



No. 08-028928- -00004-0000

Fecha: 2009-07-01 16:45:32 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 78

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:



Patente de Invención.



Patente de Modelo de Utilidad.



Diseño Industrial.



Esquema de Trazado para Circuitos Integrados.



Marcas de Productos o Servicios.



Marca Colectiva.



Marca de Certificación.



Letra Comercial.

②

Número del expediente: 08-028.928

Solicitante: SB PHARMCO PUERTO RICO INC

SOLICITUD
PUBLICADA

Apoderado: CARLOS REYNALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: COMBINACIONES DE
ROSIGLITAZONA Y DONEPEZIL PARA MEJORAR LA FUNCION COGNITIVA.

Gaceta: 602

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual	
	Teléfono: 371 99 00 Fax: 373 08 18	Número 890.106.527-5	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95	C.C. ☒	NIT ☐
	Teléfono: (571)213 12 13 Fax: (571)612 19 79	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	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".

2

⑤ Comprobante de pago No. _____ Fecha _____

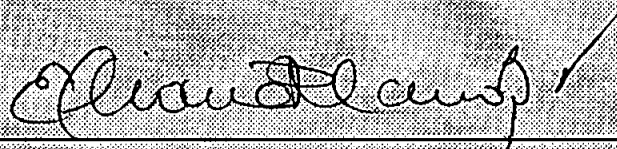
⑥ ANEXOS

- ☒ 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



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 028928 ✓
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMBINACIONES DE ROSIGLITAZONA Y
DONEPEZIL PARA MEJORAR LA FUNCION
COGNITIVA"
Solicitante : SB PHARMCO PUERTO RICO, INC
Opositora : PROCAPS S.A. ✓

Publicada en la Gaceta de la Propiedad Industrial
N° 602 del 31 de Marzo de 2009 ✓

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 y domiciliada en la ciudad de Barranquilla, 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 "**COMBINACIÓN DE ROSIGLITAZONA Y DONEPEZIL PARA MEJORAR LA FUNCIÓN COGNITIVA**", cuyo titular es **SB PHARMCO PUERTO RICO, INC**, 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 ROSIGLITAZONA. 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 19 de marzo de 2008 reivindicando prioridad bajo la solicitud US20050719353P del 2005-09-22; y US20050727377P del 2005-10-17; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009, cuya publicación internacional corresponde a la WO2007038112 del 2007-04-05.
- 2.2. La solicitud colombiana 08 028928 objeto de la presente oposición, se refiere a una composición farmacéutica que comprende tanto rosiglitazona o una sal farmacéuticamente aceptable de la misma como donepezil o una sal

farmacéuticamente aceptable del mismo que es de utilidad en el tratamiento o profilaxis de la enfermedad de Alzheimer u otras demencias y el deterioro cognitivo leve; la invención también se refiere a formas de dosificación orales que comprenden rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo.

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: WO2005074917 publicada el 18 de agosto de 2005.
- D2: WO0035437 publicada el 22 de junio de 2000.



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

2.5.El documento D1, particularmente en la descripción revela compuestos de fenserina útiles en la dirección o el tratamiento de diabetes y/o complicaciones, como la demencia vascular, y la resistencia de insulina, asociada con la diabetes donde los compuestos de fenserina son carbamatos que inhibe la actividad de acetilcolinesterasa. Como tal, según se define en las reivindicaciones, esta anterioridad D1 revela el uso de un tiazolidinediona (tal como rosiglitazona) en conjunto con donepezil (ver reivindicaciones 1, 2 y 11 de D1). Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6.Ahora bien, por su parte el documento D2 revela la utilización de un agente que mejora la sensibilidad de insulina de sistema nervioso central, que incluye el uso de una tiazolidinediona tal como rosiglitazona, ver reivindicaciones 6 y 7 para el tratamiento de la enfermedad de Alzheimer, por lo que la materia revelada en D2, en combinación con la materia de D1, cualquier persona versada en la materia puede llegar de manera obvia y evidente a lo que pretende la presente solicitud.

2.7. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD y en combinación con lo que dicta el documento D2 la presente carece de ALTURA o NIVEL INVENTIVO.

2.8.En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 028928 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

2.9.1. **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, 22 de septiembre de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un compuesto farmacéutico que combine un tiazolidinediona (tal como rosiglitazona) en conjunto con donepezil, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- “Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.” A la fecha de prioridad, 22 de septiembre de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente al uso de rosiglitazona con la adición de donepezil para el tratamiento de la enfermedad de Alzheimer, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.3. **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



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.10. 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 los tres requisitos de patentabilidad.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMBINACIÓN DE ROSIGLITAZONA Y DONEPEZIL PARA MEJORAR LA FUNCIÓN COGNITIVA”**, cuyo titular es **SB PHARMCO PUERTO RICO, INC**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009.

3. PRUEBAS

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

- D1: WO2005074917 publicada el 18 de agosto de 2005.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

- D2: WO0035437 publicada el 22 de junio de 2000.

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.

5. ANEXOS

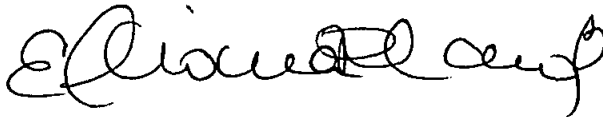
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

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: WO2005074917 publicada el 18 de agosto de 2005.
 - D2: WO0035437 publicada el 22 de junio de 2000.

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.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2.

RECIBO OFICIAL DE CAJA : 09 - 47,637
FECHA : JULIO 1 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-028928- -00004-0000

Fecha: 2009-07-01 16:45:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 78

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	104964941	11/06/2009	861,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	111824263	14/05/2009	861,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	287,000.00
	TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



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: 08-28928, titulada "**COMBINACION DE ROSIGLITAZONA Y DONEPEZIL PARA MEJORAR LA FUNCION COGNITIVA**", cuyo titular es **SB PHARMCO PUERTO RICO INC.**, publicada en la gaceta No. 602 del 31 de marzo de 2009.

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 administrativa y judicialmente 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 10 días del mes de Junio de 2009.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Aceptor:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

LA PRESENTE DILIGENCIA
SE PRACTICA A PETICION
DE PARTE INTERESADA

NOTARIA PRIMERA DEL CIRCULO
DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO

Ante el Notario Primero de Barranquilla Compareció:

Valle Tanaka Tallekama ✓

Identificado con: 0016251923 de Palmeria (valle)
declaro que es cierto el contenido del documento
anterior y suya la firma.
Barranquilla,

11 JUN. 2009

[Handwritten signature]



NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL

Este memorial dirigido a Super Intendencia de Industria y Comercio ✓

fué presentado personalmente ante el suscrito notario por Elicene Isaacs

Moiera Bohaguer

Identificado C.C. 51975664 Bogota

T.P. de Abogado No. 83823

Chia 01 JUL 2009

[Handwritten signature]





***** 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
04*****

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 *****

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

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 E R T I F I C A

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



***** Pag. 2
CAMARA DE COMERCIO
DE BARRANQUILLA
04*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B. - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-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; d) 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. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) 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; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, 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, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

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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 o 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 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		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde 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 representacion 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, disistir 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

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



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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 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

***** CONTINUA *****

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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:

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, 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	*****
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.	

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Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

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. 124 del 29 de Marzo de 1999 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 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. 127 del 22 de Marzo de 2000 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 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Lozada Villareal Milena	CC.*****32,748,111

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 condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo
Organo Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIBLES 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
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 NANAKA
TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----

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



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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: EI 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,-----
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 O N T I N U A *****

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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.

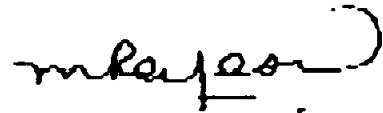
C E R T I F I C A

Que su última Renovación fue el: 27 de Marzo de 2009.

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 despues de la correspondiente inscripción, siempre 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.



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Organization
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WO 2005/074917 A1

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60/540,722 30 January 2004 (30.01.2004) US

(71) Applicant (for all designated States except US): **AX-ONYX, INC.** [US/US]; 500 7th Avenue, 10th Floor, New York, NY 10018 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BRUINSMA, Gosse** [NL/NL]; Middelstegegracht 87H, NL-2312 TT Leiden (NL).

(74) Agents: **DORLAND, G.**, Scott et al.; Traskbritt, P.O. Box 2550, Salt Lake City, UT 84110 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR TREATMENT OF COMPLICATIONS OF DIABETES

(57) Abstract: Phenserine compounds and pharmaceutically acceptable salts thereof are found to be useful in the management or treatment of diabetes and/or complications, such as vascular dementia, and insulin resistance, associated with diabetes. The phenserine compounds of the invention are carbamates that inhibit the activity of acetylcholinesterase.

WO 2005/074917 A1

METHODS FOR TREATMENT OF COMPLICATIONS OF DIABETES

5

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/540,722, filed January 30, 2004, the entirety of which is incorporated by this reference.

10

TECHNICAL FIELD

The invention relates to pharmaceutical compounds generally and, more particularly, to various methods and compositions for the treatment of diabetes and associated sequelae.

15

BACKGROUND

Physostigmines, also called "eserines," are known cholinesterase inhibitors. These compounds are also useful in the treatment of glaucoma, Myasthenia Gravis, and Alzheimer's disease, and as antidotes against poisoning with organophosphates.

20

The natural isomer of physostigmine has blocking properties, as well as, agonist properties at the neuromuscular acetylcholine receptor (AChR). By contrast, (+)-physostigmine shows only negligible inhibition of cholinesterase (ChE). *See* Brossi et al., *FEBS Lett.*, Vol. 201, pages 190-192 (1986).

25

Even though (+)-physostigmine has only negligible ChE inhibitory activity, it is effective as a protective pretreatment drug against multiple lethal doses of sarin, *see* Albuquerque et al, *Fundam. Appl. Caltoxicol.*, Vol. 5, pages 182-203 (1985). The observed beneficial protection appears to be due to direct interactions of the carbamates with the postsynaptic nicotinic AChR. The protective effectiveness of the carbamates against organophosphates appears to be related to the direct ability of the carbamates to decrease the hyperactivation caused by accumulation of the neurotransmitter.

30

Diabetes mellitus affects about 17 million citizens of the United States and is the 5th leading cause of death by disease in the United States. Direct and indirect

medical expenditures attributable to diabetes were estimated at 132 billion US dollars (see Hogan *et al.*, (2003) Economic costs of diabetes in the US in 2002, *Diabetes Care*, 26(3):917-932). Direct medical expenditures alone totaled 91.8 billion US dollars and comprised 23.2 billion US dollars for diabetes care, 24.6 billion US dollars for chronic complications attributable to diabetes, and 44.1 billion US dollars for excess prevalence of general medical conditions (*Id.*). Hogan *et al.* report that in 2002, diabetes more than doubled the cost of health care in the United States.

Thus, diabetes imposes a substantial economic burden to society and, in particular, to those individuals with diabetes and their families. Hogan *et al.* stated that "[e]liminating or reducing the health problems caused by diabetes through factors such as better access to preventive care, more widespread diagnosis, more intensive disease management, and the advent of new medical technologies could significantly improve the quality of life for people with diabetes and their families while at the same time potentially reducing national expenditures for health care services and increasing productivity in the U.S. economy" (*Id.* at 917). Therefore, a long felt need exists for improved disease management, particularly, new and improved treatments.

Diabetes mellitus is also considered a risk factor for the development of vascular dementia, such as Alzheimer's disease (AD). Insulin's role as a neuromodulator in the brain is beginning to emerge, raising a question regarding its significance for AD. Insulin dysregulation may contribute to AD pathology through several mechanisms including decreased cortical glucose utilization particularly in the hippocampus and entorhinal cortex; increased oxidative stress through the formation of advanced glycation end-products; increased Tau phosphorylation and neurofibrillary tangle formation; and increased β -amyloid ($A\beta$) aggregation through inhibition of insulin-degrading enzyme. Thus, effective treatment of diabetes mellitus may also prevent or slow the onset of diabetes associated sequelae.

It has been reported that erythrocyte membrane protein glycosylation increases by 3.4 fold in diabetes (Dave, Patel, Katyare, (2001) *Indian J. Clinical Biochem.*, 16(1):81-88). However, insulin or sulfonylurea treatment was not reported to reduce the extent of glycosylation (*Id.*). These authors also reported that

erythrocyte membrane acetylcholinesterase activity decreased only in the sulfonylurea treated group (*Id.*). In particular, the Vmax of acetylcholinesterase decreased only in the sulfonylurea treated group (*Id.*). While, serum butyrylcholinesterase activity was relatively low in the diabetic and insulin treated diabetic groups, the diabetic state exhibited a decreased Vmax for components I and II of serum butyrylcholinesterase (*Id.*). Further, these authors report that *in vitro* incubation with insulin differentially affected the Na plus, K plus-ATPase and serum butyrylcholinesterase activities (*Id.*).

In addition, erythrocyte membrane acetylcholinesterase activity has been reported to be significantly decreased in insulin-dependent diabetes mellitus, with activity negatively correlating with the fasting blood glucose level (*see* Suhail and Rizvi, (1989), Erythrocyte membrane acetylcholinesterase in type 1 (insulin-dependent) diabetes mellitus, *Biochem. J.*, 259:897-899). This report suggested that the number of active enzyme molecules (AChE) in diabetes was reduced.

Previous studies have also demonstrated that PKC-dependent processes are involved in both ACh-induced Ca²⁺-signaling and insulin secretion. For example, the neurotransmitter acetylcholine (ACh) increases cytosolic free calcium and is thought to stimulate insulin secretion from pancreatic beta-cells by activating receptors coupled to phosphatidylinositol breakdown, thereby, generating IP₃ and diacylglycerol, which activates protein kinase C (PKC).

Finally, it has been reported that ACh plays a role in the release of hepatic insulin sensitizing substance and the treatment of insulin resistance. This report stated that administration of ACh by a non-liver specific mechanism (intravenous) did not reverse insulin resistance induced by surgical denervation.

Thus, the literature provides indefinite and conflicting reports of potential links between acetylcholine, acetylcholinesterase and diabetes, including types I and II.

Accordingly, a need in the art exists for selective agents, active *in vivo*, having an acceptable therapeutic window, and minimal side effects, for treating diabetes mellitus and associated complications.

DISCLOSURE OF INVENTION

The invention relates to a method of treating a subject comprising administering an effective amount of a phenserine compound or phenserine-like compound of the invention or an effective amount of a pharmaceutical composition according to the invention to a subject, e.g., a mammal, such as a human, thought to be in need of such treatment.

The invention also relates to a method of treating diabetes mellitus and/or associated sequelae, such as reducing the risk of vascular dementia associated therewith or delaying the onset of such a complication, comprising treating a subject with an effective amount of a phenserine compound, for example, phenserine, ((-)-N-phenylcarbamoyl eseroline), and/or the (+) isomer of phenserine, and/or a pharmaceutically acceptable salt or ester thereof. A pharmaceutically acceptable salt is preferably a tartrate, a phosphate, or a fumarate salt.

The invention also relates to a method of treating diabetes mellitus and/or associated sequelae by treating a subject with a phenserine-like compound, such as donepezil, galantamine, rivastigmine and/or tacrine. Phenserine and/or phenserine-like compounds may be used to prevent or reduce insulin resistance and/or to treat dementia associated with A β protein and neurofibrillary tangles.

The invention also relates to pharmaceutical compositions comprising an effective amount of a phenserine compound and/or phenserine-like compound and/or a pharmaceutically acceptable salt or ester thereof, and a method for the treatment of diabetes mellitus associated sequelae and/or the risk of vascular dementia.

The invention also relates to pharmaceutical compositions comprising an effective amount of a phenserine compound and/or phenserine-like compound and/or a pharmaceutically acceptable salt or ester thereof, and a method for the treatment of diabetes mellitus associated sequelae and/or insulin resistance.

The invention also relates to a method according to the invention comprising administering to the subject an effective amount of a phenserine compound and/or phenserine-like compound of the invention or a pharmaceutical composition according to the invention, in combination with a hypoglycemic agent selected from

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the group consisting of sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, and/or mixtures thereof.

The invention also relates to a method of treating a diabetic condition or complication, for example, a subject's blood glucose levels (hyperglycaemia or hypoglycaemia), carbohydrate intake levels, responsiveness or non-responsiveness to hypoglycemic agents, diabetic neuropathy, diabetic retinopathy, vascular dementia, kidney function, pregnancy, ketone levels, hyperlipidaemia, and/or coronary artery disease, by administering to the subject an effective amount of a phenserine compound and/or phenserine-like compound of the invention or a pharmaceutical composition according to the invention.

The invention further relates to a use of a pharmaceutical compound of the invention in the manufacture of a medicament for the treatment of diabetes and/or diabetes associated sequelae. The invention also relates to the manufacture of a pharmaceutical composition comprising a phenserine compound and/or a phenserine-like compound and/or a pharmaceutically acceptable salt thereof for the treatment of diabetes mellitus and/or associated sequelae, such as the risk of vascular dementia and/or insulin resistance.

BEST MODES FOR CARRYING OUT THE INVENTION

Surprisingly, the phenserine compounds and phenserine-like compounds according to the present invention are useful in the management, treatment and/or prevention of diabetes and/or complications associated with diabetes. The phenserine compounds and other compounds of the invention produce fewer undesirable side effects than other carbamate analogues known in the art. Further, the phenserine compounds are more brain-targeted versus the rest of the body and are more rapidly cleared from the blood than other AChEIs. Accordingly, the method for treating diseases, such as diabetes and/or associated sequelae (e.g., vascular dementia, insulin resistance, hyperglycemia, responsiveness or non-responsiveness to hypoglycemic agents, and/or diabetic neuropathy) using compounds according to the present invention represent a significant advance over the prior art.

Diabetes mellitus is a disease in which the body does not produce and/or properly use insulin. Improper use of insulin (*e.g.*, insulin resistance) is one of the underlying causes of type II diabetes and may lead to type I diabetes if the pancreatic cells fail due to the insulin secretion demand placed on them. Insulin resistance occurs when the body fails to respond properly to the insulin it already produces. Ninety percent of people with type II diabetes are thought to be insulin resistant to some extent. Furthermore, insulin resistance may affect more than 60 million Americans, with one in four of them likely to develop type II diabetes. Additionally, research indicates that insulin resistance is associated with an increased risk for heart disease and stroke.

Insulin is a hormone that is needed to convert sugar, starches and other food into energy needed for daily life. The most common forms of diabetes are type I (also referred to as "insulin dependent diabetes" or "juvenile diabetes") or type II diabetes (also referred to as "non-insulin dependent diabetes" or "adult on-set diabetes"), although, other classifications exist, for example, diabetes bronze, which typically results from pancreatic damage caused by iron deposition, and gestational diabetes, which typically appears during pregnancy and disappears after birth.

Currently, there are five distinct classes of hypoglycemic agents available for the treatment of type II diabetes, each class displaying unique pharmacologic properties. These classes are the sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors. The invention provides another class of agents, (*e.g.*, phenserine compounds and/or phenserine-like compounds), useful in the treatment of diabetes, such as type II diabetes. The phenserine compounds and/or phenserine-like compounds may be administered alone or in combination with one or more hypoglycemic agents.

Acetylcholinesterase inhibitors, such as the phenserine and phenserine-like compounds, may be useful in the treatment of insulin resistance. However, insulin resistance develops in the liver, therefore, it may be presumed to be preferable to minimize the diffusion of the acetylcholine esterase agonist into the spinal cord and brain. In particular, administration of ACh targeted to the liver is a logical choice, as opposed to the brain and spinal cord. Thus, the development of insulin resistance

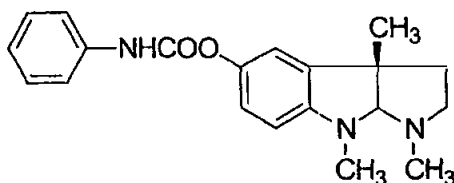
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in the liver teaches away from the use of the compounds of the present invention, as the compounds (*e.g.*, phenserine) are more brain-targeted versus the rest of the body and are more rapidly cleared from the blood than other AChEIs.

As used herein, "treatment of diabetes" and the "management of diabetes,"
5 are used interchangeably and does not necessarily mean a complete cure. It means that the symptoms or complications of the underlying disease are reduced, and/or that one or more of the underlying cellular, physiological, or biochemical causes or mechanisms causing the symptoms or complications are reduced. It is understood that "reduced," as used in this context, means relative to the untreated state of the
10 disease, including the molecular state of the disease, not just the physiological state of the disease. The term treatment of diabetes also includes within its scope the prophylactic treatment of an asymptomatic subject, such as a mammal, particularly a human, thought to be at risk of developing diabetes.

As used herein, "effective amount" means an amount of an active ingredient
15 administered to the patient, which will be effective to improve, prevent, delay the onset of, or treat the disease condition or associated complications in the patient.

Phenserine, (-)-N-phenyl carbamoylescrolone, has the structure:

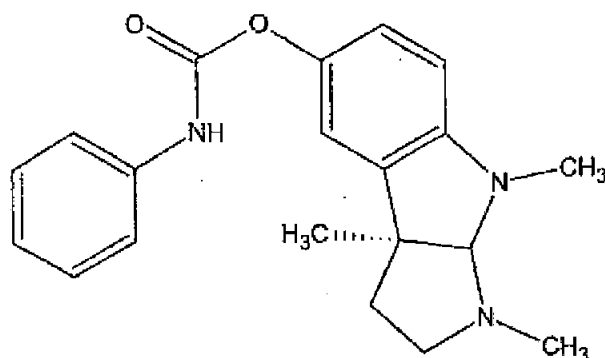


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Phenserine, ((-)-N-phenylcarbamoyl eseroline), is a carbamate analog of physostigmine (Phy), which is a long-acting inhibitor of cholinesterase. Phenserine was first prepared by Polonovski, (1916), *Bull. Soc. Chim.* 19, 46-59, and technical details were summarized by Beilstein, *Handbuch der Organischen Chemie*, 4th edn.
25 vol 23. Springer Verlag, Berlin, pp 333 (1954)). It was reported in the literature without any stated practical use.

In addition, the phenserine compounds of the present invention include the (+) isomer of phenserine, which has the following structure:

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(3aS)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl phenylcarbamate

The phenserine compounds of the invention may be synthesized, for example, by using processes known in the art. For example, U.S. Patents 6,495,700, 5,409,948, 5,171,750, 5,378,723, and 5,998,460, and International Patent Publication WO 03/082270 A1, all of which are hereby incorporated by reference in their entirety, describe the preparation of phenserine compounds of the invention and assays that may be used to test compounds of the invention. The phenserine compounds of the invention include carbamates having specificity for the inhibition of acetylcholinesterase and/or inhibition of β -AAP synthesis, including, but not limited to, (-)-N-phenylcarbamoyl eseroline (which may also be referred to as (3aR)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl phenylcarbamate or phenserine); (3aS)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl phenylcarbamate or Posiphen™; (-)-2'-methylphenylcarbamoyleseroline; (-)-2',4'-dimethylphenylcarbamoyleseroline; (-)-4'-methylphenylcarbamoyleseroline; (-)-2'-ethylphenylcarbamoyleseroline; (-)-phenylcarbamoyleseroline; (-)-(-)-2',4',6'-trimethylphenylcarbamoyleseroline; (-)-2'-chlorophenylcarbamoyleseroline; (-)-2',6'-dichlorophenylcarbamoyleseroline; (-)-physovenol; (-)-5-O-(2'-methylphenylcarbamoyl)physovenol; (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno[2,3-b]indole-5-ol butyl carbamate; (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno[2,3-b]indole-5-ol heptylcarbamate; (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno[2,3-b]indole-5-ol phenylcarbamate; (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno[2,3-b]indole-5-ol

2'-methylphenylcarbamate;

(-)-3,3a,8,8a-tetrahydro-3a,8-dimethy-2H-thieno[2,3-b]indole-5-ol

2'-isopropylphenylcarbamate; (-)-thiaphysovenine, (-)-Phenyl-thiaphysovenine;

(-)-2',4'-dimethylphenyl-thiaphysovenine and/or pharmaceutically acceptable salts

5 thereof. Additional compounds that may be used in the invention include

(3aS)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrol[2,3-b]indol-5-yl

N-4'-isopropylphenylcarbamate;

(3aR)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrol[2,3-b]indol-5-yl

N-4'-isopropylphenylcarbamate.

10 The phenserine-like compounds of the invention include functionally related compounds, such as donepezil, galantamine, rivastigine and/or tacrine. These compounds may be used to treat diabetes, including prevention or reduction in insulin resistance and/or to treat dementia associated with A β protein and neurofibrillary tangles. In addition, other AChE inhibitors are known in the art and
15 may also be used according to the methods of the present invention.

Salts, esters and the free base of the compounds of the invention are within the scope of the present invention and are included by reference to one or more compound. Hence, reference to phenserine or donepezil includes pharmaceutically acceptable salts and/or esters thereof. Pharmaceutically acceptable salts are known
20 in the art, for example, salts of phenserine, and include, but are not limited to, tartrate, phosphate, and fumarate salts.

Potential cholinesterase agents can be evaluated for potency *in vitro* by testing the agents against electric eel and human red blood cell acetylcholinesterase (AChE) and human plasma butyrylcholinesterase, (BChE) (*see*
25 *also*, U.S. Patents: 6,495,700; 5,409,948; 5,171,750; 5,378,723; and 5,998,460).

The effect of the cholinesterase agents of the invention may be tested for their potency in the reduction of insulin resistance using methods known in the art, for example, as described in U.S. Patent 5,561,165, RIST, ITT and the HIEC tests (*see*, Reid *et al.*, (2002), Comparison of the rapid insulin sensitivity test (RIST), the
30 insulin tolerance test (ITT), and the hyperinsulinemic euglycemic clamp (HIEC) to measure insulin action in rats, *Can. J. Physiol. Pharmacol.* 80:811-818). Subjects thought to have insulin resistance may be tested using methods known in the art, for

example, by the glucose tolerance test, three hour glucose tolerance test, or other tests known in the art.

The phenserine and phenserine-like compounds of the invention are also useful in the treatment of vascular dementia. In an exemplary embodiment, one or
5 more phenserine compound and/or phenserine-like compound is used to treat the presence and/or accumulation of the A β protein associated with vascular dementia and/or neurofibrillary tangles.

Two substrates of insulin-degrading enzyme (IDE), amyloid β -protein (A β) and insulin, are critically important in the pathogenesis of Alzheimer's Disease and
10 type II diabetes mellitus, respectively. IDE has been identified as a principal regulator of A β levels in neuronal and microglial cells and a mutant IDE allele has been associated with hyperinsulinemia and glucose intolerance in a rat model of type II diabetes (Farris *et al.* (2002) Insulin-degrading enzyme regulates the levels of insulin, amyloid β -protein, and the β -amyloid precursor protein intracellular domain
15 in vivo, *Proc. Natl. Acad. Sci. USA* 100(7):4162-4167). Human genetic studies have implicated the IDE region of chromosome 10 in both AD and type II diabetes. *Id.*

Type II diabetes may be a risk factor for dementia, but the associated pathological mechanisms remain unclear. However, diabetes is increasingly associated with total dementia, Alzheimer's disease, and vascular dementia.
20 Individuals with both type II diabetes and the APOE epsilon4 allele have nearly a doubled risk for AD compared with those with neither risk factor. Subjects with type II diabetes and the epsilon4 allele have a higher number of hippocampal neuritic plaques and neurofibrillary tangles in the cortex and hippocampus, and they have a higher risk of cerebral amyloid angiopathy. Thus, the association between
25 diabetes and AD is particularly strong among carriers of the APOE epsilon4 allele (Peila *et al.*, (2002) Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study, *Diabetes* 51(4):1256-62). The present invention provides methods of treating diabetes, for example, insulin resistance and/or neurological conditions associated with diabetes.

30 Compositions within the scope of the invention include compositions wherein the active ingredient is contained in an effective amount to achieve its intended purpose. Effective concentrations may range from 0.001 wt % to 1.0 wt %.

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The compounds can be administered in any pharmaceutically acceptable amount, for example, in amounts ranging from 0.001 gram to about 1 gram per kilogram of body weight. Based on the information which is presented herein, the determination of effective amounts is well within the skill of the ordinary practitioner in the art. In addition, the ordinary practitioner may formulate the dosage regimen as appropriate for the diabetic condition being treated. For example, the compositions of the invention may be administered orally prior to carbohydrate intake, at times of hypoglycemia or hyperglycemia. Where a compound of the invention is administered prior to carbohydrate intake, the compound may be administered about 3 times a day.

The compounds are generally used in pharmaceutical compositions (wt %) containing the active ingredient with a carrier, vehicle, diluent and/or excipient in the composition in an amount of about 0.1 to 99 wt % and preferably about 25-85 wt %. Pharmaceutical compositions may be formulated using carriers, diluents and/or excipients known in the art, for example, *see* REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Ed. (1990, Mack Publishing Co., Easton, Pa.). The compounds may be administered in any desired form, including parenterally, orally, injection, transdermally or by suppository using known methods.

Either fluid or solid unit dosage forms can be readily prepared for oral administration. For example, the active compounds can be admixed with conventional ingredients such as dicalcium phosphate, magnesium aluminum silicate, magnesium stearate, calcium sulfate, starch, talc, lactose, acacia, methyl cellulose and functionally similar materials as pharmaceutical excipients or carriers. A sustained release formulation may optionally be used where appropriate or desirable. Capsules may be formulated by mixing the compound with a pharmaceutical diluent which is inert and inserting this mixture into a hard gelatin capsule having the appropriate size. If soft capsules are desired, a slurry of the compound with an acceptable vegetable, light petroleum or other inert oil can be encapsulated by forming into a gelatin capsule.

Suspensions, syrups and elixirs may be used for oral administration of fluid unit dosage forms. A fluid preparation including oil may be used for oil soluble forms. A vegetable oil such as corn oil, peanut oil or sunflower oil, for example,

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together with flavoring agents, sweeteners and any preservatives produces an acceptable fluid preparation. A surfactant may be added to water to form a syrup for fluid unit dosages. Hydro-alcoholic pharmaceutical preparations may be used having an acceptable sweetener (such as sugar, saccharin, or a biological sweetener, preferably a low carbohydrate sweetener, such as manitol or sorbitol) and a flavoring agent in the form of an elixir.

Pharmaceutical compositions for parenteral and suppository administration can also be obtained using techniques standard in the art. In an exemplary embodiment, the compounds of the invention are administered as pharmaceutical agents suitable for oral administration. In another exemplary embodiment, the compounds of the invention may be administered by injection in an appropriate vehicle such as sesame oil.

The pharmaceutical carriers acceptable for the purposes of this invention include all art recognized carriers that do not exhibit a significant adverse affect on the drug, the host, or the material comprising the drug delivery device or vehicle. Suitable pharmaceutical carriers include sterile water, saline, sorbitol, sucralose, manitol, manitol in water or saline condensation products of castor oil and ethylene oxide combining about 30 to 35 moles of ethylene oxide per mole of castor oil, liquid acid, lower alkanols, oils such as corn oil, peanut oil, sesame oil and the like, with emulsifiers such as mono- or di-glyceride of a fatty acid; or a phosphatide, e.g., lecithin, and the like; glycols, polyalkylene glycols, aqueous media in the presence of a suspending agent, for example, sodium carboxymethyl cellulose, sodium alginate, poly(vinylpyrrolidone), and the like, alone, or with suitable dispensing agents such as lecithin, polyoxyethylene stearate, and the like. The carrier may also contain adjuvants such as preserving agents, stabilizing agents, wetting agents, emulsifying agents and the like together with penetration enhancer and the compounds of this invention.

The effective dose for mammals may vary due to such factors as age, weight, activity level or condition of the subject being treated. Typically, an effective dosage of a compound according to the present invention is about 1 to 800 milligrams when administered by either oral or rectal dose from 1 to 3 times daily. This is about 0.002 to about 50 milligrams per kilogram of the subject's weight

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administered per day. Preferably about 10 to about 300 milligrams are administered orally or rectally 1 to 3 times a day for an adult human. The required dose is usually considerably less when administered parenterally. Preferably about 0.01 to about 150 milligrams may be administered intramuscularly, one to three times a day
5 for an adult human.

In an exemplary embodiment, the method according to the invention comprises administering an effective amount of a phenserine compound and/or phenserine-like compound of the invention and/or an effective amount of a pharmaceutical composition according to the invention to a subject, such as a
10 mammal, thought to be in need of such treatment. For example, a subject that may benefit from the present invention is a subject suffering from insulin resistance, diabetes and/or vascular dementia. In another exemplary embodiment, the method according to the invention comprises administering to a subject an effective amount of a phenserine compound and/or phenserine-like compound of the invention and/or
15 a pharmaceutical composition according to the invention, in combination with a hypoglycemic agent selected from the group consisting of sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors or mixtures thereof. In yet another exemplary embodiment, the invention provides a method of preparing a pharmaceutical useful in the treatment of diabetes and/or
20 vascular dementia.

In another exemplary embodiment, the invention provides a prophylactic treatment, for example, a prophylactic treatment to reduce the risk of or delay the onset of gestational diabetes or to treat insulin resistance prior to the onset of diabetes. Treatment of insulin resistance prior to the onset of diabetes, or prior to
25 the onset of type I diabetes in a type II diabetic patient, may be particularly advantageous in elderly subjects. Elderly subjects may be experiencing cognitive decline and may potentially experience more than one benefit, for example, the cognitive improvement from the cholinergic effects of a phenserine compound and/or phenserine-like compound, a decrease in insulin resistance, and/or decreased
30 accumulation of A β . Elderly subjects include humans greater than about 45 years of age, greater than about 50 years of age, greater than about 55 years of age, greater than about 60 years of age, greater than about 65 years of age, greater than about 70

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years of age, greater than about 75 years of age, and greater than about 80 years of age.

In an exemplary embodiment, a phenserine compound and/or phenserine-like compound is administered in combination with an increase in insulin levels. For example, the phenserine compound and/or phenserine-like compound may be administered in combination with a bolus of insulin, either an insulin injection or the action of an agent which stimulates the release of insulin. In another exemplary embodiment, the phenserine compound and/or phenserine-like compound is administered prior to each meal.

As will be recognized by a person of ordinary skill in the art, treatment of diabetes, such as type I or II diabetes, is affected by numerous conditions. For example, the subject's blood glucose levels (hyperglycaemia or hypoglycaemia), carbohydrate intake levels, response to hypoglycemic agents, diabetic neuropathy, diabetic retinopathy, vascular dementia, kidney function, pregnancy, ketone levels, hyperlipidaemia, and coronary artery disease.

Mice useful in the study of type I diabetes may be obtained, for example, from The Jackson Laboratory Type 1 Diabetes Repository (T1DR) (stocks are available online at jax.org/t1dr/holdings.html). Protocols for the study of diabetes using mouse models are known in the art, for example, as described in Leiter, E.H. Current Protocols in Immunology §§ 15.9.1-15.9.23 (John Wiley & Sons, Inc. eds. 1997). A mouse model for type II diabetes has been described by Fernandez *et al.*, (2001) Functional inactivation of the IGF-I and insulin receptors in skeletal muscle causes type 2 diabetes, *Genes Dev.* 15(15):1926-34.

Without wishing to be bound by any theory, the phenserine compounds and/or phenserine-like compounds of the invention are believed to inhibit acetylcholinesterase activity, increasing acetylcholine levels, thereby effecting utilization of insulin by a subject. In addition, compounds of the invention reduce neurofibrillary tangle formation and decrease β -amyloid aggregation, thereby reducing the risk of developing vascular dementia (*e.g.*, cerebral amyloid angiopathy), which is associated with diabetes.

The presence of insulin in the blood elicits a hepatic parasympathetic reflex, stimulating release of ACh in the liver. The release of ACh releases nitric oxide,

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which acts to control the sensitivity of skeletal muscle to insulin through the action of a liver released hormone, the hepatic insulin sensitizing substance (HISS). HISS selectively stimulates glucose uptake and storage as glycogen in tissues including skeletal muscle. In the absence of HISS, muscle cells are resistant to insulin and insulin driven storage of glucose by skeletal muscle is reduced.

HISS release in response to insulin is affected by the fasting state of the subject. Specifically, in the fasting state HISS release is minimal and insulin produces a minimal metabolic effect. Following a meal, the parasympathetic reflex mechanism is amplified, allowing release of HISS and more efficient utilization of insulin for the storage of glucose in skeletal muscle.

Decreased release of HISS may result in severe insulin resistance, which may be referred to as HISS-dependent insulin resistance ("HDIR"). In the absence of HISS, the pancreas is required to secrete substantially larger amounts of insulin to compensate for the resistance. Persistent insulin resistance is a leading cause of type II diabetes (non-insulin dependent diabetes mellitus) and may lead to a complete exhaustion of the pancreas, thus requiring the patient to resort to insulin injections.

The phenserine compounds and/or phenserine-like compounds of the invention provide the ability to reduce insulin resistance, thereby providing a treatment for diabetes. Further, the compounds of the invention may be used to prevent cognitive disorders frequently associated with diabetes or reduce the risk of vascular dementia.

Example I

Experimental Protocol for Determining Effect on Insulin Resistance:

Test animals, for example, non-obese diabetic mice, are anesthetized and an arterial-venous shunt is introduced into the animal according to procedures known in the art. The arterial-venous shunt allows for blood sampling and infusion of test compounds.

Baseline blood glucose levels are established following surgery. Insulin is then introduced into the animal and glucose infused so as to maintain a steady glucose level throughout the period of insulin activity. By measurement of the

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glucose infusion rate throughout the experiment, the effect of the insulin is measured.

The compounds are tested by introducing the test compound at the appropriate time relative to the insulin administration and measuring the effect on glucose infusion. The compounds of the invention increase the rate of glucose
5 infusion relative to control animals.

For example, phenserine administered approximately 30 minutes prior to the administration of insulin is found to increase the rate of glucose infusion. Thus, a phenserine compound and/or phenserine-like compound is found to reduce insulin
10 resistance and increases the effectiveness of the administered insulin.

Example II

Blood glucose levels are established in fasting subjects. A predetermined dose of insulin is then administered to the patients followed by feeding the patients
15 meal having a set carbohydrate content. Blood glucose levels are monitored before, during and for at least 4 hours following administration of the insulin.

The patients are subsequently fasted and the experiment repeated with administration of the test compound prior to administration of the insulin. Comparison of the blood glucose levels for the subjects with and without the test
20 compound is performed to determine the effect of the test compound on insulin utilization by the patient.

Care is taken to avoid hypoglycemic episodes and occurrence of a hypoglycemic episode, in a subject which would not normally experience such an episode, may be taken as evidence of the compounds effect on insulin resistance.
25

Example III

β -APP synthesis may be measured *in vitro* or *in vivo* by methods known in the art. For example, by an ELISA assay or a Western. The test compound may be administered to a subject for *in vivo* testing and β -APP levels assayed at various time
30 points.

Alternatively, cells may be cultured in the presence of a pulse of a labeled amino acid, the label washed off, and the test compound applied to the cells. Label

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incorporated into the β -APP protein is then quantitated to determine the effect of the compound on the synthesis of β -APP.

The effect of the test compound on protein synthesis or protein stability may also be determined by other methods known in the art.

5 All references, including publications, patents, and patent applications, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

10 While this invention has been described in certain embodiments, the present invention can be further modified within the spirit and scope of this disclosure. This application is therefore intended to cover any variations, uses, or adaptations of the invention using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within known or customary practice in the art to which this invention pertains and which fall within the limits of
15 the appended claims.

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CLAIMS

What is claimed is:

1. A method for treating diabetes in a subject, said method comprising:
 5 admixing at least one phenserine compound or phenserine-like compound, and salts or esters thereof, and a pharmaceutically acceptable diluent, carrier or excipient to form a medicament; and
 administering the medicament to the subject, thereby treating diabetes in said subject.
- 10 2. The method according to claim 1, wherein the phenserine compound is selected from the group consisting of (-)-N-phenylcarbamoyl eseroline, (3aS)-1,3a,8-trimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl phenylcarbamate; (-)-2'-methylphenylcarbamoyleseroline,
 15 (-)-2'-4'-dimethylphenylcarbamoyleseroline, (-)-4'-methylphenylcarbamoyleseroline, (-)-2'-ethylphenylcarbamoyleseroline, (-)-phenylcarbamoyleseroline, (-)-(-)-2',4',6'-trimethylphenylcarbamoyleseroline, (-)-2'-chlorophenylcarbamoyleseroline, (-)-2',6'-dichlorophenylcarbamoyleseroline, (-)-physovenol, (-)-5-O-(2'-methylphenylcarbamoyl)physovenol, (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno-[2,3-b]indole-5-ol butyl carbamate, (-)-3, 3a, 8, 8a-tetrahydro-3a, 8-dimethyl-2H-thieno[2,3-b]indole-5-ol heptylcarbamate,
 20 (-)-3,3a,8,8a-tetrahydro-3a,8-dimethyl-2H-thieno[2,3-b]indole-5-ol phenylcarbamate, (-)-3,3a,8,8a-tetrahydro-3a,8-dimethyl-2H-thieno[2,3-b]indole-5-ol 2'-methylphenylcarbamate,
 25 (-)-3,3a,8,8a-tetrahydro-3a,8-dimethyl-2H-thieno[2,3-b]indole-5-ol 2'-isopropylphenylcarbamate, (-)-thiaphysovenine, (-)-Phenylthiaphysovenine, and (-)-2',4'-dimethylphenyl-thiaphysovenine.
- 30 3. The method according to claim 2, wherein the phenserine-like compound is selected from the group consisting of donepezil, galantamine, rivastigmine and tacrine.

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4. The method according to claim 2, wherein the phenserine compound comprises (-)-N-phenylcarbamoyl eseroline or a salt or ester thereof.

5. The method according to claim 1, claim 2, claim 3 or claim 4, wherein treating diabetes comprises delaying onset of a cognitive impairment associated with diabetes.

6. The method according to any one of claims 1-5, wherein treating diabetes comprises treating gestational diabetes.

10

7. The method according to any one of claims 1-6, wherein treating diabetes comprises a prophylactic treatment of diabetes.

8. The method according to any one of claims 1-7, wherein treating diabetes comprises treating cerebral angiopathy.

15

9. The method according to any one of claims 1-8, wherein the subject is a human above the age of 60 years.

10. The method according to any one of claims 1-9, further comprising administering said phenserine compound or phenserine-like compound prior to a meal.

20

11. The method according to claim 10, further comprising coadministering a hypoglycemic agent selected from the group consisting of a sulfonylurea, a meglitinide, a biguanide, a thiazolidinedione, an alpha-glucosidase inhibitor and mixtures thereof.

25

12. The method according to any one of claims 1-11, wherein treating diabetes comprises treating at least one condition selected from the group consisting of hyperglycaemia, hypoglycaemia, response to hypoglycemic agents, diabetic

30

-20-

neuropathy, diabetic retinopathy, kidney function, vascular dementia, ketone levels, hyperlipidaemia, and coronary artery disease.

13. The method according to any one of claims 1-5, 7, and 9-12, wherein
5 treating diabetes comprises treating insulin resistance.

14. Use of an acetylcholinesterase antagonist for the preparation of a
medicament useful in the treatment of complications associated with diabetes.

10 15. Use of the acetylcholinesterase antagonist of claim 14, wherein the
acetylcholinesterase antagonist is phenserine.

16. Use of the acetylcholinesterase antagonist of claim 14 or claim 15 for
the preparation of a medicament useful in the treatment of vascular dementia.
15

17. Use of the acetylcholinesterase antagonist of claim 14 or claim 15 for
the preparation of a medicament useful in delaying the onset of diabetes associated
cognitive impairment.

20 18. Use of the acetylcholinesterase antagonist of claim 14 or claim 15 for
the preparation of a medicament useful in the treatment of insulin resistance.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/02559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/40

US CL : 514/411

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,378,723 A (BROSSI et al.) 03 January 1995 (03.01.1995), see the entire document.	1-18

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents:	
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 April 2005 (14.04.2005)

Date of mailing of the international search report

29 APR 2005

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/02559

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

49

ANEXO 2

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00	A2	(11) International Publication Number: WO 00/35437 (43) International Publication Date: 22 June 2000 (22.06.00)
(21) International Application Number: PCT/US99/30066 (22) International Filing Date: 17 December 1999 (17.12.99) (30) Priority Data: 60/112,669 17 December 1998 (17.12.98) US 60/122,258 24 February 1999 (24.02.99) US (71) Applicant (for all designated States except US): MINDSET BIOPHARMACEUTICALS (USA), INC. [US/US]; 1450 Broadway, 41st Floor, New York, NY 10018 (US). (71) Applicant (for SD only): MCINNIS, Patricia, A. [US/US]; 2325 42nd Street, N.W., Apartment #203, Washington, DC 20007 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHAIN, Daniel, G. [GB/IL]; Beit Eshel Street 1, Old Katamon, 93227 Jerusalem (IL). CAWTHORNE, Mike [GB/GB]; The University of Buckingham, Buckingham MK 18 1EG (GB). (74) Agent: BROWDY, Roger, L.; Browdy and Neimark, P.L.L.C., 624 Ninth Street, N.W., Suite 300, Washington, DC 20001 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: INCREASING BRAIN GLUCOSE UTILIZATION		
(57) Abstract Brain glucose utilization can be increased by administering an agent that improves central nervous system insulin sensitivity. By improving the central nervous system insulin sensitivity and increasing brain glucose utilization, age-related memory loss and dementia can be prevented and/or reduced. The improvement in brain glucose utilization is independent of treatment for Type II diabetes. Among the central nervous system insulin sensitizers that can be administered to increase brain glucose utilization are thiazolidinediones, including troglitazone, rosiglitazone and pioglitazone. Other useful compounds include oxyazolidinediones, including JPP501, and non-chiral acyclic agents, including GL 262370, and substituted 4-hydroxy-phenylalcanoic acid derivatives which are PPAR gamma receptor activators. All of these agents act on the nuclear receptor PPAR gamma. In a preferred embodiment, the agents are administered in the form of prodrugs which are designed to cross the blood brain barrier.		

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EE	Estonia						

INCREASING BRAIN GLUCOSE UTILIZATION

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority from provisional applications serial number 60/112,669, filed December 17, 1998, and serial number 60/122,258, filed February 24, 1999, the contents of each of which are hereby incorporated in their entirety.

FIELD OF THE INVENTION

The present invention is directed to a method for improving central insulin sensitivity in the brain for treating senile dementia, Alzheimer's Disease and other dementias, as well as improving mental performance.

BACKGROUND OF THE INVENTION

Glucose is a major energy source for cerebral tissue. Glucose transported to the cerebral tissue is metabolized by hexokinase to glucose-6-phosphate, which is a very important intermediate in the glucose catabolism system. After this, the glucose-6-phosphate enters a metabolic pathway where it is catabolized in order to generate high-energy phosphate compounds, such as ATP, through its linked phosphorylation reaction.

There is a strong linkage between brain glucose utilization and mental performance as illustrated by the use of PET scans as an aid to identifying brain injury and in evaluating new therapies for senile dementia. It has generally been believed that brain glucose utilization is not affected by changes in circulating insulin concentration and changes in the normal diet or eating pattern. It has been argued that a function critical to maintaining life cannot be dependent upon such things as the nature and timing of meals. Indeed, measurements of whole brain glucose utilization do not show any significant overall differences in relation to diet, insulin treatment or diabetes. The ability to measure brain glucose utilization was originally developed by Sokolov and colleagues, cf. Dienel et al (1992). The principle was developed for animal studies and used radiolabelled 2-deoxyglucose, which is taken up by cells through the glucose

transport system, is converted to 2-deoxyglucose-6-phosphate, but cannot be further metabolized. Further, the glucose-6-phosphate only minimally accumulates in the brain. Thus, measurement of trapped 2-deoxyglucose-6-phosphate can be used
5 as an index of brain glucose utilization. In animals, this involves direct extraction of tissues. In humans, 18-fluoro-2-deoxyglucose is used, and this can be detected by PET scanning.

These techniques have been used in both animals and
10 humans to demonstrate that the rate of glucose utilization is not uniform throughout the brain. Furthermore, certain portions and cell types, such as astrocytes, are clearly insulin sensitive (Clarke et al, 1984). Astrocytes are important communicating cells, and the insulin sensitivity of
15 these cells can be demonstrated by *in vitro* studies (Clarke et al, 1984). Diabetes severely affects glucose utilization by astrocytes, and it has also been shown that astrocytes can develop insulin resistance.

In vivo studies in rats have shown that glucose
20 utilization is reduced 50% by anesthetic, and that overall glucose utilization by insulin-resistant fa/fa rats is less than in lean littermates. Corticosterone decreased glucose utilization in the limbic regions, but increased utilization in thalamic regions. Adrenalectomy increased glucose
25 utilization in limbic regions. Minipump infusion of insulin for four days to create hyperinsulinaemia reduced glucose utilization in the suprachiasmatic nucleus (affecting circadian rhythm), locus coeruleus and basolateral amygdala. All of these studies indicate that glucose utilization in discrete areas of
30 the brain is under complex control and can be modified by circulating hormones and possibly by nutrients (Doyle et al, 1995).

The development of memory loss and dementia is generally an age-related process. It is well known that insulin-
35 stimulated fuel utilization in peripheral tissues, such as skeletal muscle, often declines with age and insulin resistance develops. The nature of the insulin resistance is generally related to a reduced amplification of the insulin

signaling process, so that insulin is less efficient in activating the normal insulin response. Glucose utilization in the brain also decreases with age (Smith and Sokoloff in The Aging Brain). This might suggest that insulin resistance in discrete brain areas and cell types may play a role in central glucose utilization, resulting in reduced mental performance. On the other hand, as glucose utilization in the brain is believed to be under complex control, one cannot predict whether or not insulin resistance plays a major role in age- decreased brain glucose utilization.

A number of therapies have been developed to inhibit memory loss and dementia in aging patients. However, none of these therapies depends upon controlling insulin action in the brain.

Duelli et al (1994) disclose that a decrease in cerebral glucose utilization may correspond to changes in morphobiological parameters which have been found in patients with Alzheimer's Disease. However, there is no indication that any type of treatment of this decrease in cerebral glucose utilization could be used to prevent or treat Alzheimer's Disease.

Blum-Degen et al (1995) disclose that there is a measurable decrease of *in vivo* and post-mortem cerebral glucose metabolism, and that insulin plays an important role in regulating brain glucose homeostasis in the central nervous system. It has been suggested that the reduction of brain glucose metabolism in neuro-degenerative disorders may be related to a defect of the neuronal insulin-insulin receptor interaction. However, there is no specific disclosure of treating neuro-degenerative disorders with substances which improve insulin sensitivity.

Hoyer et al (1996) disclose that intracerebroventricularly-administered insulin exerts anabolic effects on cerebral glucose/energy metabolism. However, there is no indication that administering a substance to improved insulin sensitivity could be useful in treating age-related brain disorders, such as dementia.

Dore et al, (1997) disclose that insulin receptor sites are not markedly altered during the normal aging process in the Long Evans rat, despite significant learning deficits in memory- impaired aged animals. This suggests that insulin
5 action in the brain does not contribute to the age-related memory loss.

Cullingford (1998) reported that PPAR (peroxisome proliferator-activated receptor) gamma mRNA was expressed at a similar level to PPAR alpha mRNA in adult rat astrocytes, but
10 there is no indication that this receptor might be involved with regulating insulin action and glucose metabolism in this cell type.

Granneman et al (1998) show that PPAR is strongly expressed in immature oligodendrocytes, suggesting a role in
15 oligodendrocyte differentiation. One thazolidinedione compound, Pfizer CP68722, increased the number of oligodendrocytes in glial cultures. However, there is no indication of a connection between this work and improved central glucose utilization.

Romeo et al, in U.S. Patent 5,556,843, disclose that phosphoryl-L-serine-N-acyl-sphingosine can increase glycemia and histamine levels, resulting in cerebral glucose
20 accumulation. This compound can be used in therapies associated with a slowdown of cerebral metabolism, in involutive cerebral syndromes of different origins, and
25 Alzheimer's Disease, memory loss, senile dementia, etc. Phosphoryl-L-serine-N-acyl-sphingosine is said to be useful in treating insulin-dependent diabetes. However, there is no indication that any other drug used for treating diabetes
30 could be used to treat senile dementia or other types of neurological conditions. In fact, phosphoryl-L-serine-N-acyl-sphingosine has no connection to insulin action or insulin resistance.

Ohmoto et al, in U.S. Patent 5,710,153, disclose
35 tetrazole compounds which are used in treating, among other conditions, insulin-dependent diabetes and neural diseases, such as Alzheimer's Disease and Parkinson's Disease. This treatment depends on inhibition of ICE enzymatic activation

which leads to prevention of conversion of pre-IL-1 β to IL-1 β and presumably relates to preventing the inflammatory action of IL-1 β . Thus, these compounds have no correlation to insulin action or insulin resistance.

5 Guthikonda et al, in U.S. Patent 5,629,322 disclose cyclic amidine analogs as inhibitors of nitric oxide synthase which can be used to treat Type I diabetes and dementia. However, there is no indication that there is any effect on glucose metabolism directly from these compounds. In fact,
10 the inhibitors of nitric oxide synthase are associated with inflammatory reactions in insulin-dependent diabetes rather than glucose utilization.

Shapiro, in U.S. Patent 5,668,117, discloses treating neurological diseases, such as diabetic neuropathy, with at
15 least one carbonyl trapping agent, alone or in combination with a therapeutically effective co-agent. However, there is no indication that the carbonyl trapping agent acts by increasing glucose metabolism. The carbonyl trapping agents can be used with insulin derivatives and other conventional
20 medicaments for treating diabetes.

Torii et al, in U.S. Patent 5,693,614, disclose the use of α -FGF for treating senile dementia of the ischemic and hypoglycemic types, stating that the failure of energy
25 metabolism in the brain resulting from hypoglycemia elicits this type of lesion formation. However, α -FGF is not related to any insulin-stimulated process, and there is no indication that this is a conventional treatment for diabetes which can then be used to treat hypoglycemic dementia.

Nakagama et al (1996) disclose that TAK-147, a novel
30 acetylcholinesterase inhibitor when given daily for 40 days to aged rats, increased energy metabolism and increased brain glucose utilization. However, there is no indication that this compound has any effect whatsoever on insulin sensitivity, nor does it act at the PPAR gamma receptor.

35 Jannetta, in U.S. Patent No. 5,962,004, discloses neurogenic diabetes mellitus can be treated by relieving pressure from a region of the brainstem within the cranium of a patient with a neuroendocrine servomechanism. By relieving

pressure on the neuroendocrine servomechanism, the disease is ameliorated. However, this has nothing to do with increasing brain function.

Kumagai, in *Diabetes Metab. Res. Rev.* 15(4):261-273, Jul-
5 Aug, 1999, discloses that neural tissue is entirely dependent on glucose for normal metabolic activity, and that metabolism in the brain is dependent upon adequate glucose delivery from the systemic circulation. Changes in endothelial glucose
10 transport may have profound consequences on glucose delivery to these tissues and major implications in the development of two major diabetic complications, namely, insulin-induced hypoglycemia and diabetic retinopathy.

Hasselbalch et al., in *Diabetes* 48:(10): 1915-1921, October, 1999, disclose that hyperinsulinaemia within the
15 normal physiologic range does not affect blood brain barrier glucose transport or net cerebral glucose metabolism. However, there is nothing in this article that deals with increasing brain glucose metabolism.

Another problem associated with treating dementia by
20 increasing brain glucose metabolism is that for patients with normal serum glucose it is important to treat only brain glucose metabolism. Accordingly, it is important to deliver agents for treating brain glucose metabolism to the cerebral tissue. Unfortunately, the blood brain barrier is the major
25 obstacle for delivering most medication to the central nervous system. The capillaries in the brain parenchyma possess high-resistance, tight junctions between the endothelial cells. The cells also lack pores, so that the brain capillary endothelium behaves like a continuous lipid bilayer.
30 Diffusion through this bilayer, the physical blood brain barrier, is largely dependent on the lipid solubility of the solute. Water-soluble molecules (such as glucose, essential amino acids, glutamate) enter the brain almost exclusively by carrier-mediated transport.

35 Various strategies have been applied to direct medications specific for the central nervous system into the brain. An invasive procedure that includes surgical implantation of an intraventricular catheter followed by

pharmaceutical infusion into the ventricular compartment delivers a metabolically unstable compound only to the surface of the brain, cf. Poplack et al (1981). Transient opening of the tight junctions of the intracarotid infusion of an
5 osmotically active substance (e.g., mannitol, arabinose) in high concentrations (>1M) may facilitate an indiscriminate delivery of molecules that otherwise cannot cross the blood brain barrier, as shown in Neuwelt et al (1984). However, this procedure is accompanied by severe toxic effects which
10 can lead to inflammation, encephalitis, and seizures. These invasive procedures are only justified for some life-threatening conditions and are not acceptable for less serious illness.

A non-invasive method for peptide delivery into the
15 central nervous system has been suggested that uses the formation of chimeric peptides, cf. Pardridge (1986). This strategy relies on the presence of specific receptor-mediated transcytosis systems in the blood brain barrier for certain larger peptides, such as insulin, insulin-like growth factor, transferrin, and albumin. Covalently coupling (e.g., via
20 disulfide bonds) a non-transportable peptide to these transport vectors results in a chimeric peptide that can also undergo receptor-mediated transcytosis, and the active peptide can be released by its enzymatic cleavage in the central
25 nervous system. However, these carriers are not brain-specific, as uptake by non-neural cells or cells outside the central nervous system has been shown. Low amounts of the peptide relative to the carrier molecule, as well as the receptor-based cellular transport mechanism that has
30 physiologically limited transporter capacity (saturable) also prevent pharmacologically significant amounts from entering the brain. Finally, release of the active peptide from the conjugate has not been documented.

Another method for peptide delivery is a simple
35 pharmacologically based approach in which peptide "prodrugs" are administered that are lipophilic esters or amides of the molecule (Tsuzuki et al, 1991). Although the acquired lipophilicity of these prodrugs may assure penetration of the

blood brain barrier, as well as other membranes, this is not the sole factor involved in the transport of a peptide into the central nervous system. Blood brain barrier transport of cyclosporin, which is one of the most lipid soluble peptides, is paradoxically low because of peptide degradation, cf. Beagley et al, 1990).

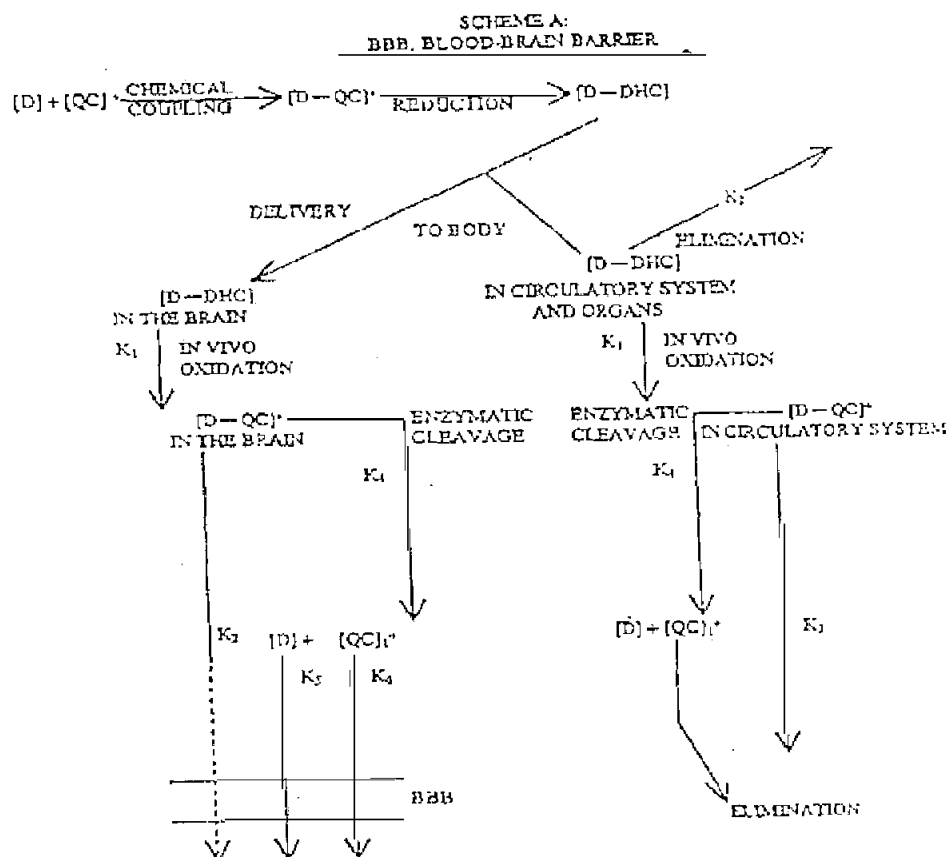
A dihydropyridine-pyridinium redox system has recently been successfully applied to delivery to the brain of a number of drugs. Generally speaking, according to this system, a dihydropyridine derivative of a biologically active compound is synthesized, which derivative can enter the central nervous system through the blood-brain barrier following its systemic administration. Subsequent oxidation of the dihydropyridine species to the corresponding pyridinium salt leads to delivery of the drug to the brain.

Four main approaches have been used thus far for delivering drugs to the brain using a redox system. The first approach involves derivation of selected drugs which contain a pyridinium nucleus as an integral structural component. This approach was first applied to delivering to the brain methylpyridinium-2-carbaldoxime chloride (2-PAM), the active nucleus of which constitutes a quaternary pyridinium salt, by way of the dihydropyridine latent-initiated prodrug form thereof. Thus, a hydrophilic compound (2-PAM) was made lipoidal by making its dihydropyridine form (Pro-2-PAM) to enable its penetration through lipoidal barriers. This simple prodrug approach allowed the compound to get into the brain, as well as into other organs. However, this manipulation did not and could not result in any brain specificity. On the contrary, such approach was limited to relatively small molecule quaternary pyridinium ring-containing drug species, and did not provide the overall ideal result of brain-specific, sustained release of the desired drug, with concomitant rapid elimination from the general circulation, enhanced drug efficacy and decreased toxicity. There was no "trapping" in the brain of the 2-PAM formed *in situ*, and consequently there was no sustained delivery of the 2-PAM. The 2- PAM was eliminated as quickly from the brain as from

the general circulation and other organs, cf. U.S. Patents 3,929,813 and 3,962,447, and 5,624,894, which are hereby incorporated by reference in their entireties, including all references cited therein.

5 Subsequent extension of this approach to delivering a much larger quaternary salt, berberine, to the brain via its dihydropyridine prodrug form was, however, found to provide site-specific, sustained delivery to the brain of that anticancer agent, cf. Bodor et al (1981). However, this approach is limited to delivery of active quaternary pyridinium salts.

15 A second approach for delivering drugs to the brain using a redox system involves the use of a dihydropyridine/pyridinium carrier chemically linked to a biologically active compound. Bodor et al (1981) outlines a scheme for this specific and sustained delivery of drug species to the brain, as depicted in the following Scheme A:



According to the scheme, a drug [D] is coupled to a quaternary carrier [QC]⁺ and the resulting [D-QC]⁺ is then chemically reduced to the lipoidal dihydro form [D-DHC]. After administration of [D-DHC] *in vivo*, it is rapidly distributed throughout the body, including the brain. The dihydro form [D-DHC] is then *in situ* oxidized (rate constant k_1) by the NAD-NADH system to the ideally inactive original [D-QC]⁺ quaternary salt which, because of its ionic hydrophilic character, should be rapidly eliminated from the general circulation of the body, while the blood-brain barrier should prevent its elimination from the brain ($K_3 \gg K_2$; $K_3 \gg K_1$). Enzymatic cleavage of the [D-QC]⁺ that is "locked" in the brain effects a sustained delivery of the drug species [D], followed by its normal elimination (K_5), metabolism. A properly selected carrier [QC]⁺ will also be rapidly eliminated from the brain ($K_6 \gg K_2$). Because of the facile elimination of [D-QC]⁺ from the general circulation, only minor amounts of drug are released in the body ($K_3 \gg K_1$); [D] will be released primarily in the brain ($K_4 \gg K_2$). The overall result ideally is a brain-specific sustained release of the target drug species.

Specifically, Bodor et al worked with phenylethylamine as the drug model. That compound was coupled to nicotinic acid, then quaternized to give compounds that were subsequently reduced by sodium dithionite. Testing of the N-methyl derivative *in vivo* supported the criteria set forth in Scheme A. Bodor et al speculated that various types of drugs might possibly be delivered using such carrier systems and indicated that use of N-methylnicotinic acid esters and amides and their pyridine ring-substituted derivatives was being studied for delivery of amino- or hydroxyl-containing drugs, including small peptides, to the brain. No other possible specific carriers were disclosed. Other reports of this work with the redox carrier system have appeared, particularly as disclosed in U.S. Patent 4,430,601 and Bodor et al (1983) and Bodor U.S. Patent 4,540,564.

Bodor '564, which patent is hereby incorporated by reference in its entirety, specifically discloses applying the dihydropyridine-pyridinium salt carrier system to amino acids

and peptides, particularly small peptides having 2 to 20 amino acid units. Thus, in the carrier system applied to amino acids and peptides, the free carboxy function is protected in an effort to prevent premature metabolism, e.g., with an ethyl ester, while the trigoneline-type carrier is linked to the amino acid or peptide through its free amino function.

Oxidation of the dihydropyridine carrier moiety *in vivo* to the ionic pyridinium salt carrier/drug entity prevents elimination thereof from the brain, while elimination from the general circulation is accelerated. Subsequent cleavage of the quaternary carrier/drug species results in sustained delivery of the amino acid or peptide (e.g., tryptophan, GABA, leu-enkephalin, etc.) to the brain and facile elimination of the carrier moiety. This method is quite useful for delivery of amino acids. In the case of peptides, however, the typical suggested carboxy protecting groups do not confer sufficient lipophilicity to the peptide molecule. Moreover, this approach neither addresses the problem of the enzymatic blood-brain barrier nor suggests a means of avoiding that problem.

The third approach for delivering drugs to the brain using a redox system provides derivatives of centrally acting amines in which a primary, secondary or tertiary amino function has been replaced with a dihydropyridine/pyridinium salt redox system. These brain-specific analogs of centrally acting amines have been described in U.S. Patents 4,771,059, 5,082,853 and 5,296,483, all of which are hereby incorporated by reference in their entirety. The dihydropyridine analogs act as a delivery system for the corresponding biologically active quaternary compounds *in vivo*. Due to its lipophilic nature, the dihydropyridine analog will distribute throughout the body and has easy access to the brain through the blood brain barrier. Oxidation *in vivo* then provides the quaternary form, which is preferentially "locked" in the brain. In contradistinction to the drug-carrier entities described in Bodor '564 and related publications, however, there is no readily metabolically cleavable bond between drug and quaternary portions, and the active species delivered is not

the original drug from which the dihydro analog was derived, but rather is the quaternary analog itself.

5 In the analog systems described in Bodor U.S. Patents 5,082,853, 4,771,059; and 5,296,483, as applied to amino acids and peptides, the free carboxyl function is, thus, protected to prevent premature metabolism while the dihydropyridine-pyridinium salt type redox system replaces the free amino function in the amino acid or peptide.

10 As described in the above Bodor patents, the chemical processes for preparing the redox analog derivative replace any free amino function in the selected drug with the redox analog system. When these processes are applied to amino acids, they provide a redox amino acid which no longer contains a free amino function for linkage to another amino
15 acid or peptide via a peptide bond (-CONH-). Such an analog amino acid can, thus, only be used to prepare a peptide having the analog amino acid located at the peptide's N-terminus. This limits use of the redox analog amino acids in peptide synthesis. Moreover, this approach is not designed to deliver
20 the original peptide to the brain, since there is no cleavable bond between peptide and quaternary portions. Rather, the redox portion in this approach becomes an inherent, essentially inseparable, part of a new peptide analog. Furthermore, this approach does not address the problem of the
25 enzymatic blood-brain barrier or suggest a means for avoiding the premature degradation caused by the highly active neuropeptide degrading enzymes.

The fourth redox approach is designed to provide redox amino acids which can be used to synthesize peptides having a
30 redox analog system inserted at a variety of locations in the peptide chain, including non-terminal positions, and has been described in Bodor U.S. Patent 4,888,427. These amino acids contain a redox system appended directly or via an alkylene bridge to the carbon adjacent to the carboxyl carbon.

35 However, this fourth redox approach, like the third approach discussed above, is not designed ultimately to deliver the original peptide to the brain because there is no cleavable bond between the peptide and the quaternary

5 portions. Again, the redox system becomes an integral part of a new peptide analog, not a means for ultimately delivering the original peptide to the brain. Moreover, this approach also does not address the problem of the enzymatic blood brain barrier or suggest a means for avoiding deactivation of the peptide by enzymes before it achieves its therapeutic objectives.

SUMMARY OF THE INVENTION

10 It is an object of the present invention to overcome the aforementioned deficiencies in the prior art.

It is another object of the present invention to increase brain glucose utilization in circumstances where brain glucose utilization is sub-optimal for normal mental performance by increasing insulin sensitivity of insulin-sensitive cells in the brain.

15 It is a further object of the present invention to prevent and treat age-related memory loss and dementia.

It is another object of the present invention to act on the nuclear receptors PPAR gamma, PPAR delta, and PPAR alpha to prevent or reduce age-related memory loss and dementia.

20 It is still another object of the present invention to provide a method for delivering drugs which increase brain glucose utilization directly to the central nervous system.

It is another object of the present invention to provide drugs which increase brain glucose utilization in the central nervous system in the form of prodrugs.

25 According to the present invention, brain glucose utilization can be increased by administering an agent that improves central nervous system insulin sensitivity. By improving insulin sensitivity in the central nervous system, brain glucose utilization is improved and age-related memory loss and dementia can be prevented and/or reduced. More specifically, compounds that interact with the PPAR gamma PPAR delta and PPAR alpha receptors, such as thiazolidinedione and other agents that improve insulin sensitivity, are used to treat senile dementia, Alzheimer's Disease and other dementias, as well as to improve mental performance. These

compounds are known to improve insulin sensitivity of peripheral tissues in non-insulin-dependent diabetic patients and are useful in treating non-insulin-dependent diabetes. It has now, surprisingly, been found that the same compounds
 5 improve glucose utilization in the central nervous system, leading to improved mental performance, particularly in patients who are otherwise not sensitive to insulin.

More specifically, the present invention provides, in one embodiment, administering certain known thiazolidinedione
 10 compounds and derivatives thereof and/or non-thiazolidinedione insulin sensitizers/anti-hyperglycemic agents and derivatives thereof, to an individual who is neither in a state of non-insulin-dependent diabetes (NIDD) nor in a state of general impaired glucose tolerance, but who has symptoms of reduced
 15 mental performance. Any pharmaceutical useful in improving insulin sensitivity in non-insulin dependent diabetes patients would be expected to be useful in improving the mental capacity of patients who are neither in a state of NIDD or in a state of general impaired glucose performance.

A number of compounds for the treatment of NIDD have been developed or are under development. These compounds include thiazolidinediones, including troglitazone (Sankyo, Warner-Lambert/Parke Davis, Glaxo), rosiglitazone (Smith
 20 Kline Beecham) and pioglitazone (Takeda, Lilly). Other useful compounds include oxyazolidinediones, such as JTT 501 (Japan Tobacco), and non-chiral acyclic agents, such as GW 262570 (Glaxo Wellcome). All of these agents act on the nuclear receptor PPAR gamma. According to the present invention, these compounds may also be used to improve central nervous
 25 system insulin sensitivity in non-NIDD patients who have symptoms of reduced mental performance. Willson et al., in WO 97/31907 describe substituted 4-hydroxy-phenylalcanoic acid derivatives with agonist activity to PPAR gamma which can be used to improve central nervous system insulin sensitivity in
 30 NON-IDD patients in need thereof. The entire contents of this patent are hereby incorporated.

It is believed that activation of PPAR gamma receptors is the basis of the metabolic action. PPAR gamma receptors form

heterodimers with RxR receptors and the heterodimers interact with PPAR response elements to regulate transcription. Thus, activators for the RxR receptors are also insulin sensitizers (Mukherjee et al, 1997).

- 5 Petrova et al., in *Proc. Natl. Acad. Sci. USA* 96(8):4668-73, April 13, 1999, and Kitamura et al., *Neurosci. Lett.* 262(2):129-32, March 5, 1999, note that the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) in glial cells is activated by anti-diabetic thiazolidinediones as well as by natural ligands. Kitamura et al. in *Biochem. Biophys. Res. Comm* 1999 January 27, 254(3):582-6, found that in brains of patients with Alzheimer's disease, PPAR gamma level was increased in the cytosolic fraction but not in the particulate fraction. These results suggest that PPAR gamma
- 10
- 15 activators have inhibitory effects on inflammatory events in the brains of patients with Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Brain glucose utilization is improved, either in the entire brain, or in discrete areas or in specific cell types, by administering an agent that improves insulin sensitivity in the brain. Specific types of cells affected include astrocytes, which are major communicating cells, glial cells and cells in the blood brain barrier. Specific areas of the brain affected which affect memory loss and dementia are the blood brain barrier microvessels and/or the areas of the brain associated with mental performance or memory.

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Of particular importance in improving brain glucose utilization are thiazolidinediones, such as troglitazone, rosiglitazone, pioglitazone, darglitazone and englitazone and derivatives thereof. Other types of agents that have been found to improve brain glucose utilization are oxazolidinediones, such as JTT 501, and non-chiral acyclic agents, such as GW 262570, as well as substituted 4-hydroxy-phenylalcanoic acid derivatives with agonist activity to PPAR

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gamma. More specific types of compounds which improve brain glucose utilization are compounds which activate the PPAR gamma receptor, or where the agent has agonist or partial agonist activity at the PPAR gamma receptor.

5 Among the thiazolidinedione compounds which have been found to improve brain glucose utilization are those described in Olefsky et al, U.S. Patents 5,478,852 and 5,708,012, the entire contents of each of which are hereby incorporated in their entirety, including all references cited therein.
10 Additional such thiazolidinedione derivatives are disclosed in Antonucci et al, U.S. Patents 5,457,109 and 5,602,133, the entire contents of which are hereby incorporated by reference, including all references cited therein.

15 Substituted thiazolidinedione derivatives, such as those disclosed in Hindley et al U.S. Patents 5,464,169 and 5,756,525, and in Cantello et al (1994), are also expected to be useful in improving brain glucose utilization and, thus, mental performance in patients in need thereof. The entire contents of each of these are also hereby incorporated by
20 reference, including all references cited therein.

25 Non-thiazolidinedione insulin sensitizer agents, such as those disclosed by Buckle et al (1996a and 1996b) and substituted 4-hydroxy-phenylalcanoic acid derivatives, such as those described in Willson et al. patent number WO 9731907, the entire contents of each of which are hereby incorporated by reference in their entirety, including all references cited therein, are also expected to improve brain glucose utilization, and, thus, mental performance in patients in need thereof.

30 Hypoglycemic alkaloids, such as quindoline and cryptolepine, which may be obtained from extracts from *Cryptolepis* sp., as disclosed in Luo et al U.S. Patent 5,629,319, as well as triterpenoid substances, such as those disclosed in Inman et al U.S. Patent 5,691,386, and
35 eremophilanolide sesquiterpenes, such as described in Inman et al U.S. Patent 5,747,527, the entire contents of each of which being hereby incorporated by reference in their entirety,

including all references cited therein, can also be used to treat or prevent dementia and memory loss in accordance with the present invention.

Other compounds for improving insulin sensitivity are disclosed in Vyas et al U.S. Patent 5,700,820; Ubillas et al U.S. Patent 5,674,900; and Dominianni et al U.S. Patent 5,641,796, the entire contents of each of which is hereby incorporated by reference in their entirety, including all references cited therein. These compounds include polymorphic forms of troglitazone, terpenoid-type quinones and C-substituted pentacycloazoles and N-alkyl substituted pentacycloazoles.

Other types of agents which improve brain glucose utilization for improving insulin sensitivity are those which selectively activate one of the sub-types of the human PPAR gamma receptor, namely PPAR gamma 1 and PPAR gamma 2, or where the agent activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor, for example, ligand 100268, which is an RxR receptor ligand.

In addition to the compounds enumerated above, the agent can be a natural product, such as extract of *Cryptolepis* or derived from a natural product such as cryptoleptine.

More specifically, compounds which activate the PPAR gamma receptor or which have agonist activity at the PPAR gamma receptor are useful in improving insulin sensitivity, thereby improving central glucose utilization and ameliorating the memory loss and dementia associated with Alzheimer's Disease and various other types of dementia. Additional types of compounds which are useful include those which activate the PPAR delta receptor or the PPAR alpha receptor.

For purposes of the present invention, "derivative" of the compounds enumerated means chemical modifications of the active compounds which substantially retain the desired activity of the compounds, i.e., the activity of improving central nervous system insulin sensitivity and increasing brain glucose utilization.

Strategies have been specifically tailored to achieving delivery of an agent directly to the central nervous system, i.e., to crossing the blood brain barrier, based upon "sequential metabolism" of a prodrug (cf. Bodor et al, 1992; Prokai et al, 1994; Bodor et al, 19??). In one embodiment of a prodrug form of an agent according to the present invention, the modifying group comprises an alkyl ester to facilitate blood-brain barrier permeability.

In one embodiment of the present invention, the compounds for activation of PPAR gamma receptors or which have agonist activity at the PPAR gamma receptor are delivered across the blood brain barrier by packaging the compounds in a molecular environment which disguises the nature of the compound. This environment provides a biolabile, lipophilic function to penetrate the blood brain barrier by passive transport.

In another embodiment of the present invention, the pharmacologically active molecule provides a dihydropyridine-type redox moiety for targeting the compound to the brain and providing "lock-in" as the pyridinium salt. A spacer is placed between the redox moiety and compound designed to enhance the sequential metabolism of the "molecularly packaged" compound. The spacer may be an amino acid or di- or tri-peptide spacer, or any other short group that is compatible with the compound to be administered and that can readily be cleaved *in vivo* to release the active compound.

In another embodiment of the present invention, a cell scattering factor, hereinafter denoted "egressin", isolated from a clone derived from a human metastatic melanoma (M3827), as described in Wier et al U.S. Patent 5,039,794, the entire contents of which are hereby incorporated by reference, is used to aid in transporting drugs across the blood brain barrier to increase glucose metabolism in the central nervous system. Egressin disperses endothelial cells and acts on the cell-cell junctions of the endothelial cells lining the blood vessels. The dissociation of these junctions increases the permeability of the vessels and decreases the effectiveness of

the blood brain barrier. Thus, egressin aids in transporting drugs for improving glucose utilization across the blood brain barrier for treating the central nervous system.

5 In this embodiment, an amount of egressin effective for the dissociation of the cell-cell junction of endothelial cells is administered intravenously along with a therapeutically effective compound for improving glucose utilization in the brain.

10 Another method for enabling the compounds used in the present invention to cross the blood brain barrier is to formulate the compounds such that the compounds are non-ionic when they reach the blood stream and would be subsequently enzymatically oxidized to release the compound in a therapeutic amount at the brain. These prodrugs include
15 compounds which contain a tertiary nitrogen atom exhibiting a low basicity, i.e., a pKa below 7.4. On this basis, the skilled artisan can readily appreciate that such compounds, when introduced into the bloodstream of a warm-blooded animal whose pH is about 7.4, would remain essentially non-ionic,
20 thus permitting the prodrug form to be highly protein bounded and/or enter the erythrocytes and, thus, to pass through the blood brain barrier and be subsequently enzymatically oxidized to release the active compound in high bioavailability at the brain.

25 Where appropriate, the compounds can be provided in the acid addition salt form for the sole purpose of rendering stability to the prodrug free base form prior to administration. Once the prodrug compounds are administered by any route, the salt moiety is "cleaved", thus releasing the
30 remaining tertiary amine form, which readily transcends the blood brain barrier. Next, the prodrug can be enzymatically oxidized to the active compound in an analogous manner to the nicotinamide dinucleotide co-enzyme mediated oxido-reduction system, wherein the coenzyme, in turn, is reduced to the
35 dihydro form (NADH). For purposes of the present invention, the term "prodrug" refers to a derivatized form of a proven drug which, when administered to an individual, is

enzymatically or otherwise acted upon in the bloodstream to release the drug at the therapeutic site or sites of activity. In the present invention, the therapeutic site is the central nervous system.

5 The compounds used to increase glucose utilization in the brain can be provided in the form of prodrugs to alter the biodistribution of the compounds, e.g., to allow compounds which would not typically cross the blood-brain barrier to cross the blood-brain barrier. For example, an anionic group, 10 e.g., a sulfate or sulfonate, can be esterified, e.g., with a methyl group or a phenyl group to yield a sulfate or sulfonate ester. When the sulfate or sulfonate ester is administered to a subject, the ester is cleaved, enzymatically or non-enzymatically, reductively or hydrolytically, to reveal the 15 anionic group. Such an ester can be cyclic, e.g., a cyclic sulfate of sultone, or two or more anionic moieties may be esterified through a linking group.

 An anionic group can be esterified with moieties (e.g., acyloxymethyl esters) which are cleaved to reveal an 20 intermediate compound which subsequently decomposes to yield the active compound. In another embodiment, the prodrug is a reduced form of a sulfate or sulfonate, e.g., a thiol, which is oxidized *in vivo* to the therapeutic compound. Furthermore, an anionic moiety can be esterified to a group 25 which is actively transported *in vivo*, or which is selectively taken up by target organs. The ester can be selected to allow specific targeting of the therapeutic moieties to the brain.

 Carrier molecules may also be used to transport the active compounds to the brain. The carrier molecule may 30 include a moiety capable of targeting the therapeutic compound to the brain by either active or passive transport. Illustratively, the carrier molecule may include a redox moiety. Many targeting moieties are known, including those disclosed in patents to Bodor 4,540,564, 5,389,623, and 35 5,525,727, the entire contents of which are hereby incorporated by reference, as well as asialoglycoproteins, such as those disclosed in Wu et al. U.S. Patent 5,166,320.

Other carrying moieties include ligands which are transported into cells via receptor-mediated endocytosis.

Other means for carrying a prodrug or an active agent across the blood-brain barrier involve coupling either a prodrug or an active agent to a carrier. These carriers include fatty acids, inositol, 1,4-dihydropyridine, lipids, proteins, and peptides. The proteins and peptides can be synthetic or naturally occurring. The term peptide is intended to include small proteins and particularly those molecules having on the order of about 100 amino acids or fewer. Examples of proteins useful as carriers include antibodies specific for receptors within the brain, albumin, insulin, drugs, or growth factors.

Fatty acid carriers preferably have between about 16 and 26 carbon atoms, and preferably between about 20 and 24 carbon atoms. The length, degree of saturation, and whether the fatty acid is naturally occurring in the brain affects the ability of the fatty acid to serve as a carrier to deliver the agent across the blood brain barrier to an active site in the brain. Fatty acids which are partially unsaturated and occur naturally in the brain are particularly preferred as carriers. Fatty acids which occur naturally in the brain include those with 16 carbon atoms and 0, 1 or 2 double bonds. It has been found that C18:3 is superior in its ability to deliver a compound across the blood brain barrier, and 4, 7, 10, 13, 16, 19 docosahexaenoic acid has also been found to be particularly useful in delivering agents across the blood brain barrier.

Branched chain fatty acids having between 16 and 26 carbon atoms can also be used in the present invention. A hydrogen atom of the foregoing fatty acids can be replaced with a methyl, ethyl or isopropyl substituent at various positions along the carbon chains.

Other carrier include the naturally occurring polyisoprenoids (dolichols) and analogs thereof.

The active agent can be coupled to the fatty acid via a group capable of being attached directly or indirectly to the hydroxyl group of the fatty acid. The hydroxyl group of the

fatty acid can form, for example, an ester or amide bond with the agent. A hydroxyl group or amino group of the active agent can form a bond with the fatty acid. A variety of reactions can be used involving reacting the agent or a
5 protected derivative thereof with the corresponding fatty acid carrier or an activated derivative thereof. A free hydroxyl group can form an ester bond with the fatty acid or activated derivative thereof, and the free amino group can form an amide bond with the fatty acid or activated derivative thereof.

10 The targeting and prodrug strategies described above can be combined to produce a compound that can be transported as a prodrug to a desired site of action and then unmasked to reveal an active compound.

In another embodiment of the present invention, the
15 active agent is contained within a compatible biodegradable polymer in the form of microspheres. As used herein the term "microspheres" includes microcapsules, nanocapsules, and nanospheres.

Microcapsules and microspheres are conventionally free
20 flowing powders consisting of spherical particles of 2 millimeters or less in diameter, usually 500 microns or less in diameter. Particles less than 1 micron are conventionally referred to as nanocapsules or nanospheres. For the most part, the difference between a microcapsule and a nanocapsule,
25 or a microsphere and a nanosphere, is size. Generally, there is little, if any, difference between the internal structure of the two.

The microcapsule or nanocapsule has its encapsulated agent centrally located within a membrane. This membrane may
30 be termed a wall-forming polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release their agent at a
35 constant rate (called a "zero order" rate of release).

In addition, the microspheres may encompass "monolithic"
35 and similar particles in which the active agent is dispersed throughout the particle. That is, the internal structure is a matrix of the bioactive agent and a polymer excipient.

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Usually such particles release their bioactive agents at a declining rate (a "first order" rate of release). However, these particles may be designed to release active agents within the matrix at a near zero order rate. Thus, as used in the present invention, microspheres also include microparticles in general which have an internal structure comprising a matrix of bioactive agent and polymer excipient.

One particularly useful polymer for preparing a microcapsule or microsphere according to the present invention is poly(lactide-co-glycolide). This polymer is similar to materials used in the manufacture of conventional resorbable sutures. This polymer is biocompatible with the tissues of the central nervous system. Additionally, this polymer is biodegradable within the tissues of the central nervous system without producing any toxic by-products of degradation. A still further advantage of this material is the ability to modify the duration of drug release by manipulating the polymer's biodegradation kinetics, i.e., by modifying the ratio of lactide and glycolide in the polymer to deliver the glucose-affecting molecules to specific regions of the brain at a controlled rate over a predetermined period of time. Microspheres made with this polymer, thus, serve two functions: they protect the active agents from degradation, and they release the active agents at a controlled rate over a predetermined time. Although this specific polymer meets the criteria necessary for implantation within the central nervous system, other biocompatible, biodegradable polymers and copolymers having properties which are similar to those named properties of poly(lactide-co-glycolide) may be substituted therefor.

Pharmaceutical compositions for administration according to the present invention can comprise at least one agent according to the present invention in a pharmaceutically acceptable form, optionally combined with a pharmaceutically acceptable carrier. These compositions can be administered by any means that achieve their intended purposes. Amounts and regimens for the administration of a composition according to

the present invention can be determined readily by those with ordinary skill in the art of treating memory loss or senile dementia.

5 For example, administration can be by parenteral, such as subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively or concurrently, administration can be by the oral route, transdermally, transmucosally, or rectally. While oral dosage is preferred, administration by suppositories may be useful. The dosage
10 administered depends upon the age, health and weight of the recipient, type of previous or concurrent treatment, if any, frequency of the treatment, and the nature of the effect desired.

15 Preferably, the compounds in the form of prodrugs can be administered parenterally (intravenously, intraperitoneally, or intramuscularly) by simply combining a therapeutic amount of the prodrug with any pharmaceutically acceptable inert parenteral carrier. With respect to oral administration, since the compounds of the present invention are absorbed
20 effectively through the intestine, but are highly sensitive compounds, they are preferably administered in an enteric coated medium. Of course, the carrier material in either case must be inert, i.e., non-oxidizing, in nature. The reason for this is that if the compounds of the present invention are
25 contacted with an oxidizing agent prior to entry into the bloodstream, the compound will immediately be oxidized to the active form, and will not cross the blood brain barrier. The only limitation on the enteric coating is that it preserve the prodrug from dissolution until it reaches the small intestine,
30 and that the enteric coating medium be inert, i.e., non-oxidizing. Consequently, most conventional enteric coating compositions can be used.

35 Compositions within the scope of this invention include all compositions comprising at least one agent according to the present invention in an amount that is safe and effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each

component is within the skill of the art. Typical dosages can comprise from about 0.0001 to about 100 mg/kg body weight daily.

5 The effective amounts of agents for improving brain glucose utilization can be readily determined. For *in vivo* prevention or reduction of memory loss and dementia, the presently preferred daily dosage is between about 1 microgram and about 100 grams of the active agent. Of course, the actual preferred amount of agent to be administered varies
10 according to the particular form of the agent, whether it is the agent *per se* or an analog thereof, the particular composition formulated, and the mode of administration.

Administration can be conducted continuously or periodically within the maximum dose tolerated by the
15 individual patient. Of course, optimal administration rates for a given set of conditions can be ascertained by those skilled in the art using conventional dosage administration tests.

Brain glucose utilization is improved where the
20 administration of the agent activates the insulin transduction process so that the net effect is to increase the sensitivity or responsiveness of the insulin signal. Surprisingly, it is a discovery of the present invention that improving brain glucose utilization in non-diabetic patients does not affect
25 the glycemic profile of these patients. That is, the agent only improves glucose utilization in the brain and does not affect the level of peripheral glycemia, because delivery of the agent solely to the central nervous system does not affect the peripheral blood glucose.

30 The preferred dose of an effective compound is from about 0.01 mg to about 4 grams, administered up to eight times daily depending upon the degree of impairment of glucose utilization in the individual patient. Typically, the dose is from about 0.1 mg to about 1 gram administered up to four times daily,
35 and the preferred dose is in the range of about 0.1 mg to about 400 mg, administered once or twice daily.

The insulin sensitizer of the present invention may be co-administered with other agents designed to improve mental performance, particularly agents that increase energy utilization. These agents include acetyl-carnitine, other
5 forms of carnitine, and cerebral enhancers such as cognex.

The compounds of the present invention can be administered in the form of pharmaceutically acceptable compositions, that is, with the active ingredient mixed with or encapsulated in a pharmaceutically acceptable carrier.
10 Compositions within the scope of the invention, thus, include compositions wherein the active component is present in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the skill in the art.

In addition to the compounds of the present invention, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active
15 compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees and capsules, and also preparations which can be administered rectally, such as suppositories, as well as
20 suitable solutions for administration by injection or orally, contain from about 0.1 to 99%, and preferably from about 1-85% of the active ingredient, together with a suitable excipient.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for
25 example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if
30 desired or necessary, to obtain tablets of dragee cores.

Examples of suitable excipients include lactose, sucrose, mannitol, sorbitol, cellulose preparations, calcium phosphates, binders, such as starch paste from maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydropropylmethlycellulose, sodium carboxymethylcellulose and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches, as well as carboxymethyl starch, cross-linked polyvinyl pyrrolidone, agar, alginic acid, sodium alginate, and the like.

Auxiliaries include flow-regulating agents and lubricants, such as silica, talc, stearic acid or salts thereof and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures.

In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate are used. Dyestuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize different combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with filler, such as lactose, binder, such as starches, and/or lubricants, such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols, or higher alkanols. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous suspensions of the active ingredients, as well as appropriate oily injection suspensions. Suitable lipophilic vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The compounds of the present invention may be administered in a variety of convenient forms, orally, parenterally, rectally, or percutaneously to treat dementia. The dosage required for each patient may vary widely, depending upon the degree of dementia and the individual patient response. However, in general, a dosage of from about 0.001 to about 100 mg/kg of body weight is appropriate for most patients.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the

phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention. Thus the expressions "means to..." and "means for...", or any method step language, as may be found in the specification above and/or in the claims below, followed by a functional statement, are intended to define and cover whatever structural, physical, chemical or electrical element or structure, or whatever method step, which may now or in the future exist which carries out the recited function, whether or not precisely equivalent to the embodiment or embodiments disclosed in the specification above, i.e., other means or steps for carrying out the same function can be used; and it is intended that such expressions be given their broadest interpretation.

All references cited herein, including journal articles or abstracts, published or unpublished U.S. or foreign patent applications, issued U.S. or foreign patents, or any other references are entirely incorporated by reference herein, including all data, tables, figures, and text present in the cited references. Additionally, the entire contents of the references cited within the references cited herein are also incorporated by reference in their entirety.

References to known method steps, conventional method steps, known methods or conventional methods is not in any way an admission that any aspect, description, or embodiment of the present invention is disclosed, taught, or suggested in the relevant art.

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WHAT IS CLAIMED IS:

1. A method for improving mental performance in patients having symptoms of reduced mental performance and are neither in a state of non-insulin dependent diabetes nor a state of
5 general impaired glucose tolerance, comprising administering to such a patient an effective amount of an agent to improve insulin sensitivity in the brain.
2. The method according to claim 1, wherein the agent increases glucose utilization in discrete brain areas.
- 10 3. The method according to claim 2, wherein the discrete areas are selected from the group consisting of blood brain barrier microvessels and areas in the brain associated with mental performance or memory.
4. The method according to claim 1, wherein the agent
15 improves glucose utilization in astrocytes or glial cells.
5. A method according to claim 1, wherein the agent is selected from the group consisting of insulin sensitizers.
6. The method according to claim 5, wherein the agent is a thiazolidinedione.
- 20 7. The method according to claim 6, wherein the thiazolidinedione is selected from the group consisting of

troglitazone, rosiglitazone, pioglitazone, darglitazone and
englitazone.

8. The method according to claim 5, wherein the agent is
an oxyzolidinedione.

5 9. The method according to claim 8, wherein the agent is
JTT 501.

10. The method according to claim 1, wherein the agent
activates the PPAR gamma receptor.

11. The method according to claim 1, wherein the agent
10 has agonist or partial agonist activity at the PPAR gamma
receptor.

12. The method according to claim 11 wherein the agent
is a substituted 4-hydroxy-phenylalcanoic acid derivative.

13. The method according to claim 11, wherein the agent
15 is a non-thiazolidinedione, non-oxyzolidinedione.

14. The method according to claim 13 wherein the agent
is GL 262570.

15. The method according to claim 1, wherein the agent
selectively activates one of the sub-types of the human PPAR
20 gamma receptor.

16. The method according to claim 1, wherein the agent activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor.

17. The method according to claim 1, wherein the agent
5 is a combination of a PPAR gamma activator and an RxR receptor activator.

18. The method according to claim 1, wherein the agent is a natural product or is derived from a natural product.

19. The method according to claim 1, wherein the agent
10 interacts with a PPAR alpha receptor or a PPAR delta receptor.

20. The method according to claim 1, wherein the agent interacts with the insulin transduction process so that the net effect is to increase the sensitivity or responsiveness of the insulin signal.

21. The method according to claim 1, wherein the agent
15 is administered in conjunction with at least one agent to improve mental performance.

22. The method according to claim 19, wherein the agent
to improve mental performance is selected from the group
20 consisting of carnitine, acetyl-carnitine and cerebral enhancers.

2020
Bogotá, D.C.,

Doctor:
Carlos Reinaldo Olarte García
Apoderado

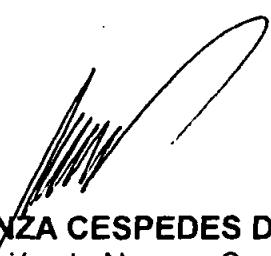
Oficio N°: 9871

ASUNTO:	Radicación PCT N°	08-28928
	Trámite	011
	Evento	379
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

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

28 AGO. 2009

202021

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo junto con un diluyente o vehículo farmacéuticamente aceptable.

10 2.- Una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo junto con un diluyente o vehículo farmacéuticamente aceptable, para uso en la mejora de la función cognitiva en un individuo que padece o es susceptible a deterioro cognitivo leve, enfermedad de Alzheimer u otras demencias.

15 3.- Un método para mejorar la función cognitiva en un individuo que padece o es susceptible a deterioro cognitivo leve, enfermedad de Alzheimer u otras demencias, comprendiendo el método administrar al individuo una cantidad segura y eficaz de una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil
20 o una sal farmacéuticamente aceptable del mismo.

 4.- El uso de una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo en la preparación de un agente para

mejorar la función cognitiva en un individuo que padece o es susceptible a deterioro cognitivo leve, enfermedad de Alzheimer u otras demencias.

5 5.- Una combinación de rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo para uso simultáneo, separado o secuencial en la mejora de la función cognitiva en un individuo que padece o es susceptible a deterioro cognitivo leve, enfermedad de Alzheimer u otras demencias.

10 6.- La composición de la reivindicación 2, el método de la reivindicación 3, el uso de la reivindicación 4 o la combinación de la reivindicación 5, donde el individuo no es homocigótico para el alelo APOE4.

7.- La composición de la reivindicación 2, el método de la reivindicación 3, el uso de la reivindicación 4 o la combinación de la reivindicación 5, donde el individuo no lleva el alelo APOE4.

15 8.- Un método para mejorar la función cognitiva en un individuo que padece o es susceptible a MCI, enfermedad de Alzheimer u otras demencias, y que no es homocigótico para el alelo APOE4, que comprende las etapas de: i) investigar al individuo para determinar que el individuo no sea homocigótico para el alelo APOE4; y después, ii) administrar una cantidad
20 segura y eficaz de una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo a dicho individuo.

9.- El método de conformidad con la reivindicación 8,

caracterizado además porque la etapa de investigación (i) implica determinar que el individuo lleva una sola copia del alelo APOE4.

10.- El método de conformidad con la reivindicación 8, caracterizado además porque la etapa de investigación (i) implica determinar que el individuo es APOE4-.

11.- El método de conformidad con cualquiera de las reivindicaciones 8 a 10, caracterizado además porque el individuo padece o es susceptible a MCI (particularmente MCI amnésico).

12.- El método de conformidad con cualquiera de las reivindicaciones 8 a 10, caracterizado además porque el individuo padece o es susceptible a la enfermedad de Alzheimer.

13.- Un método para investigar si un individuo padece o es susceptible a MCI, enfermedad de Alzheimer u otras demencias como ayuda para predecir la respuesta del individuo a la administración de una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo, que comprende la investigación para determinar si el individuo no lleva ninguna o lleva una copia del alelo APOE4.

14.- El método de conformidad con la reivindicación 13, caracterizado además porque incluye la selección para determinar si el individuo es APOE4-.

15.- Un equipo que comprende (i) una composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma

y donepezil o una sal farmacéuticamente aceptable del mismo y (ii) instrucciones sobre la administración del agonista de PPAR gamma (típicamente en forma de una composición farmacéutica) a un individuo que no es homocigótico para el alelo APOE4.

5 16.- La composición, método, uso, combinación o equipo de cualquiera de las reivindicaciones 1 a 15, donde la rosiglitazona está en forma de maleato de rosiglitazona.

10 17.- La composición, método, uso, combinación o equipo de cualquiera de las reivindicaciones 1 a 15, donde el donepezil está en forma de clorhidrato de donepezil.

15 18.- La composición de conformidad con cualquiera de las reivindicaciones 1, 2, 16 o 17, caracterizada además porque se formula para administración oral, parenteral (incluyendo subcutánea, intradérmica, intramuscular, intravenosa e intraarticular), inhalación (incluyendo polvos o neblinas en partículas finas que pueden generarse por medio de diversos tipos de aerosoles, nebulizadores o insufladores dosificadores presurizados), transdérmica (incluyendo por medio de un parche cutáneo), rectal y tópica (incluyendo dérmica, bucal, sublingual e intraocular).

20 19.- Una forma de dosificación oral que comprende: una primera composición que comprende rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo formulada para liberación inmediata tras el contacto con medios acuosos; y una segunda composición que comprende rosiglitazona o una sal

farmacéuticamente aceptable de la misma formulada para liberación modificada tras el contacto con medios acuosos.

20.- La forma de dosificación oral de conformidad con la reivindicación 19, caracterizada además porque la primera y la segunda composiciones están en forma de múltiples partículas.

21.- La forma de dosificación oral de conformidad con la reivindicación 20, caracterizada además porque las múltiples partículas son esferas de lactosa recubiertas de fármaco o que contienen fármaco.

22.- La forma de dosificación oral de conformidad con la reivindicación 20 o la reivindicación 21, caracterizada además porque las múltiples partículas que comprenden la primera composición están sin recubrir y las múltiples partículas que comprenden la segunda composición tienen un recubrimiento entérico.

23.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 20 a 22, caracterizada además porque las múltiples partículas se introducen en una cápsula.

24.- La forma de dosificación oral de conformidad con la reivindicación 19, caracterizada además porque toma la forma de un comprimido en el que la primera y la segunda composiciones se disponen en dos o más capas separadas.

25.- La forma de dosificación oral de conformidad con la reivindicación 24, caracterizada además porque la primera y la segunda composiciones se disponen en dos capas separadas.

26.- La forma de dosificación oral de conformidad con la reivindicación 24, caracterizada además porque la composición de liberación inmediata incluye una sacarosa.

27.- La forma de dosificación oral de conformidad con la
5 reivindicación 26, caracterizada además porque la composición de liberación inmediata incluye lactosa y opcionalmente estearato de magnesio.

28.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 19 a 27, caracterizada además porque la liberación modificada comprende la liberación retardada y/o sostenida.

10 29.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 24 a 27, caracterizada además porque la segunda composición comprende una composición de liberación sostenida en formulación de comprimido.

15 30.- La forma de dosificación oral de conformidad con una cualquiera de las reivindicaciones 20 a 23, caracterizada además porque la segunda composición comprende una composición de liberación sostenida en forma de múltiples partículas recubiertas con una membrana semipermeable.

20 31.- La formulación de dosificación oral de conformidad con cualquiera de las reivindicaciones 19 a 30, caracterizada además porque está recubierta con un recubrimiento entérico.

32.- Una formulación de dosificación oral que comprende un núcleo erosionable que comprende una formulación de dosificación oral de cualquiera de las reivindicaciones 19 a 30 y un recubrimiento erosionable

alrededor del núcleo, donde el recubrimiento erosionable comprende una o más aberturas que se extienden de una forma sustancialmente completa por todo dicho recubrimiento pero no penetran en el núcleo y que comunican el medio de uso con el núcleo, donde la liberación de la rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo desde el núcleo tiene lugar sustancialmente a través de dicha abertura o aberturas y por medio de la erosión del recubrimiento en condiciones de pH predeterminadas.

33.- La formulación de dosificación oral de conformidad con la reivindicación 32, caracterizada además porque la erosión del recubrimiento es dependiente del pH.

34.- La forma de dosificación oral de conformidad con la reivindicación 33, caracterizada además porque el recubrimiento erosionable es un recubrimiento entérico.

35.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 32 a 34, caracterizada además porque las aberturas en el recubrimiento tienen un tamaño en el intervalo de aproximadamente 0.19 a aproximadamente 50.3 mm², que corresponde a una abertura circular que tiene un diámetro en el intervalo de 0.5 mm a 8 mm.

36.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 32 a 35, caracterizada además porque el núcleo comprende capas discretas de la primera y segunda composiciones y el recubrimiento tiene dos aberturas dispuestas de tal forma que una primera

abertura proporciona acceso a la primera composición y una segunda
abertura proporciona acceso a la segunda composición.

37.- La forma de dosificación oral de conformidad con cualquiera
de las reivindicaciones 19 a 36, caracterizada además porque es para uso en
5 la mejora de la función cognitiva en un individuo que padece o es susceptible
a deterioro cognitivo leve, enfermedad de Alzheimer u otras demencias.

38.- Un método para mejorar la función cognitiva en un individuo
que padece o es susceptible a deterioro cognitivo leve, enfermedad de
Alzheimer u otras demencias, comprendiendo el método administrar al
10 individuo una forma de dosificación oral de cualquiera de las reivindicaciones
19 a 36.

39.- El método de conformidad con la reivindicación 38,
caracterizado además porque el individuo no es homocigótico para el alelo
APOE4.

15 40.- El método de conformidad con la reivindicación 38,
caracterizado además porque el individuo no lleva el alelo APOE4.

41.- Un método para mejorar la función cognitiva en un individuo
que padece o es susceptible a MCI, enfermedad de Alzheimer u otras
demencias, y que no es homocigótico para el alelo APOE4, que comprende
20 las etapas de: i) investigar al individuo para determinar que el individuo no sea
homocigótico para el alelo APOE4; y después ii) administrar una forma de
dosificación oral de cualquiera de las reivindicaciones 19 a 36 a dicho
individuo.

42.- El método de conformidad con la reivindicación 41, caracterizado además porque la etapa de investigación (i) implica determinar que el individuo lleva una sola copia del alelo APOE4.

5 43.- El método de conformidad con la reivindicación 41, caracterizado además porque la etapa de investigación (i) implica determinar que el individuo es APOE4-.

44.- El método de conformidad con cualquiera de las reivindicaciones 38 a 43, caracterizado además porque el individuo padece o es susceptible a MCI (particularmente MCI amnésico).

10 45.- El método de conformidad con cualquiera de las reivindicaciones 38 a 43, caracterizado además porque el individuo padece o es susceptible a la enfermedad de Alzheimer.

46.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 19 a 36, caracterizada además porque la rosiglitazona
15 está en forma de maleato de rosiglitazona.

47.- La forma de dosificación oral de conformidad con cualquiera de las reivindicaciones 19 a 36, caracterizada además porque el donepezil está en forma de clorhidrato de donepezil.

RESUMEN DE LA INVENCION

La invención se refiere a una composición farmacéutica que comprende tanto rosiglitazona o una sal farmacéuticamente aceptable de la misma como donepezil o una sal farmacéuticamente aceptable del mismo que es de utilidad en el tratamiento o profilaxis de la enfermedad de Alzheimer u otras demencias y el deterioro cognitivo leve; la invención también se refiere a formas de dosificación orales que comprenden rosiglitazona o una sal farmacéuticamente aceptable de la misma y donepezil o una sal farmacéuticamente aceptable del mismo.

15

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P08/428F



AVISO DE NOTIFICACIÓN

CORREO CERTIFICADO

**Industria y Comercio**

SUPERINTENDENCIA

Radicación : 8-28928- -7-0 Fecha: 2009-10-29 07:52:48
Trámite : 11 PATENTEIYII
Evento : 378 FASENACIONALI
Actuación : 432 COMUNICACTOADM
Destinatario : ELIANA ISAURA MORENO BOHORQUEZ Folios 1

Señor (a) (es)
ELIANA ISAURA MORENO BOHORQUEZ
CARRERA 13 NO. 119-95 OFC. 104
BOGOTA D.C.

Referencia RESOLUCION : 54871
Fecha : 29/10/2009
Expediente : 8-28928
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 378 FASE NACIONAL INCLUIDO CAPITULO I
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

Comedidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Quinto (5), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:00 a.m. a 4:30 p.m. jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción servicios en línea bases de datos - otros servicios - consulta actos administrativos.

En caso de que se haya notificado, haga caso omiso de este aviso.

Secretaría General

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Al contestar favor indique el número de
radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 pisos 2, 5, 7 y 10 PBX: 5870000

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Bogotá D.C. Colombia