



No. 07-104772- -00003-0000

Fecha: 2008-07-30 13:06:10 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 37

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A :

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

②

SOLICITUD
PUBLICADA

Número del expediente: 07-104772
Solicitante: N.V. ORGANON
Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo: "FORMA DE CRISTAL DE MALEATO DE ASENAPINA"
Gaceta: 591

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual <u> </u>	
	Teléfono: (571)3719900 Fax: (571)3730818	Número <u>802.006.279-4</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 104	C.C. ☒	NIT ☐
	Teléfono: (571) 2131213 Fax: (571) 6121979	C.E. ☐	Otro ☐
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Número <u>51'975.664</u> TP <u>83823</u>	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
Signo opositor: No cumple con los requisitos de patentabilidad.
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".

69

⑤ Comprobante de pago No. _____

Fecha _____

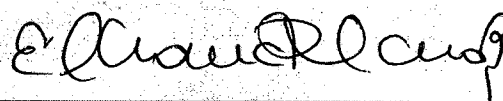
⑥ ANEXOS

- ☒ 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

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 104.772
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMA DE CRISTAL DE MALEATO DE ASENAPINA"
Solicitante : N.V. ORGANON.
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 591 del 30 de abril de 2008

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 **GYNOPHARM 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 "FORMA DE CRISTAL DE MALEATO DE ASENAPINA", cuyo titular es N.V. ORGANON, 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 medicamentos que comprenden maleato de asenapina. 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 5 de octubre de 2007, reivindicando prioridad bajo las solicitudes EP20050102742 del 2005-04-07; y, EP20050102969 del 2005-04-14; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 591 del 30 de abril de 2008, cuya publicación internacional corresponde a la WO2006106135 del 2006-10-12.

2.2. La solicitud colombiana 07 104.772 objeto de la presente oposición, se refiere a un compuesto Trans-5-cloro-2,3,3a, 12b-tetrahidro-2-metil-1H-dibenz [2,3:6,7] oxepino [4,5-c] pirrol (Z)-2-butenodioato ortorómbico; donde el compuesto es una forma de cristal ortorómbica que contiene 10% o menos de otra forma cristalina, 5% o menos de otra forma cristalina, o ninguna cantidad detectable de otra forma cristalina; donde el patrón de difracción en polvo de rayos x obtenido con radiación Cuka con picos en valores de 2-teta (2 θ) de 10.5 ° y 15.7 °; donde el

patrón de difracción en polvo de rayos x obtenido con radiación Cuka con picos en valores de 2-teta (2θ) de 10.5° , 15.7° , 18.3° , 19.0° , 22.2° , 23.2° y 27.5° ; donde el patrón de difracción en polvo de rayos x obtenido con radiación Cuka con picos en valores de 2-teta (2θ) de 10.5° , 15.7° , 18.3° , 19.0° , 20.3° , 20.8° , 22.2° , 23.2° , 25.6° y 27.5° ; donde el patrón espectroscópico Raman con picos en valores de 2888 cm^{-1} y 824 cm^{-1} ; donde el patrón espectroscópico Raman con picos en valores de 3051 cm^{-1} , 3029 cm^{-1} , 3011 cm^{-1} , 2888 cm^{-1} , 824 cm^{-1} y 717 cm^{-1} ; y, donde patrón espectroscópico Raman con picos en valores de 3072 cm^{-1} , 3051 cm^{-1} , 3029 cm^{-1} , 3011 cm^{-1} , 2909 cm^{-1} , 2888 cm^{-1} , 1245 cm^{-1} , 824 cm^{-1} , 747 cm^{-1} , 717 cm^{-1} y 194 cm^{-1} .

2.3. En primera instancia, se debe advertir que las reivindicaciones 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: WO2004110437 publicada el 23 de diciembre de 2004.
- D2: US5763476 publicada el 9 de junio de 1998.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un medio para el tratamiento de esquizofrenia con un agente antipsicótico administrado a un paciente con el sobrepeso, o a un paciente que tenía el beneficio de peso debido a un agente antipsicótico, o a un paciente que tiene que ser protegido contra el aumento de peso debido a la presencia de factores de riesgo para una enfermedad para la cual el sobrepeso es también un factor de riesgo o debido a la presencia de otro peso factores crecientes por el uso de la asenapina. Como tal, esta anterioridad D1 en el capítulo reivindicatorio ya define con anterioridad la asenapina y su uso en tratamientos de la esquizofrenia. Por su parte el documento D2, revela una composición sublingual o bucal farmacéutica que comprende trans-5-chloro-2-methyl-2,3,3a, 12b-tetrahydro-1H-dibenz [2,3:6,7] oxepino-pyrrole [4,5-c] o una sal farmacéuticamente aceptable del mismo y auxiliares farmacéuticamente aceptables convenientes para el empleo en composiciones sublinguales o bucales y el uso de para la fabricación de una composición sublingual o bucal farmacéutica para el tratamiento de trastornos mentales, como la psicosis y la esquizofrenia. Así las cosas, dicho conocimiento en combinación con aquel revelado en la solicitud D1 puede derivar de manera evidente el derivados de asenapina (Maleato de trans-5-cloro-2-metil-2,3,3a,12b-tetrahydro-1H-dibenz(2,3:6,7)oxepino(4,5-c)pirrol), llegando de manera evidente a dicha composición tal y como aquella revelada en la presente solicitud para tratar afecciones del sistema nervioso central, en particular

esquizofrenia. Como se demuestra es conocida la asenapina y mucho mas que es útil para el tratamiento de afecciones del sistema nervioso central, en particular esquizofrenia. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 en combinación con el documento D2, carece de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 104.772 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. 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, 7 de abril de 2005 ya era conocido, pues como se demostró, era parte del arte anterior a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto Trans-5-cloro-2,3,3a, 12b-tetrahidro-2-metil-1H-dibenz [2,3:6,7] oxepino [4,5-c] pirrol (Z)-2-butenodioato ortorómbico para tratar afecciones del sistema nervioso central, en particular esquizofrenia, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes*

para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMA DE CRISTAL DE MALEATO DE ASENAPINA"**, cuyo titular es N.V. **ORGANON**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 591 del 30 de abril de 2008.

3. PRUEBAS

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

- D1: WO2004110437 publicada el 23 de diciembre de 2004.
- D2: US5763476 publicada el 9 de junio de 1998.

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 **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO2004110437 publicada el 23 de diciembre de 2004.
 - D2: US5763476 publicada el 9 de junio de 1998.

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.

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PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, 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 **GYNOPHARM 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. **07104772**, titulada "**FORMA DE CRISTAL DE MALEATO DE ASENAPINA**", cuyo titular es N.V. **ORGANON.**, publicada en la gaceta No. 591 del 30 de abril de 2008.

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.

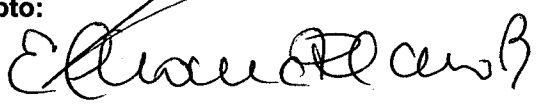
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

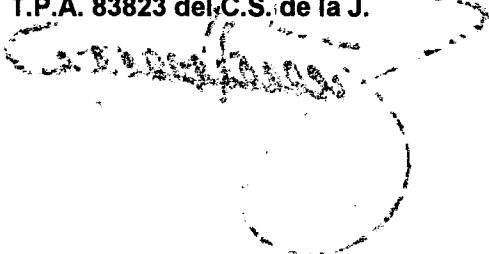
Dado y Firmado en Barranquilla (Colombia) a los 24 días del mes de Junio de 2008.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.
NIT: 802.006.279-4
Representante Legal

Acepto:


ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.



RECONOCIMIENTO DEL INSTRUMENTO PRIVADO

Ante mí, **WILMA ZAFRA TURBAY**,
 Veinticinco de Julio de 2008, en la ciudad de Bogotá, con

Elis Salas
Aragón

identificado con cédula de ciudadanía
CC 319 788 118

y declara que la firma puesta en el presente
 instrumento privado es suya y que el contenido
 del mismo es cierto. **24 JUN. 2008**
 Bogotá D.C.

FIRMA *[Firma]*

WILMA ZAFRA TURBAY
 NOTARIA VEINTICINCO

DECLARACION DE RECONOCIMIENTO

Ante la Notaria 2ª del Circuito de Chia Cundinamarca

Compareció *Eliez Tseur Moreno*
Bohorquez T.P. 83823

quien exhibió la C.C. No. *51.975.664*
 expedida en *Bogotá*.

y declaró que reconoce como suya la firma que aparece
 en el presente documento y que el contenido de este es cierto

El declarante *[Firma]*

Chia (Cund) **29 JUL 2008**

La Notaria,

Luz Adenis Segura Gil

REPUBLICA DE COLOMBIA
CHIA CUNDINAMARCA
 Notaria 2ª (E)

79

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 60,983
FECHA : JULIO 30 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-104772- -00003-0000

Fecha: 2008-07-30 13:06:10 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 37

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
SYNOFARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	4638626	19/06/2008	1,596,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	4791510	08/07/2008	266,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	81213510	22/07/2008	532,000.00

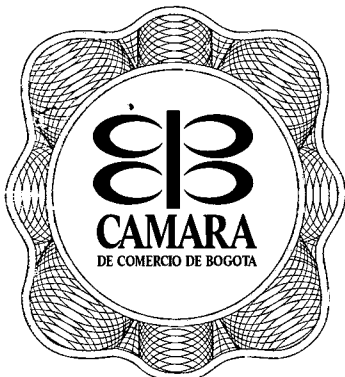
***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



01



* 7 1 8 2 2 3 5 1 *



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080625

Hora Certificado 11:29:31

Operacion : 02NA40625037

PAGINA No. 1

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

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 P?blica No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta C?mara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM 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
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

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:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

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 t?rmino de duraci?n de la sociedad se fij? hasta el 16 de Dic/bre de 2047. ✓

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro 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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080625

Hora Certificado 11:29:31

Operacion : 02NA40625037

PAGINA No. 2

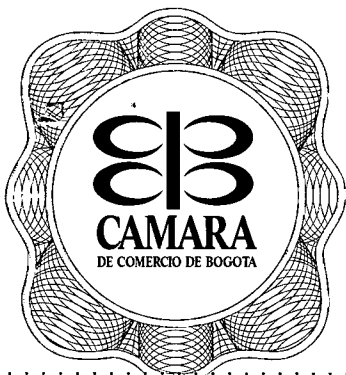
y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal.

c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas 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) 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 cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, 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 GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas 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, 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 gravamenes 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 lo de sus socios.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci?n
Autorizado		
\$*****4,000,000,000	*****4,000,000	*****1,000
Suscrito		
\$*****2,672,646,000	*****2,672,646	*****1,000
Pagado		
\$*****2,672,646,000	*****2,672,646	*****1,000

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080625

Hora Certificado 11:29:31

Operacion : 02NA40625037

PAGINA No. 3

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, 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\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le correspondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que segun Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.-----
cuya parte pertinente se inscribi? en esta Camara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Llobet Poal Manuel	CC.*****14,670,196
2. Zanatta Reheman Leonardo Andres	CC.*****2,760,271
3. Munoz Marroquin Diego	CC.*****7,688,292
4. Montealegre Gonzalez Andres Leonardo	CC.*****79,950,262

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080625

Hora Certificado 11:29:31

Operacion : 02NA40625037

PAGINA No. 4

Suplentes

1. Agudelo Pelaez Luis Hernando	CC.*****14,238,997
2. Aroca Almanza Arleth Ayelina	CC.*****36,718,415
3. Penaranda Urbina Adriana Paola	CC.*****53,120,683
4. tovar Vasquez Ruth	CC.*****52,175,756

C E R T I F I C A

Que seg?n Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Gerente General.	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

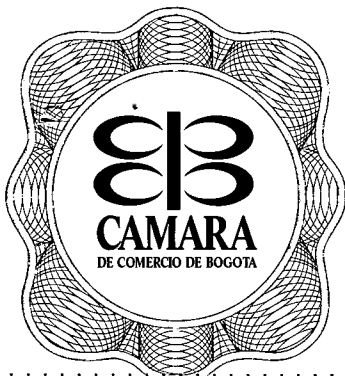
Que seg?n Acta No. 16 del 08 de Mayo de 2008 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Revisor Fiscal	
Marroquin Sepulveda Edgar	CC.*****17,147,542

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080625

Hora Certificado 11:29:31

Operacion : 02NA40625037

PAGINA No. 5

732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

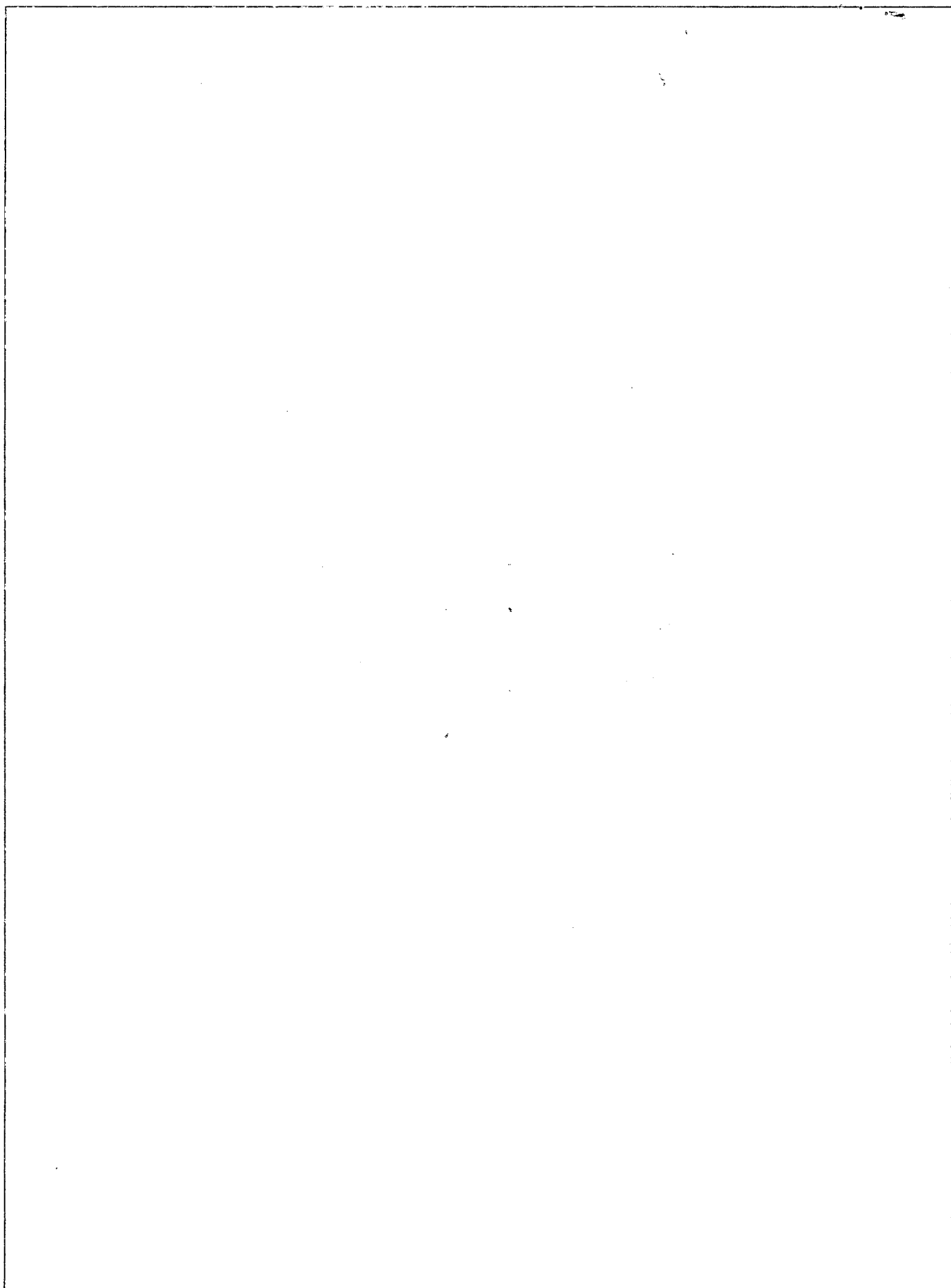
Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Abril de 2008.

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

mka



ANEXO 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Organization
International Bureau



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PCT

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(71) Applicant (for all designated States except US):
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(72) Inventor; and

(75) Inventor/Applicant (for US only): **TONNAER, Jeroen**,
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(74) Agent: **VAN WEZENBEEK, P.M.G.F.**; P.O. Box 20,
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(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, IT, 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
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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: **ASENAPINE FOR THE TREATMENT OF SCHIZOPHRENIA IN A PATIENT WITH OVERWEIGHT OR PREDISPOSITION FOR OVERWEIGHT**

(57) Abstract: The invention provides means for the treatment of schizophrenia with an antipsychotic agent administered to a patient with overweight, or to a patient that was having weight gain due to an antipsychotic agent, or to a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors by using asenapine for the manufacture of a medicine for such treatment.

WO 2004/110437 A1



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ASENAPINE FOR THE TREATMENT OF SCHIZOPHRENIA IN A PATIENT WITH OVERWEIGHT OR PREDISPOSITION FOR OVERWEIGHT

The invention relates to a method for the treatment of schizophrenia with an antipsychotic agent administered to a patient with overweight.

5

The average human population is afflicted with a life-time occurrence of schizophrenia at a rate of about 0.5 - 1% (Goldber et al.; Canadian J. of Psychiatry Vol 47; pp 833-843; 2002). The disease, if untreated, is completely debilitating with regard to social and economic functioning of the afflicted person. Fortunately, considerable progress has been made during the last 45 years in the treatment of the disease, resulting in some social behaviour benefits for many patients. It is the use of effective anti-psychotic drugs that has produced this dramatic improvement in treatment outcome. With the classic antipsychotic agents, such as chlorpromazine, haloperidol, spiperone etc. the importance of dopamine receptor blockade as the mechanism of action for antipsychotic effects has been demonstrated. These drugs nevertheless had shortcomings which were the challenge to be overcome by new agents. These side effects, collectively referred to as extrapyramidal side (EPS) effects, are Parkinson-like behaviour, akathisia, dystonias and serious, sometimes irreversible disturbances in muscle control, known as tardive dyskinesia (TD). Clozapine, an older drug showed that antipsychotic effects could be obtained without frequent inducement of the afore-mentioned side effects. This led to the class of atypical antipsychotic agents, which are those that are as effective as the first generation of antipsychotic drugs, but less prone to induce extrapyramidal side effects and having a broader therapeutic efficacy. The latter refers to efficacy against the negative symptoms of schizophrenia. The atypical anti-psychotic drugs can be further subdivided into three categories based upon receptor-binding profiles and the side effects that follow. These categories are (a) the relatively pure dopamine antagonists (D2 antagonists, including sulpiride and amisulpiride), (b) the dopamine (D2)-serotonin (5-HT₂)-norepinephrine (alpha 1) antagonists (risperidone, ziprasidone and sertindole) and (c) the multireceptor antagonists (clozapine, olanzapine and seroquel) (See Gerlach and Peacock, International Clinical Psychopharmacology 10 Suppl 3: 39-48, 1995.; Tamminga and Lahti, International Clinical Psychopharmacology 11 Suppl 2: 73-76, 1996). These atypical antipsychotics, however, cause substantial weight gain that is both greater than conventional antipsychotics and of clinically meaningful magnitude. This leads in individual cases to poor compliance and other adverse health effects. The largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose

related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when selecting a treatment (Nasrallah, Psychoneuroendocrinology. Vol 28, Suppl 1 pp 83-96, 2003; Homel, Casey and Allison Schizophrenia Research Vol 55(3) pp 277-284, 2002). This is the more
5 relevant because obesity is commonly seen in patients with schizophrenia. According to some surveys the mean body mass index (BMI) for individuals with schizophrenia is significantly higher than individuals who are not schizophrenic (Homel, Casey and Allison, Schizophrenia Research, Vol 55(3) pp 277-284, 2002; Ananth et al Expert Review of Neurotherapeutics Vol 3(1) pp 59-68, 2003). Since overweight and obesity
10 are risk factors for other health diseases, such as diabetes and cardiovascular disorders, the need for an improved drug treatment for individuals having both schizophrenia and overweight is clear.

It has now been found that treatment of such patients with asenapine is safer than
15 treatment with just any one of most other antipsychotic agents.

The term treatment is used here to refer to a measure or set of measures taken and/or prescribed by a doctor in order to combat symptoms or consequences of disease. Treatment with a drug is by administration to the patient by any means
20 known in the art directly to the patient or indirectly by prescription. The benefit of the improved treatment can be observed in individual patients, for example when switching to the new treatment from a treatment with any other antipsychotic agent with weight increasing side effect in that particular patient. The benefit can also be observed as a group effect, whereby it cannot be excluded that certain individuals
25 still gain weight, but the overall group result definitely shows less average weight gain effect in comparison to a known treatment. In view of the favourable property of asenapine on weight it is an aspect of the invention to treat a patient for schizophrenia with asenapine, whereby the patient was having weight gain effect due to another antipsychotic agent. In this aspect of the invention the patient is not
30 necessarily a patient with overweight. In another aspect, the need to avoid weight gain due to drug treatment is related to the special risk effect of overweight in that particular patient, for example due to the presence of other risk factors, for example for diabetes or cardiovascular disease. Such risk factors may stem from genetic disposition or behavioural habits, such as smoking. or sudden abstinence from
35 smoking. It is therefore another aspect of the invention to treat a patient for schizophrenia with asenapine, whereby the patient needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor. Again such a patient in need of avoidance of weight increasing

effect is not necessarily already overweight. In still a further aspect the patient is in need of avoidance of weight increasing effect because of the presence of other weight increasing factors per se, such as abstinence from nicotine in relation to a decision to stop the smoking habit.

- 5 Schizophrenia is defined in the field of psychiatry as a disease falling in a specific diagnostic category with characteristic cognitive disturbances. Diagnosis can be made in accordance with the criteria given in handbooks for psychiatry, for example in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) published by the American Psychiatric Association, Washington, D.C. (1994).
- 10 Antipsychotic agent is a drug with therapeutic activity, be it curative or preventive, on patients with schizophrenia and other psychoses. In this description of the invention no difference is made in meaning between an antipsychotic drug, a neuroleptic drug and an antischizophrenia drug. In the art the terms are used interchangeably, although the term neuroleptic is usually avoided in modern times, since it is
- 15 associated with the classic drugs having the strongest Parkinson-like side effects, resulting from uncompensated inhibition of dopaminergic neurotransmission in the brain.

Administration to a patient can be by any means aimed at making the drug available near the receptors in the body mediating the therapeutic effect. Tablets and capsules

20 for oral intake are the most commonly known. For asenapine a sublingual formulation is developed so that the drug can be given in the oral cavity and is made available to the general circulation. See for example WO9523600

- Obesity and overweight are used in the present context as obesity and overweight according to a judgment by a doctor, so that this term is used here with a medical
- 25 meaning rather than with a meaning referring to (un)desirable physical appearance of people. Quantitative measures are defined in the art in order to have more objective criteria for overweight and obesity. A commonly used parameter is the body mass index (BMI) defined with the formula G/L^2 ; wherein G is body weight in kg and L is body height in meters. An acceptable BMI from the medical point of view is 25 kg/m^2 .
- 30 Higher values are considered overweight. Overweight as risk factor for other health problems is proportionally operative as such, that is, the higher the overweight, the higher the chance for emergence of other diseases, such as diabetes and cardiovascular disease. The World Health Organisation and the NIH have defined that the term obesity as a physical condition is characterised by a BMI of $\geq 30 \text{ kg/m}^2$.
- 35 Note, for the purpose of clarity of terms that the term overweight includes the term obese, the latter being a more serious form of overweight. Since the effect of overweight is relative to the degree of overweight, different cut-off points than the mentioned 25 kg/m^2 are used to define unhealthy overweight. One can find in expert

literature values of 26 kg/m² and 27.3 kg/m² as starting criteria for obesity in women and 28 and 27.8 as starting criteria for obesity in men. The present invention has as further specific embodiments the use of asenapine for methods of treatment of schizophrenia in individuals with overweight defined objectively as those men

5 selected with a BMI of ≥ 26 , ≥ 26.5 , ≥ 27 , ≥ 27.3 , ≥ 27.5 , ≥ 28 , ≥ 29 , ≥ 30 , ≥ 35 or ≥ 40 and/or those women selected with a BMI of ≥ 26 , ≥ 26.5 , ≥ 27 , ≥ 27.5 , ≥ 27.8 , ≥ 28 , ≥ 29 , ≥ 30 , ≥ 35 or ≥ 40 .

Asenapine refers to the compound as registered by the WHO under that name, which is chemically named trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-

10 dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. It is usually made available as the 1:1 maleate salt, so that asenapine may refer to the maleate salt specifically or to the base, or to any salt or hydrate of the base. In the present description the latter and broad meaning is used. The term encompasses also the separate enantiomeric forms of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-

15 c]pyrrole, which can be used in pure form for the same purpose. When amounts of asenapine are given, reference is made to the base content of the substance, unless explicitly stated otherwise.

Asenapine is administered in an amount to the patient in a therapeutically effective
20 amount. By a therapeutically effective amount is meant that amount which is capable of at least partially preventing, reversing, reducing, ameliorating or otherwise suppressing the psychotic disease being treated. The ultimate dosage to provide relief for the patient depends a.o. on individual characteristics, such as condition and age. A therapeutically effective amount can be determined by one of ordinary skill in
25 the art using no more than routine experimentation.

Daily dose is the amount of drug administered per 24 hours in any pharmaceutical formulation. For extended release formulations the intended duration for effective dose administration is divided by the number of days in order to arrive at an indication of the daily dose of the treatment. Asenapine can effectively be used in the
30 category of overweight patients in a daily dose range of 0.5 – 50 mg per person, whereby the exact amount is selected depending on route of administration, desired intensity of effect, and individual patient needs and tolerance. In particular the body weight can influence the daily dose, because portions of the drug may be stored in fat tissue, where it is temporarily not available for the receptors involved in the
35 antischizophrenic effect. The preferred range for daily dose is 5-20 mg. Preferred is to administer the daily dose with a sublingual or buccal formulation in one or more dosage units (see WO 9523600) containing an amount of asenapine selected from the range of from 1- 15 mg, with preference for 5 or 10 mg.

It is an aspect of the invention to provide for the use of asenapine in a method for the manufacture of a medicine, which medicine comprises asenapine and is made to be suitable for the treatment of a patient with overweight, or a patient that was having

5 weight gain effect due to another antipsychotic agent or a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors.

In another aspect, the invention provides for a pharmaceutical formulation comprising

10 asenapine suitable for the treatment of a patient with overweight, or a patient that was having weight gain effect due to another antipsychotic agent or a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors.

15 Pharmaceutical formulations are commonly prescribed to the patient in "patient packs" containing a number dosing units or other means for administration of metered dose units for use during a distinct treatment period in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk

20 supply, in that it can be provided that the patient has access to a package insert contained in the patient pack. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions. Thus, the invention further includes a pharmaceutical formulation, as herein before described, in combination with packaging material suitable for said treatment. In such a patient

25 pack the intended use of the formulation for the treatment according to the invention can be inferred by instructions, facilities, provisions, adaptations and/or other means to help using the formulation most suitably for the treatment. Such measures make a patient pack specifically suitable for and adapted for use for treatment according to the present invention.

30

Thus, the invention provides a patient pack for the treatment of a schizophrenia patient with overweight or at risk for overweight with asenapine. comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, which patient pack comprises means to help a patient

35 using the dose units most suitably.

Example

Assessment of the efficacy and safety of asenapine (5 mg twice a day) in subjects with acute exacerbation of their schizophrenic illness, compared to risperidone (3 mg
5 twice daily and placebo in a randomized double blind, fixed-dose 6-week trial. The treatment period of 42 days consisted of a 21-day inpatient phase and a 21-day outpatient phase.

The study was done as a multicenter trial. Patients in the study were recruited in 27 centers and randomly assigned to one of the three trial groups.

10

Screening of candidate subjects for recruitment into the trial was done immediately after the informed consent was signed. The investigator or subinvestigator determined whether the subject met the DSM-IV criteria for schizophrenia. On day 0, the day before the first dose of trial medication was given, the health status of each
15 subject was re-assessed to ensure eligibility for randomization of the subject in the trial. A total of 182 subjects were included into the trial, of these 180 received treatment: 59 asenapine, 59 risperidone, 62 placebo.

To be considered for inclusion in the trial, male or non-pregnant female subjects of
20 18 years of age or older and experiencing an acute exacerbation of their schizophrenic illness diagnosed according to DSM IV criteria with schizophrenia of the paranoid type [295.30], disorganised type [295.10], catatonic type [295.20], or undifferentiated type [295.90] were selected. Subjects were to have a PANSS score of at least 60 at baseline.

25

Asenapine and placebo were prepared as indistinguishable sublingual tablets according to WO9523600, example 1, with adaptation of the amount of asenapine in order to obtain proper amounts into the dosage units.

After a washout period of 3-7 days, subjects in the trial were randomized to the three
30 treatment groups (asenapine, risperidone, placebo). Subjects randomized to the asenapine group received trial medication according to the following schedule: 1 mg twice daily on day 1, 2 mg twice daily on day 2, 3 mg twice daily on day 3, 4 mg twice daily on day 4, and 5 mg twice daily on days 5 through 42. Subjects randomized to the risperidone group received trial medication according to the following schedule: 1
35 mg twice daily on day 1, 2 mg twice daily on day 2, and 3 mg twice daily on days 3 through 42. Subjects randomized to the placebo group received placebo twice daily throughout the treatment period. Assessments during the treatment period were

conducted weekly, except for vital sign assessments during the inpatient phase which were conducted daily.

Among other tests the efficacy on disease symptoms is evaluated with the positive
5 and negative syndrome scale (PANSS). Body weight was measured at screening
and on day 42, or the subjects final day of treatment.

Demographic and other subject characterisation were performed and descriptive
statistics were obtained for age, weight, and height by treatment group and pooled
10 across treatment groups

Baseline characteristics by treatment group: age, weight, and height

		Asenapine 5 mg (N=59)	Risperidone 3 mg (N=59)	Placebo (N=62)	Total (N=180)
Age(years)	N	59	59	62	180
	Median	39	41	41.5	41
	Maximum	70	61	68	70
	Minimum	21	22	22	21
Weight (kg)	N	57	58	58	173
	Median	84.40	82.25	84.15	83.60
	Maximum	155.0	161.9	150.0	161.9
	Minimum	58.6	57.2	54.9	54.9
Height (cm)	N	57	57	59	173
	Median	173	170	173	172
	Maximum	188	193	189	193
	Minimum	152	150	150	150
BMI*		28.20	28.46	28.12	28.26

* BMI was calculated with the median values of weight and height.

5 Results

Asenapine and risperidone were both significantly more effective than placebo in reducing the symptoms of schizophrenia. Clinically significant weight gain (i.e., an increase from baseline of $\geq 7\%$) was reported in 4% (N=2) of the asenapine subjects, 17% (N=8) of the risperidone-treated subjects, and 2% (N=1) of the placebo-treated subjects.

Table: Number of subjects with clinically significant change from baseline in body weight by treatment group (All-Subjects-Treated Group)

	Asenapine 5 mg			Risperidone 3 mg			Placebo		
	N	n	%	N	n	%	N	n	%
Increase of $\geq 7\%$	46	2	4.3	47	8	17.0	54	1	1.9
Decrease of $\geq 7\%$	46	0	0.0	47	1	2.1	54	4	7.4

N is total number of subjects with data and n is number of subjects in category

Of the 147 subjects in the All-Subjects-Treated Group who had weight data recorded at baseline and at the end of the trial, 11 had a clinically significant increase from baseline in body weight and 5 had a clinically significant decrease from baseline in

body weight. The percentage of subjects with clinically significant weight gain from baseline was highest in the risperidone group (17.0%), lower in the asenapine group (4.3%), and lowest in the placebo group (1.9%). Four subjects experienced a greater than 10% weight gain from baseline: 1 asenapine subject, 2 risperidone subjects,

5 and 1 placebo subject.

At end point the risperidone group showed 1.9% increase in body weight from baseline, compared with a 0.5% increase of the asenapine group and a 0.3% increase for the placebo group.

10 Overall conclusion

The low incidence of clinically significant weight gain and minimal other side effects demonstrated that asenapine has a favorable benefit-risk profile.

Claims

1. Method for the treatment of schizophrenia with an antipsychotic agent administered to a patient with overweight wherein that the antipsychotic agent is
5 asenapine.
2. Method for the treatment with asenapine of schizophrenia in a patient that was having weight gain due to another antipsychotic agent.
- 10 3. Method for the treatment with asenapine of schizophrenia in a patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors.
- 15 4. The method according to claim 1 wherein the overweight is defined to be a BMI of ≥ 25 .
5. The method according to claim 4 wherein the overweight is defined to be a BMI of ≥ 27.8 for men and ≥ 27.3 for women.
20
6. The method according to any one of claims 1 – 5 wherein asenapine is administered to the patient by the sublingual route.
7. Use of an antipsychotic agent in the manufacture of a medicament for the
25 treatment of schizophrenia in a patient with overweight wherein the antipsychotic agent is asenapine.
8. Use of asenapine in the manufacture of a medicament for the treatment of schizophrenia administered to a patient wherein the patient was having weight gain
30 due to another antipsychotic agent.
9. Use of asenapine in the manufacture of a medicament for the treatment of schizophrenia administered to a patient wherein the patient needs to be protected against weight increase due to the presence of risk factors for a disease for which
35 overweight is also a risk factor or due to the presence of other weight increasing factors.
10. The use of claim 7 wherein the overweight is defined to be a BMI of ≥ 25 .

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11. The use of claim 9 wherein the overweight is defined to be a BMI of ≥ 27.8 for men and ≥ 27.3 for women.

- 5 12. The use of claims 7-11 wherein the medicament is to be administered to the patient by the sublingual route.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051069

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/407 A61P25/18

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)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, MEDLINE, WPI Data, BIOSIS, PAJ, CHEM ABS Data,
PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/156067 A1 (SVENSSON TORGNY ET AL) 24 October 2002 (2002-10-24) abstract paragraphs '0003!', '0014!', '0015!', '0018!' - '0020!', '0030!', '0035!', '0037!' - '0042!' claims 1,5,9,10,19	1-5,7-11
Y		6,12
A	----- WO 95/23600 A (AKZO NOBEL NV ; DELBRESSINE LEONARDUS PETRUS C (NL); WIERINGA JOHAN) 8 September 1995 (1995-09-08) cited in the application abstract page 1, line 1 - page 2, line 19 page 5, line 11 - line 16	1-12
Y	----- -/--	6,12

☒ Further documents are listed in the continuation of box C☒ Patent family members are listed in annex

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *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)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *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
- *Z* document member of the same patent family

Date of the actual completion of the international search

19 November 2004

Date of mailing of the international search report

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Authorized officer

Langer, O

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/051069

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/051069

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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A	BAZIRE S: "Schizophrenia" CHEMIST&DRUGGIST, 'Online! 3 August 2002 (2002-08-03), pages 17-20, XP002266562 Retrieved from the Internet: URL: http://www.dotpharmacy.co.uk/up1243.pdf f> 'retrieved on 2004-01-12! page 19 - page 20	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/051069

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims 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. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/051069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			RU 2139051 C1 10-10-1999

ANEXO 2

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US005763476A

United States Patent [19]
Delbressine et al.

[11] **Patent Number:** **5,763,476**
[45] **Date of Patent:** **Jun. 9, 1998**

[54] **SUBLINGUAL OR BUCCAL
PHARMACEUTICAL COMPOSITION**

[75] Inventors: **Leonardus Petrus Carla Delbressine**,
Nijmegen; **Johannes Hubertus**
Wieringa, Heesch, both of Netherlands

[73] Assignee: **Akzo Noble N.V.**, Arnhem, Netherlands

[21] Appl. No.: **693,064**

[22] PCT Filed: **Mar. 1, 1995**

[86] PCT No.: **PCT/EP95/00765**

§ 371 Date: **Oct. 11, 1996**

§ 102(e) Date: **Oct. 11, 1996**

[87] PCT Pub. No.: **WO95/23600**

PCT Pub. Date: **Sep. 8, 1995**

[30] **Foreign Application Priority Data**

Mar. 2, 1994 [EP] European Pat. Off. 94200521

[51] Int. Cl.⁶ **A61K 31/40**

[52] U.S. Cl. **514/410**; 514/270; 514/289;
514/315; 514/318

[58] Field of Search 424/274; 514/410.
514/206, 270, 289, 315, 318

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Primary Examiner—Keith D. MacMillan

Attorney, Agent, or Firm—Sharon N. Klesner; Mary E.
Gormley

[57] **ABSTRACT**

The invention relates to a sublingual or buccal pharmaceutical composition comprising *trans*-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino-[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable auxiliaries suitable for use in sublingual or buccal compositions, and the use thereof for the manufacture of a sublingual or buccal pharmaceutical composition for the treatment of mental disorders, such as psychosis and schizophrenia.

13 Claims, No Drawings

SUBLINGUAL OR BUCCAL PHARMACEUTICAL COMPOSITION

This application is a 371 of PCT/EP95/00765, filed Mar. 1, 1995.

The invention relates to a sublingual or buccal pharmaceutical composition, and more specifically to a sublingual or buccal composition for the treatment of various mental disorders.

The compound trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole and the preparation thereof are disclosed in U.S. Pat. No. 4,145,434. The compound is described as having CNS-depressant activity and antihistamine and antiserotonin activities.

The pharmacological profile of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, its kinetics and metabolism, as well as the first safety and efficacy studies in human volunteers and in schizophrenic patients were reviewed by De Boer et al. (*Drugs of the Future* 1993, 18(12), 1117-1123). It has been established that Org 5222 [5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1)] is a very potent dopamine and serotonin antagonist with potential antipsychotic activity.

Phase I clinical studies on the effects of perorally administered trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole however, revealed that serious cardiotoxic effects, e.g. postural hypotension and/or impairment of baroreceptor functioning, occurred.

Surprisingly, it has now been found that on sublingual or buccal administration, trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole has substantially less cardiovascular side effects.

The invention therefore relates to a sublingual or buccal pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable auxiliaries suitable for use in sublingual or buccal compositions.

The compositions of the invention are useful in treating mammals, including humans, suffering from diseases which are susceptible to treatment by trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. Such diseases include mental disorders, such as tension, excitation, anxiety, psychosis, and schizophrenia. The compositions may also be used for antihistamine and for antiserotonin related diseases.

In its simplest form the pharmaceutical composition of the invention consists of an aqueous solution, for instance comprising 0.9% (w/v) of sodium chloride and the active compound 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, or a pharmaceutically acceptable salt thereof. The maleate salt (Org 5222) is a preferred salt. The active compound is rapidly absorbed from these aqueous pharmaceutical compositions, when kept under the tongue or in the mouth of a patient.

Preferred pharmaceutical compositions are solid pharmaceutical compositions which rapidly disintegrate in the mouth of a subject, upon insertion into the buccal pouch or upon placement under the tongue. Rapid disintegration means that the pharmaceutical composition is disintegrated within 30 seconds in water at 37° C., and preferably within 10 seconds, as measured according to the procedure described in Remington's *Pharmaceutical Sciences*, 18th Edition (Ed. A. R. Genaro), 1990, pp 1640-1641; see also US Pharmacopeia, Chapter <701>.

In a preferred embodiment the pharmaceutical compositions of the invention are tablets or lozenges which comprise

a rapidly disintegrating composition of a pharmaceutically acceptable water-soluble or water-dispersible carrier material. Tablets and lozenges comprising a rapidly disintegrating composition of a pharmaceutically acceptable water-soluble or water-dispersible carrier material are known in the art, for example as disclosed in U.S. Pat. No. 4,371,516. Such tablets may be prepared by freeze-drying of an aqueous solution comprising 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, a water-soluble or water-dispersible carrier material and, optionally, pharmaceutically acceptable excipients. Such excipients are known in the art, see for instance Remington's *Pharmaceutical Sciences*, 18th Edition (Ed. A. R. Genaro), 1990, pp 1635-1638, and are commonly used in pharmaceutical compositions, for instance surfactants, colouring agents, flavouring agents, preservatives and the like.

The water-soluble or water-dispersible carrier material is preferably water-soluble. Suitable water-soluble carrier materials are (poly)saccharides like hydrolysed dextran, dextrin, mannitol, and alginates, or mixtures thereof, or mixtures thereof with other carrier materials like polyvinylalcohol, polyvinylpyrrolidone and water-soluble cellulose derivatives, like hydroxypropyl cellulose.

A preferred carrier material is gelatin, especially partially hydrolysed gelatin. The partially hydrolysed gelatin can be prepared by heating of a solution of gelatin in water, for example in an autoclave at about 120° C. for up to 2 hours. The hydrolysed gelatin is used in concentrations of about 1 to 6% (w/v), and preferably in concentrations of about 2 to 4% (w/v).

The preferred dosage forms of the composition of the invention, i.e. tablets or lozenges, can be prepared by methods known in the art. For example, according to a method as disclosed in British Patent 2,111,423, an aqueous composition comprising a predetermined amount of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole, a pharmaceutically acceptable water-soluble or water-dispersible carrier material and optionally pharmaceutically acceptable auxiliaries and excipients, is transferred into a mould, after which the composition is frozen and the solvent is sublimed, preferably by freeze-drying. The composition preferably contains a surfactant, for example Tween 80 (polyoxyethylene (20) sorbitan mono-oleate), which may help to prevent the freeze-dried product from sticking to the surface of the mould.

The mould may comprise a series of cylindrical or other shape depressions, each having a size corresponding to the desired size of the dosage form. Alternatively, the mould may have a larger size than the desired size of the dosage form, and after the contents are freeze-dried the product can be cut into the desired size. Preferably the dosage form is freeze-dried in the form of a lyosphere, which is a freeze-dried spherical-shaped droplet containing the active ingredient.

A preferred mould would correspond to a depression in a sheet of film material, as for example disclosed in U.S. Pat. No. 4,305,502 and U.S. Pat. No. 5,046,618. The film material may be similar to that employed in conventional blister packs.

Each dosage form of the pharmaceutical composition of the present invention comprises one dosage unit of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole as active ingredient. A dosage unit may contain between 0.005 mg and 15 mg of the active ingredient. Preferably the dosage unit contains 0.03-0.50 mg of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole.

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The invention further relates to the use of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole for the manufacture of a sublingual or buccal pharmaceutical composition for treating mental disorders, such as psychosis and schizophrenia.

A method of providing therapy using the pharmaceutical composition of the present invention comprises the insertion of a dosage form according to this invention in the buccal pouch or under the tongue of a subject, such as a human. The ultimate dosage to provide relief for the patient depends, apart from individual characteristics, on the patient's weight, condition and age. Usually, administration of 1-4 dosage units of the pharmaceutical composition of the invention per day is sufficient for obtaining a therapeutic effect. The therapy may be continued as long as necessary or desired.

The invention is further illustrated by the following examples.

Example 1

a: Preparation of Hydrolysed Gelatin (3% w/v)

Gelatin (30 g) was dissolved in 1 l of distilled water under heating and constant stirring. The resulting solution was autoclaved at 121° C. (10⁵ Pa) for one hour, upon which the solution was allowed to cool to room temperature to give hydrolysed gelatin (3% w/v).

b: Preparation of a Solid Pharmaceutical Dosage Form

A sheet of polyvinyl chloride (PVC) containing cylindrical depressions was cooled with solid carbon dioxide. 0.2 g of Org 5222 [5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1)] were dissolved in 1 l of hydrolysed gelatin under mixing. While mixing was continued, in each of the depressions 0.5 ml of the solution were placed. When the contents of the depressions were frozen, the PVC sheet was placed in a freeze-drying system. An aluminum foil was finally sealed to the sheet so as to close off the depressions containing the freeze-dried pharmaceutical dosage forms. Each depression contains a pharmaceutical unit dosage comprising 0.10 mg of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1).

Examples 2

In a manner as described in Example 1b a pharmaceutical composition was prepared comprising:

0.2 g of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222), 0.50 g of Tween 80 (polyoxyethylene (20) sorbitan mono-oleate, 30 g of sucrose and 1 l of hydrolysed gelatin (3% w/v).

Example 3

In a manner as described in Example 1b a pharmaceutical composition was prepared comprising:

2 g of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222), 0.50 g of Tween 80 (polyoxyethylene (20) sorbitan mono-oleate, 30 g of sucrose and 1 l of hydrolysed gelatin (3% w/v), 1 l of hydrolysed gelatin (3% w/v).

Example 4

A pharmaceutical composition was prepared comprising:

0.2 g of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222), 17 g of sodium alginate, 35 g of dextran (MW approx.

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40,000), 17.5 g of dextrose, and distilled water to a volume of 1 l, which composition was freeze-dried into unit dosage forms.

Example 5

A pharmaceutical composition was prepared comprising:

0.4 g of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222), 50 g of dextrin, 0.20 g of Tween 80 (polyoxyethylene (20) sorbitan mono-oleate, 30 g of polyvinylpyrrolidone and distilled water to a volume of 1 l, which composition was freeze-dried into unit dosage forms.

Example 6

Lyospheres were prepared by dissolving 138.9 g of sucrose, 40.8 g of sodium citrate, and 111 mg of polysorbate 20 in 300 ml of distilled water, adjusting the pH to 7 using 1N hydrochloric acid and 1N sodium hydroxide and adding water to 500 ml. The solution was homogenized by stirring and filtered through a sterile 0.22 µm filter, after which the solution was freeze-dried into droplets of 0.1 ml, which droplets were transferred in the frozen state into a freeze dryer and then freeze-dried to unloaded spherical lyophilized dosage units (lyospheres).

120 mg of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222) were dissolved in 1 ml of ethanol and 83 µl of this solution were added to one lyospheres, after which the ethanol was removed by gentle heating, to obtain a lyosphere containing 10 mg of Org 5222. Lyospheres containing 1 and 0.1 mg of Org 5222 respectively, were prepared in a similar manner by dissolving 60 or 6 mg of Org 5222 respectively in 1 ml of ethanol, after which 16.6 µl of this solution were added to one lyosphere.

Example 7

A pharmaceutical composition was prepared comprising:

0.094 g of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1) (Org 5222), 30 g of mannitol, 40 g of gelatine, and distilled water to a volume of 1 l, which composition was freeze-dried according to the method of Example 1b into unit dosage forms, each of which comprises 10 µg of Org 5222.

Example 8

Orthostatic hypotension (tilt challenge) and direct haemodynamic and electrophysiologic effects were determined as follows:

Method

Beagle dogs (10-20 kg, Harlan, France) were instrumented under anesthesia. A micromanometer (Königsberg Instruments) was placed into the aorta near the aortic arch and another in the left ventricle. A pair of segment length piezoelectric crystals (Triton Technology) were sutured into the endocardial left ventricular wall at a distance of approximately 1 cm from each other. All connecting wires were tunneled subcutaneously and exteriorized at the back of the neck. Two weeks postoperatively the dogs were placed in a Pavlov-stand and transducers connected to an eight-channel recorder (Gould ES3000). An electrocardiogram (standard lead II) was also recorded using conventional bipolar limb leads.

Org 5222 (or placebo) was administered either orally (1, 2.5, 5, 10, or 50 mg/kg) or sublingually (0.01, 0.1, or 1 mg/kg) to conscious dogs.

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Aortic arterial systolic, diastolic and mean blood pressures (mmHg), heart rates (beats/min), ventricular systolic segmental shortenings (mm) and the QT intervals were continuously registered and automatically analysed every 15 minutes during the 5 hour observation period following Org 5222 administration. QTc (which reflects cardiac repolarisation time) was calculated according to Bazett's formula.

Dogs were tilted to the 90° upright position for periods of 30 seconds by lifting their forelimbs. Tilt responses refer to the maximum changes observed in aortic blood pressure and heart rate during the 30 second observation period and were assessed both 30 minutes and just before Org 5222 administration and then 15, 30, 60, 90, 120, 180, 240, and 300 minutes after administration.

Blood samples were taken just before drug administration and at 15, 30, 60, 90, 120, 240, 300, 360 minutes and at 21 hours after administration in each case just after tilt challenge. To plasma, prepared from the blood samples, internal standard (cis-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1); Org 5033) was added and Org 5222 and internal standard were isolated by extracting the alkalized plasma with n-hexane. The Org 5222 concentration was determined by capillary gas chromatography (cGC) with NPD-detection.

Results

The hypotensive response to tilt was modestly and dose-dependently augmented by Org 5222, irrespective of the route of administration. However, for equivalent Org 5222 plasma levels, the accompanying tachycardia was always more marked after oral administration of Org 5222 than after sublingual administration (Table 1)

TABLE 1

Org 5222 plasma concentration (ng/ml)	Mean heart rate change due to tilt (corrected for placebo effects), calculated per concentration range (ng/ml) and for each of the two administration routes, oral (po) and sublingual (sl).	
	Mean heart rate change per concentration range	
	po	sl
0-3	5.7	4.6
3-10	21.3	0.6
10-30	21.1	18.3
30-100	47.8	14.9
100-300	52.8	8.9

Conclusions

Tachycardia accompanying orthostatic hypotension was more marked after oral than after sublingual administration of Org 5222. Direct haemodynamic and electrophysiological effects were also less marked after sublingual than after oral administration with regard to negative inotropy and QTc prolongation.

Moreover, dogs treated orally showed marked side effects such as excitation of long duration, whereas dogs treated sublingually showed only short excitation periods followed by long lasting sedation.

We claim:

1. A pharmaceutical composition comprising as a medicinally active compound: trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or

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a pharmaceutically acceptable salt thereof; wherein the composition is a solid composition and disintegrates within 30 seconds in water at 37° C.

2. The pharmaceutical composition of claim 1, wherein the composition further comprises a pharmaceutically acceptable water-soluble or water-dispersable carrier material.

3. The pharmaceutical composition of claim 2, wherein the carrier material is partially hydrolysed gelatin.

4. A method for treating tension, excitation, anxiety, and psychotic and schizophrenic disorders, comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of claim 1, wherein the composition disintegrates within 10 seconds in water at 37° C.

6. The composition of claim 1, further comprising one or more pharmaceutically acceptable auxiliaries selected from the group consisting of hydrolyzed dextran, dextrin, mannitol, algenates, polyvinyl alcohol, polyvinyl pyrrolidone and water soluble cellulose derivatives.

7. A pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof; and pharmaceutically acceptable auxiliaries, wherein the composition is made by the process of

a) providing an aqueous solution comprising said compound and a water soluble or water dispersable carrier material;

b) transferring the composition of a) into a mold;

c) freezing the composition in the mold; and

d) subliming the solvent by freeze-drying.

8. A pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate, mannitol, and gelatin.

9. The method of claim 4, wherein the composition is a solid pharmaceutical composition which rapidly disintegrates in the mouth of a subject upon insertion into the buccal pouch or upon placement under the tongue.

10. The method of claim 4, wherein the pharmaceutical composition further comprises pharmaceutically acceptable auxiliaries selected from the group consisting of hydrolyzed dextran, dextrin, mannitol, algenates, polyvinyl alcohol, polyvinyl pyrrolidone and water soluble cellulose derivatives.

11. The method of claim 10, wherein the pharmaceutically acceptable auxiliary is partially hydrolyzed gelatin.

12. The method of claim 4 wherein the pharmaceutical composition comprises trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate, mannitol, and gelatin.

13. A method for treating antihistamine and antiserotonin related diseases comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 11576

ASUNTO:	Radicación PCT N°	07-104772
	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 Gynopharm 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.

12 SET. 2008

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

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