5 g of the metformin.

14. The pharmaceutical combination of claim 1, which comprises an oral controlled release form comprising less than 2 g of the metformin.

15. The pharmaceutical combination of claim 2, which comprises an oral controlled release form comprising the therapeutically effective amount of the metformin.

16. The pharmaceutical combination of claim 15, in which the oral controlled release form comprises a therapeutically effective amount of less than 3 g of the metformin.

17. The pharmaceutical combination of claim 2, which comprises an oral controlled release form comprising a therapeutically effective amount of less than 2.5 g of the metformin.

18. The pharmaceutical combination of claim 1, which comprises an oral controlled release form comprising a therapeutically effective amount of less than 2.5 g of the metformin.

19. The combination of claim 1, which comprises an oral controlled release form comprising pharmaceutically acceptable betaine.

20. The combination of claim 1, which comprises an oral controlled release form comprising the therapeutically effective amount of the pharmaceutically acceptable betaine.

21. The pharmaceutical combination of claim 3, which comprises a therapeutically effective amount of more than 1 g pharmaceutically acceptable betaine.

22. The combination of claim 1, which comprises an oral controlled release form comprising the therapeutically effective amount of more than 1.5 g of the pharmaceutically acceptable betaine.

23. The combination of claim 1, which comprises an oral controlled release form comprising the therapeutically effective amount of more than 2 g of the pharmaceutically acceptable betaine.

24. The pharmaceutical combination of claim 1, which has the form of at least one solid or semi-solid unit for oral administration.

25. The pharmaceutical combination of claim 24, in which the at least one solid or semi-solid unit form is selected from the group consisting of beads and particles comprising metformin, whereby said beads and particles are provided with a water insoluble polymer coating, said coating being enteric soluble.

26. The pharmaceutical combination of claim 24, in which the said at least one solid or semi-solid unit form is selected from the group consisting of beads and particles comprising pharmaceutically acceptable betaine, said beads and particles being provided with a water insoluble polymer coating, said coating being enteric soluble.

27. The pharmaceutical combination of claim 1, which has the form of at least one solid or semi-solid unit for oral administration, whereby the said at least one solid or semi-solid unit for oral administration is selected from the group consisting of beads and particles comprising metformin and pharmaceutically acceptable betaine, said beads and particles being provided with a water insoluble polymer coating, said coating being enteric soluble.

28. The pharmaceutical combination of claim 1, in which the therapeutically effective amount of the metformin and the therapeutically effective amount of the pharmaceutically acceptable betaine are placed in one single sealed bag.

29. The pharmaceutical combination of claim 28, in which each bag forms a unit dose comprising from 500 mg to 3000 mg metformin and from 500 mg to 6000 mg pharmaceutically acceptable betaine.

30. A method for treating a human suffering from diabetes mellitus, said method comprising the step of administering orally at least daily a pharmaceutical combination comprising a therapeutically effective amount of metformin and a therapeutically effective amount of a pharmaceutically acceptable betaine.

31. (canceled)

32. The method of claim 30, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine and pharmaceutically acceptable salts thereof.

33. The method of claim 30, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine anhydrous, glycine betaine monohydrate and mixtures thereof.

34. The method of claim 31, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine and pharmaceutically acceptable salts thereof.

35. The method of claim 31, in which the pharmaceutically acceptable betaine is selected from the group consisting of glycine betaine anhydrous, glycine betaine monohydrate and mixtures thereof.

36. The method of claim 30, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine of the administered pharmaceutical combination is comprised between 1:10 and 10:1.

37. The method of claim 30, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine of the administered pharmaceutical combination is comprised between 1:8 and 8:1.

38. The method of claim 30, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine of the administered pharmaceutical combination is comprised between 1:5 and 5:1.

39. The method of claim 30, in which the weight ratio therapeutically effective amount of metformin/therapeutically effective amount of pharmaceutically acceptable betaine of the administered pharmaceutical combination is greater than 1.

40. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising the metformin.

41. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising less than 3 g of metformin.

42. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising less than 2.5 g of the metformin.

43. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising less than 2 g of the metformin.

44. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising a therapeutically effective amount of less than 2.5 g of the metformin.

45. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising pharmaceutically acceptable betaine.

46. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising the therapeutically effective amount of the pharmaceutically acceptable betaine.

47. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising a therapeutically effective amount of more than 1 g pharmaceutically acceptable betaine.

48. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising the therapeutically effective amount of more than 1.5 g of the pharmaceutically acceptable betaine.

49. The method of claim 30, which comprises the step of administering at least daily an oral controlled release form comprising the therapeutically effective amount of more than 2 g of the pharmaceutically acceptable betaine.

50. The method of claim 30, in which the pharmaceutically acceptable betaine is administered before the therapeutic effective amount of the metformin being administered.

51. The method of claim 30, in which the therapeutic effective amount of the pharmaceutically acceptable betaine and the therapeutic effective amount of the metformin are simultaneously administered.

52. A method for modulating conditions associated with diabetes or diabetes-related disorders in a human, comprising administering orally to the human at least daily a pharmaceutical combination comprising a therapeutically effective amount of metformin and a therapeutically effective amount of a pharmaceutically acceptable betaine.

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