



No. 10-075713- -00003-0000

Fecha: 2011-10-14 10:00:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSRVTER Folios: 27

FORMULARIO UNICO DE OPOSICION

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

Número del expediente: 10-075.713

Solicitante: JANSSEN PHARMACEUTICA N.V.

SOLICITUD
PUBLICADA

Apoderador: DILIA MARIA RODRIGUEZ D' ALEMAN

Título de la nueva creación o denominación del signo: "REGIMEN DE DOSIFICACION
ASOCIADO CON ESTERES DE PALIPERIDONA INYECTABLES DE ACCION PROLONGADA"

Gaceta: 630

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: LABORATORIOS SYNTHESIS S.A.S.	IDENTIFICACIÓN	
	Dirección: Carrera 14 N° 20 C 73	C.C. ☐ NIT ☒	
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐ Otro ☐	
	Lugar de Constitución: BOGOTÁ	Cual	
	Teléfono: 3692222 Fax: 3693542	Número: 860.000.760-1	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 104 N°119-95 OF 194	C.C. ☒ NIT ☐	
	Teléfono: 2131213 Fax: 6121979	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".

⑤ Comprobante de pago No. 11-0072653 Fecha 12/04/2011

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: 

C.C. 51'975.664 TP. 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0072053

Bogotá D.C., Julio 27 de 2011 - 14:03:25

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	53059823	26/07/2011	2.432.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-075713- -00003-0000

Fecha: 2011-10-14 10:00:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 27

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

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

Julio 27 de 2011 - 14:03:27

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

Referencia : Expediente N° 10 075713
Asunto : Oposición a la solicitud de patente de Invención titulada
"REGIMEN DE DOSIFICACION ASOCIADO CON
ESTERES DE PALIPERIDONA INYECTABLES DE
ACCION PROLONGADA"
Solicitante : JANSSEN PHARMACEUTICA N.V.
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la ~~Gaceta~~ de la Propiedad Industrial
N° 630 del 21 de julio de 2011

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad LABORATORIOS SYNTHESIS S.A.S. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, 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 "REGIMEN DE DOSIFICACION ASOCIADO CON ESTERES DE PALIPERIDONA INYECTABLES DE ACCION PROLONGADA", cuyo titular es JANSSEN PHARMACEUTICA N.V., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **ESTERES DE PALIPERIDONA**. 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 23 de junio de 2010, reivindicando prioridad bajo la solicitud US20070014918 del 2007-12-19; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 630 del 21 de julio de 2011, cuya publicación internacional corresponde a la WO 2009080651 del 2009-07-02.

2.2. La solicitud colombiana 10 075713 objeto de la presente oposición, se refiere a un método para tratar pacientes que necesitan un tratamiento con formulaciones de palmitato de paliperidona inyectable de acción prolongada que comprende la administración intramuscular de una primera dosis de palmitato de paliperidona, una segunda dosis de palmitato de paliperidona en nanopartículas (100-150 mg) entre el día 6 y el día 10 y dosis de mantenimiento entre el día 34 al 38.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren a métodos 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 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: US 2007197591 publicada el 23 de agosto de 2007.

2.5. Ahora bien, el documento D1, que se considera que representa el estado de la técnica más cercano a la solicitud revela particularmente en la descripción la administración intramuscular de una suspensión acuosa de palmitato de paliperidona en nanopartículas para el tratamiento de enfermedades psiquiátricas como las reclamadas por la solicitud objeto de la presente oposición, donde dicho documento D1 da a conocer que la composición debe ser administrado cada tres semanas o en intervalos superiores en una dosificación equivalente a 2.4mg por Kg de peso corporal (mg/ kg).

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

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 075713 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, 19 de diciembre de 2007, a partir del documento D1, un experto en la materia puede llegar de manera evidente a un a un método para tratar pacientes que necesitan un tratamiento con formulaciones de palmitato de paliperidona inyectable de acción prolongada que comprende la administración intramuscular de una primera dosis de palmitato de paliperidona, una segunda dosis de palmitato de paliperidona en nanopartículas (100-150 mg) y dosis de mantenimiento en tiempos como los mencionados en la solicitud objeto de la presente oposición; 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 reclama un 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 métodos terapéuticos, no cumple 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 *"REGIMEN DE DOSIFICACION ASOCIADO CON ESTERES DE PALIPERIDONA INYECTABLES DE ACCION PROLONGADA"*, cuyo titular es JANSSEN PHARMACEUTICA N.V., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 630 del 21 de julio de 2011.

3. PRUEBAS

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

- D1: US 2007197591 publicada el 23 de agosto de 2007.

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

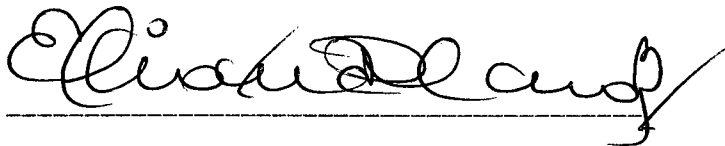
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS
SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US 2007197591 publicada el 23 de agosto de 2007.

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.

PÓDER ESPECIAL

Yo, **LUIS RALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 10 075.713, titulada "**RÉGIMEN DE DOSIFICACIÓN ASOCIADO CON ÉSTERES DE PALIPERIDONA INYECTABLES DE ACCIÓN PROLONGADA**", cuyo titular **JANSSEN PHARMACEUTICA N.V** publicada en la gaceta No. 630 del 21 de julio de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa 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.

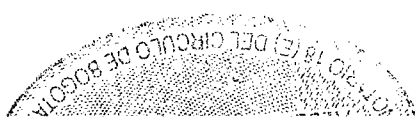
Dado y Firmado en Bogotá (Colombia) a los 03 días del mes de octubre de 2011

LABORATORIOS SYNTHESIS S.A.S.

Cédula de Extranjería: No. 319788.

NIT: 860.000.760-1

Gerente





DILIGENCIA DE RECONOCIMIENTO

NOTARIA DE BOGOTÁ DEL CÍRCULO DE BOGOTÁ D.C. 18
HUELLA SE AUTENTICA POR
FIRMA DEL INTERESADO

Compareció ante el Notario 18 del Círculo de Bogotá,

Juan Alberto Palacios Aragon
quien exhibió la C.E. *379788*

Expedida en _____ y
declaró que la firma y huella que
aparecen en el presente documento
son suyas y que el contenido del mismo
es cierto.

30 SEP 2011

BOGOTÁ, D.C.

FIRMA



FIRMA

EL NOTARIO





01



* 1 1 0 9 8 0 0 4 7 *

12

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

26 DE SEPTIEMBRE DE 2011 HORA 08:47:33

R032656440

PAGINA: 1 de 5

* * * * *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL : synthe@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : synthe@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950; BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LABORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE COMERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LIBRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE: "LABORATORIOS --- BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS REFORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301
5942	7-X -1.996	1A.STAFE BTA	11- X- 1.996 NO.558.222
6305	24-X--1.996	1A.STAFE BTA	07-XI--1.996 NO.561.207
6929	25-XI-1.996	1A.STAFE BTA	12-XII-1.996 NO.565.961
787	19-II-1.997	1A.STAFE BTA	25-II -1.997 NO.575.141



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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

26 DE SEPTIEMBRE DE 2011 HORA 08:47:33

R032656440

PAGINA: 2 de 5

* * * * *

1024

28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245
CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837
139	2011/06/07	0000	BOGOTA D.C.	2011/06/20	01489422

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL
27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANSTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS

~~GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES.~~

CERTIFICA:

CAPITAL:

**** CAPITAL AUTORIZADO ****

VALOR : \$20,000,000,000.00
NO. DE ACCIONES : 20,000,000.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL SUSCRITO ****

VALOR : \$18,091,180,000.00
NO. DE ACCIONES : 18,091,180.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL PAGADO ****

VALOR : \$18,091,180,000.00
NO. DE ACCIONES : 18,091,180.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ DOS SUPLENTE DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUÉL.

CERTIFICA:

**** NOMBRAMIENTOS ****

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
GERENTE PALACIOS LUIS ALBERTO	C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
SUBGERENTE MUÑOZ MARTINEZ ORLANDO	C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE 2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
SUBGERENTE PICART LAURENZ FRANCISCO JAVIER	P.P. 000000036717704

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C)



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PAGINA: 3 de 5

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MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. L. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES. N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA.

CERTIFICA:

** REVISOR FISCAL **

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	
AGUILLON ROJAS SANDRA MILENA	C.C. 000000047436442
REVISOR FISCAL SUPLENTE	
PRADA SANCHEZ NUBIA MARCELA	C.C. 000001032358923

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	
DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134

CERTIFICA:

PERMISO DE FUNCIONAMIENTO: QUE POR RESOLUCION NO. 05952 DEL 11 DE JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA SOCIEDAD.



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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

26 DE SEPTIEMBRE DE 2011 HORA 08:47:33

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PAGINA: 4 de 5

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CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERINTENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR SETENTA Y CUATRO MIL (\$74.000) ACCIONES DE LAS QUE TIENE EN RESERVA, A SU VALOR NOMINAL DE CIEN PESOS (\$100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 28 DE JUNIO DE 2011, INSCRITO EL 1 DE JULIO DE 2011 BAJO EL NUMERO 01492789 DEL LIBRO IX, SE COMUNICO QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL POR PARTE DE LA SOCIEDAD MATRIZ: LABORATORIOS SYNTHESIS S A S, RESPECTO DE LAS SIGUIENTES SOCIEDADES SUBORDINADAS:

- SOCIEDAD PARA LA ENSEÑANZA DE LA HOMEOPATIA CLINICA S A S QUIEN SE IDENTIFICARA CON LA SIGLA S E C H

DOMICILIO: BOGOTA D.C.

FECHA DE CONFIGURACION DE LA SITUACION DE CONTROL : 2011-05-31

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 9 DE MARZO DE 2011, INSCRITO EL 18 DE MARZO DE 2011 BAJO EL NUMERO 01462396 DEL LIBRO IX, COMUNICO LA SOCIEDAD MATRIZ:

- EUROPEAN CHEMICALS & CO

DOMICILIO: (FUERA DEL PAIS)

QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL CON LA SOCIEDAD DE LA REFERENCIA.

CERTIFICA:

*** ACLARACIÓN SITUACIÓN DE CONTROL Y DE GRUPO EMPRESARIAL ***
SE ACLARA LA SITUACIÓN DE CONTROL Y GRUPO EMPRESARIAL INSCRITA CON EL NO. 01462396 DEL 9 DE MARZO DE 2011 DEL LIBRO IX EN EL SENTIDO DE INDICAR QUE SE CONFIGURÓ DESDE EL 19 DE NOVIEMBRE DE 2010.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM

MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

CERTIFICA:

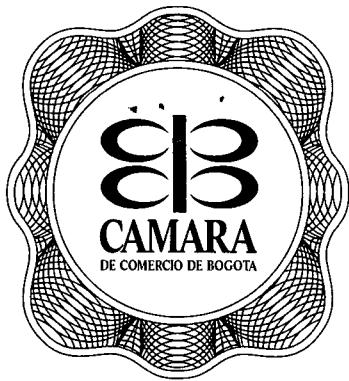
DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,



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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

26 DE SEPTIEMBRE DE 2011

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VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

* * *

NO ES VALIDO POR ESTA CARA

* * *

ANEXO 1



US 20070197591A1

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0197591 A1**
Boom et al. (43) **Pub. Date: Aug. 23, 2007**

(54) **USE OF PALIPERIDONE FOR THE
TREATMENT OF A MENTAL DISORDER IN
A PSYCHIATRIC PATIENT WITH REDUCED
HEPATIC FUNCTION**

Related U.S. Application Data

(60) Provisional application No. 60/745,229, filed on Apr. 20, 2006. Provisional application No. 60/749,515, filed on Dec. 12, 2005.

(76) Inventors: **Sandra Boom**, Dordrecht (NL);
Marielle-Henriette Eerdeken,
Dilsen-Stokkem (BE)

Publication Classification

(51) **Int. Cl.**
A61K 31/445 (2006.01)
(52) **U.S. Cl.** **514/317**

Correspondence Address:
PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003 (US)

(57) **ABSTRACT**

The present invention provides a method for the treatment of psychiatric patients having or at risk of hepatic impairment comprising administering a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms and esters thereof to psychiatric patients in need thereof.

(21) Appl. No.: **11/534,623**
(22) Filed: **Sep. 22, 2006**

USE OF PALIPERIDONE FOR THE TREATMENT OF A MENTAL DISORDER IN A PSYCHIATRIC PATIENT WITH REDUCED HEPATIC FUNCTION

[0001] This application claims priority from and benefit of provisional patent applications 60/745,229 filed Apr. 20, 2006 and 60/749,515 filed Dec. 12, 2005, both of which are hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] This invention relates to the use of paliperidone in the treatment of a mental disorder in patients that are hepatically impaired.

BACKGROUND OF THE INVENTION

[0003] Psychiatric patients often have comorbid conditions that may lead to hepatic impairment. Consequently, to treat these patients with comorbid conditions that potentially cause impaired hepatic function it would be highly desirable to be able to treat these patients for their mental illness with pharmaceuticals that are not to any appreciable degree metabolized in the liver.

SUMMARY OF THE INVENTION

[0004] We have discovered that paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms, and esters, are not to any appreciable extent metabolized in the liver. Therefore, these compounds are particularly useful in the treatment of psychiatric patients with impaired liver function.

[0005] In one embodiment, the invention provides for the use of a pharmaceutical composition comprising a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms or esters thereof, together with a pharmaceutically acceptable carrier, for the treatment of a mental disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

[0006] In another embodiment, the invention provides for the use of a pharmaceutical composition comprising a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms, or esters thereof, together with a pharmaceutically acceptable carrier, in the manufacture of a medicament for the treatment of a mental disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

[0007] In yet another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of paliperidone, its pharmaceutically acceptable acid addition salts, enantiomeric forms, or esters thereof, for the treatment of a mental disorder in a patient in need thereof, the patient having or at risk of hepatic impairment.

[0008] These and other objects and advantages of the present invention may be appreciated from a review of the present applications.

DETAILED DESCRIPTION

[0009] A variety of comorbid conditions which psychiatric patients may present also may lead to hepatic impairment in psychiatric patients such as Wilson's disease, alcoholism,

viral hepatitis (e.g. hepatitis B, Hepatitis C adenovirus, Epstein Barr virus, cytomegalovirus and viral haemorrhagic fevers), drug toxicity, hepatocellular carcinoma or metastatic carcinoma, poisoning by various substances, illicit drug use (including Ecstasy and cocaine), Reyes' syndrome, Budd-Chiari syndrome, veno-occlusive disease and autoimmune liver disease. Psychiatric patients that are suspected of hepatic impairment can be identified by examination of their medical records, taking their histories, physical examination or by laboratory testing. Physicians and nurses treating psychiatric patients should be familiar with the symptoms and tests for impaired liver functions. For example patients presenting with symptoms such as jaundice, liver palms, cerebral oedema, etc. should be further examined for liver impairment. Laboratory tests showing thrombocytopenia, raised bilirubin, low pseudocholinesterase, elevated lactate, raised creatinine etc., should be further investigated. Appropriate techniques to determine whether there is impairment of liver function are known in the art. Normally a battery of tests will be run such as tests for the levels of transaminase (e.g. aspartate aminotransferase, alanine aminotransferase, etc.) and γ -glutamyltransferase, Hepatitis C serologies, Hepatitis B serologies, Hepatitis A serology, Ceruloplasmin, serum protein electrophoresis, hepatic sonogram prothrombin time, CBC with platelet count and serum albumin.

[0010] Hepatically impaired patients are those patients that one of ordinary skill in the art, such as a physician, would recognize from testing or diagnosis as having impaired liver function requiring monitoring of their liver condition and/or care being taken in the administration of medication to avoid adverse events (e.g. further damage or failure to properly metabolize and/or clear medicines).

[0011] Paliperidone, including its pharmaceutically acceptable acid addition salts, enantiomeric forms, and esters, may be administered for the practice of the present invention. Paliperidone is well known in the art and is described in U.S. Pat. No. 5,158,952 incorporated herein by reference.

[0012] As noted in U.S. Pat. No. 5,158,952, paliperidone has basic properties and, consequently, this compound may be converted to its therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted into the free base form by treatment with alkali. The term acid addition salt as used hereinabove also comprises the solvates which such compounds are able to form and said solvates are meant to be included within the scope of the present invention. Examples of such solvates are e.g., the hydrates, alcoholates and the like.

[0013] Esters of paliperidone are known in the art and are described in U.S. Pat. No. 5,254,556 incorporated herein by reference. Esters of paliperidone include octanoic acid,

decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid (palmitic acid). The currently preferred ester of paliperidone is paliperidone palmitate.

[0014] Paliperidone may be formulated with pharmaceutical excipients into a variety of dosage forms as described in U.S. Pat. No. 5,158,952. Paliperidone will in one embodiment of the present invention be provided in an oral dosage form. Suitable oral dosage forms include but are not limited to tablets, pills, fast dissolving dosage forms, controlled release or extended release dosage forms. Currently preferred are extended release OROS oral dosage forms which are well known in the art. Examples of oral dosage forms of paliperidone are described in US 20040092534, US 20050208132 and US 20050232995, all hereby incorporated by reference herein. Paliperidone palmitate, including its pharmaceutically acceptable acid addition salts, and stereoisomeric forms, is also well known in the art and may also be formulated with pharmaceutical excipients into a variety of dosage forms as described in U.S. Pat. No. 5,254,556. Currently, it is preferred to administer paliperidone palmitate in a depot.

[0015] Paliperidone palmitate is considered to be a potentially valuable prodrug of paliperidone. A pharmaceutical composition suitable as an injectable solution of paliperidone palmitate may comprise a formulation of paliperidone palmitate in an appropriate oil for prolonged action; for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils.

[0016] In another embodiment, a pharmaceutical composition suitable as an efficient, well-tolerated, sustained or delayed release (depot) formulation for administration of paliperidone palmitate by intramuscular or subcutaneous injection may comprise a suspension of paliperidone palmitate in aqueous solution. Ideally, suitable aqueous depot formulations will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition:

- (a) from 3 to 20% (w/v) of the prodrug;
- (b) from 0.05 to 2% (w/v) of a wetting agent;
- (c) one or more buffering agents;
- (d) from 0.5 to 2% (w/v) of a suspending agent;
- (e) up to 2% (w/v) preservatives; and
- (f) water q.s. ad 100%.

[0017] In yet another embodiment, the above composition may comprise a dispersion of particles consisting essentially of a therapeutically effective amount of crystalline paliperidone palmitate having a surfactant absorbed to the surface thereof in an amount effective in maintaining a specific surface area $>4 \text{ m}^2/\text{g}$ (corresponding to an effective average particle size of less than 2,000 nm), in a pharmaceutically acceptable carrier comprising water. Preferably, the specific surface area is $>6 \text{ m}^2/\text{g}$, and in particular is in the range from 10 to $16 \text{ m}^2/\text{g}$. Useful surface modifiers are believed to include those which physically adhere to the surface of the paliperidone palmitate but do not chemically bond thereto. Suitable surface modifiers can preferably be selected from

known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

[0018] Suitable aqueous depot formulations are well known in the art and specific details are provided in U.S. Pat. No. 6,077,843, U.S. Pat. No. 6,320,048 and U.S. Pat. No. 6,555,544, which are all incorporated by reference herein. Typically, suitable aqueous depot formulations will be administered approximately every three weeks or even at longer intervals where possible. The dosage should range from about 2 to 4 mg/kg body weight.

[0019] The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment, for a "mental disorder", and the term "mental disorder" also encompasses mental illnesses and refers to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone, its salts, enantiomers and esters can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a conditions characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to, the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The numbers in parenthesis refer to the DSM-IV-TR categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

[0020] Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type

(314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9) Conduct Disorder (Childhood-Onset and Adolescent Type 312.8) Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic

or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

[0021] The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

[0022] Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. In general it is contemplated that an effective amount would be from about 0.01 mg/kg to about 2 mg/kg body weight. In one embodiment of present invention wherein paliperidone is orally administered a dosage form to a subject once a day is preferred. The mg of compound delivered in such a dosage form to the patient may be from 0.25 to about 20 mg (e.g. 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7

mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, and 20 mg) per oral dosage form.

[0023] The following non-limiting examples are provided to further illustrate the present invention.

EXAMPLE 1

[0024] Objectives: to investigate the metabolic pathways of paliperidone and excretion of paliperidone and its metabolites in healthy adult male subjects, both CYP2D6 poor and extensive metabolizers, after administration of a single 1-mg oral dose of ^{14}C -paliperidone. In addition, to evaluate the safety and tolerability of paliperidone, as well as the relationship between genotypes (CYP2D6, CYP3A4, CYP3A5, UGT1A1, and UGT1A6) and exposure to paliperidone and its metabolites.

[0025] Methodology: Single-center, single-dose open-label study of the absorption, metabolism, and excretion (AME) of paliperidone in healthy men (3 extensive and 3 poor metabolizers based on CYP2D6 phenotype). Eligible subjects were admitted to the study center the evening before study drug administration and remained at the study center until 168 hours after dosing (or longer if required up to a maximum of 14 days). Each subject received a single oral dose of ^{14}C -paliperidone with total radioactivity below 10000 μSv (16 μCi). Blood samples for plasma pharmacokinetic profile were obtained immediately before study drug administration and 0.5, 1, 1.5, 3, 6, 12, 16, 36, 48, 72, 96, 120, 144 and 168 hours postdose. Blood samples were obtained 2, 4, 8, and 24 hours postdose for determination of ^{14}C in whole blood. Samples for determination of serum creatinine were obtained 2, 4, 8, and 24 hours postdose. Urine was collected immediately prior to drug administration and from 0-4, 4-8, 8-12, 12-16, 16-24, 24-36, 36-48, 48-72, 96-120, 120-144, and 144-168 hours after study drug administration. Fecal samples were collected per each stool, once before study drug administration and in the period from 0-168 hours after study drug administration. Collections of urine and feces (per 24 hours) were to continue beyond 168 hours, to a maximum of 336 hours (Day 15) for subjects who excrete radioactivity slowly (2 latest 24-hour urine collections each $>2\%$ of total radioactive dose) or have <7 feces stool samples over the 0 to 168-hour period. ^{14}C radioactivity was measured in plasma, urine, and feces. Aliquots of the 0- through 24-hour urine collections were analyzed for creatinine. Plasma concentrations of paliperidone and risperidone were determined by means of a validated LC-MS/MS method. The ^{14}C -labeled moiety in plasma and urine was determined by liquid scintillation counting. For all plasma samples, the lower limits of quantification for paliperidone and risperidone were 0.100 ng/mL. For all plasma and urine samples the lower limits of quantification for ^{14}C -paliperidone was 72 dpm/mL (≈ 2.0 ng-eq/mL).

[0026] Number of Subjects (Planned and Analyzed): Six healthy men, 3 extensive and 3 poor metabolizers based on CYP2D6 phenotype were to participate in the study. Five subjects, 3 extensive and 2 poor metabolizers, received a single dose of ^{14}C -paliperidone, completed the study (i.e., completed all assessments through Day 8) and were considered valuable for safety (the Safety Analysis Set), as well as for pharmacokinetics.

[0027] Diagnosis and Main Criteria for Inclusion: Subjects were healthy white males between the ages of 40 and

60 years. Subjects were healthy based on medical history, physical examination, clinical laboratory evaluate, and electrocardiogram. Dextromethorphan metabolic ratio of >0.345 (poor metabolizer) or <0.0255 (extensive metabolizer). Body Mass Index (MBI): (weight [kg]/height [m^2]) between 20 and 28 kg/m^2 , inclusive.

[0028] Test Product, Dose and Mode of Administration Batch No.: Single oral 0.988-mg dose of ^{14}C -paliperidone, oral solution (aqueous formulation at a final concentration of 0.0984 mg/mL). Batch No.: unlabeled paliperidone oral solution: ZR076477EIA031 (manufacturing date: 23 Apr. 2003, retest date: 23 Oct. 2004): ^{14}C -paliperidone: 1763 (expiration date: not applicable)

[0029] Criteria for Evaluation: Pharmacokinetics: Plasma paliperidone. ^{14}C radioactivity and metabolite profiles were determined. Plasma C_{max} , t_{max} , AUC_{last} , AUC_{24} , AUC_{∞} , λ_z , $t_{1/2\text{elim}}$, CL/F of ^{14}C and paliperidone were estimated by non-compartmental analysis. Based on the individual urine excretion data and on the serum creatinine concentrations, Ae , Ae , % dose, CL_R , $\text{CL}_{R,24\text{h}}$ and CL_{ex} and paliperidone and CL_{CFR} and CL_{acc} of paliperidone were estimated. The excretion half-life of ^{14}C in urine was also estimated based on excretion rate-time profiles.

[0030] Safety: Evaluation was based on the incidence, type, and severity of all treatment-emergent adverse events, and on change from screening to the end of the study in clinical laboratory results, vital sign measurements, and postural changes in blood pressure and heart rate.

[0031] Statistical Methods: Pharmacokinetics: Plasma concentrations of ^{14}C and paliperidone as well as estimates for pharmacokinetic parameters were listed and graphically presented, and the excretion analysis of total radioactivity in plasma, urine and feces were summarized. Descriptive statistics were calculated, including summaries by CYP2D6 phenotype.

[0032] Safety: The number of subjects with adverse events was summarized. Summary statistics were calculated for clinical laboratory values. Other safety data were listed by individual sect. Changes in blood pressure and heart rate measurements were also presented graphically.

SUMMARY—CONCLUSION

[0033] Demographic and baseline characteristics: Five white men, 3 extensive metabolizers and 2 poor metabolizers, received study medication and completed the study. The ages ranged from 40 to 63 years (mean: 51.2 year), the body weights ranged from 68.7 to 78.6 kg (mean: 73.38 kg), and BMI ranged from 24 to 28 kg/m^2 (mean: 25.5 kg/m^2).

[0034] Pharmacokinetic Results:

[0035] Pharmacokinetics of Total Radioactivity (TR) and paliperidone (UD) in plasma;

[0036] The mean (SD) pharmacokinetic parameters of TR and UD after administration of a single oral dose of ^{14}C -paliperidone are summarized in Table A.

TABLE A

Plasma Pharmacokinetic Parameters of ^{14}C -Labeled Moiety and Unchanged Paliperidone (Mean $\pm$ SD) After a Single Dose of 1-mg ^{14}C -Paliperidone

	ALL (N = 5)	EM (N = 3)	PM (N = 2)
^{14}C -Labeled Moiety (TR)			
$C_{\max}$, ng-equivalent/mL	9.54 $\pm$ 1.35	9.40 $\pm$ 1.73	9.75 $\pm$ 1.06
$t_{\max}$, h	1.40 $\pm$ 0.224	1.50 $\pm$ 0.00	1.25 $\pm$ 0.354
AUC_{24} , ng-eq $\cdot$ h/mL	114 $\pm$ 19.9	116 $\pm$ 27.3	112 $\pm$ 7.8
$\text{AUC}_{24\text{ng-eq}}$, ng-eq $\cdot$ h/mL	175 $\pm$ 30.7	179 $\pm$ 41.9	168 $\pm$ 9.90
$t_{1/2\text{term}}$, h	15.2 $\pm$ 2.15	15.4 $\pm$ 1.35	14.9 $\pm$ 3.82
CL/F, mL/min	97.9 $\pm$ 17.6	96.8 $\pm$ 24.4	99.6 $\pm$ 6.22
Unchanged Paliperidone (UD)			
$C_{\max}$, ng/mL	8.85 $\pm$ 1.31	8.59 $\pm$ 1.79	9.24 $\pm$ 0.00707
$t_{\max}$, h	1.30 $\pm$ 0.274	1.33 $\pm$ 0.289	1.25 $\pm$ 0.354
AUC_{24} , ng $\cdot$ h/mL	111 $\pm$ 22.0	113 $\pm$ 30.1	109 $\pm$ 9.90
AUC_{∞} , ng $\cdot$ h/mL	187 $\pm$ 29.3	190 $\pm$ 38.4	182 $\pm$ 19.8
$t_{1/2\text{term}}$, h	24.8 $\pm$ 4.35	24.1 $\pm$ 4.49	26.0 $\pm$ 5.59
CL/F, mL/min	91.0 $\pm$ 15.0	90.3 $\pm$ 20.0	92.1 $\pm$ 10.0
Ratio $\text{AUC}_{24}\text{UD/TR}$	0.970 $\pm$ 0.0250	0.965 $\pm$ 0.0311	0.977 $\pm$ 0.0205

EM: extensive metabolizer; PM: poor metabolizer

[0037] In the overall population, average peak plasma concentration of TR (9.54 ng-eq/mL) was attained 1.40 hours after dosing. Average peak plasma concentration of UD (8.85 10 ng/mL) was reached after 1.30 hours. The terminal half-life of TR and UD was on average 15.2 hours and 24.9 hours, respectively. This difference was probably caused by a higher LLOQ for TR compared to UD. AUC_{∞} values of TR averaged 175 ng-eq.h/mL, those of UD were 187 ng.h/mL. At 24 hours after dosing the percentage of UD versus TR in plasma is on average 97.0%. No differences are found between CYP2D6 extensive and poor metabolizers.

[0038] Excretion in Urine and Feces:

[0039] At 7 days after a single oral dose of ^{14}C -paliperidone, 91% of the administered radioactivity has been excreted as ^{14}C -labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine (Table B) and 11% in the feces. There were no differences between extensive and poor metabolizers in urinary excretion (% of the dose) of ^{14}C -labeled moiety. Furthermore no discrimination could be made between extensive (13%) and poor (8%) metabolizers of excretion of ^{14}C labeled moiety in feces.

TABLE B

Clearance and Urine Parameters of ^{14}C -Labeled Moiety (Mean $\pm$ SD) After Single Dose of 1-mg ^{14}C Paliperidone

	All (N = 5)	EM (N = 3)	PM (N = 2)
^{14}C -Labeled Moiety			
Ae, % dose	79.6 $\pm$ 4.20	77.6 $\pm$ 0.775	82.7 $\pm$ 6.15
CL_R , mL/min	76.8 $\pm$ 13.6	74.1 $\pm$ 18.5	80.8 $\pm$ 1.20
CL_{CR} , mL/min	113 $\pm$ 10.3	108 $\pm$ 7.37	121 $\pm$ 10.5
Unchanged Paliperidone			
Ae, % dose	59.4 $\pm$ 7.12	55.7 $\pm$ 6.66	64.9 $\pm$ 3.68
CL_R , mL/min	53.1 $\pm$ 9.47	49.2 $\pm$ 8.59	59.1 $\pm$ 9.69

[0040] Safety Results:

[0041] Two of the 5 subjects who received study education experienced treatment-emergent adverse events: moderately severe postural hypotension and syncope in 1 subject and mild allergic reaction (described as infraorbital swelling probably due to an allergic reaction, and considered doubtfully related to the study medication) and asthenia in the second subject. With the exception of allergic reaction which was persisting at the end of the study, the adverse events resolved without treatment intervention. There were no deaths, no serious adverse events, and no subject discontinued from the study due to an adverse event.

[0042] There were no clinically relevant changes in laboratory test results. With the exception of postural hypotension which was reported as an adverse event in 1 subject, there were no clinically relevant changes in vital sign measurements.

[0043] Conclusion:

[0044] The unchanged drug paliperidone accounted for a large part of the total radioactivity in plasma. The percentage of UD versus TR in plasma is on average 97%. There were no differences in paliperidone pharmacokinetic parameters observed between CYP2D6 extensive and poor metabolizers. No effect of genotype was observed for CYP2D6, UGT1A1 or UGT1A6 on the plasma exposure of TR and UD. Seven days after administration of a single oral dose of 1 mg ^{14}C -paliperidone to 5 healthy male subjects, 91% of the dose was excreted in urine and feces as ^{14}C -labeled moiety. The cumulative excretion of the TR amounted to 80% in the urine and 11% in the feces. The cumulative urinary excretion of unchanged paliperidone amounted to 59%. About 50% of the UD is excreted by means of filtration; the other half of UD is cleared renally by active processes.

[0045] The administration of a single oral 1-mg dose of ^{14}C -paliperidone as a normal solution was safe and well tolerated in healthy men.

EXAMPLE 2

[0046] Objectives: The primary objective of this study was to investigate the single-dose pharmacokinetics of immediate-release (IR) paliperidone, after oral administration, in subjects having moderate hepatic impairment ("hepatically-impaired subjects") compared with subjects having normal hepatic function ("healthy subjects"). The secondary objective was to document the plasma protein binding and disposition of the enantiomers of paliperidone. In addition, the tolerability and safety profile of IR paliperidone was compared between hepatically impaired subjects and healthy subjects.

[0047] Methodology: This was a single-dose, parallel-group, open-label, single-center, Phase I study of IR paliperidone in subjects having either normal or moderately impaired hepatic function. The groups, consisting of 10 subjects each, were demographically matched with respect to age, weight, sex, and ethnicity. The study consisted of a screening period of up to 3 weeks and an open-label, single-dose treatment period (Days 1 through 5). On Day 1, a single dose of 1 mg IR paliperidone oral solution was administered after a fast of at least 10 hours; subjects continued to fast for 4 hours following study drug administration. The 96-hour follow-up consisted of serial sample collection of blood and urine for pharmacokinetic analysis and safety and tolerability assessments. Subjects remained confined to the study site through the 72-hour pharmacokinetics sampling, and consumed standard institutional meals while in the study site. Subjects were released after the 72-hour sampling, then returned to the study site on Day 5 before the 96-hour pharmacokinetics sampling; end-of-study procedures were performed immediately hereafter. A blood sample for DNA isolation was collected to allow for genetic analysis as necessary.

[0048] Number of Subjects (Planned and Analyzed): Ten subjects were planned for each hepatic function group; 10 subjects in each group completed the study and were analyzed for pharmacokinetics and safety.

[0049] Diagnosis and Main Criteria for Inclusion: The study was conducted in men and women, aged 18 through 75 years, inclusive. One group of subjects had moderate hepatic impairment, with stable hepatic disease, a total Child-Pugh score of between 7 and 9, inclusive, and blood pressure that was controlled and stable on antihypertensive agents; the other group had normal hepatic function.

[0050] Test Product, Dose and Mode of Administration, Batch No: 1 mg IR paliperidone (R076477) oral solution; batch 04C29/F044.

[0051] Duration of Treatment: This was a single-dose study.

[0052] Criteria for Evaluation: Pharmacokinetics: Plasma and urine concentrations of the paliperidone enantiomers (+) R078543 and (-) R078544 were determined using an LC-MS/MS method. Concentrations of paliperidone were calculated as the sum of the enantiomer concentrations. In addition, serum and urine concentrations of creatinine were determined for the calculation of CLCR. The protein binding and unbound fraction was determined for the 2 paliperidone enantiomers. The unbound fraction for paliperidone was calculated.

[0053] Based on the actual pharmacokinetic blood sampling times and actual urine collection periods, the following plasma and urine pharmacokinetic parameters were deter-

mined for paliperidone and its enantiomers: C_{max} , t_{max} , t_{last} , AUC_{last} , λ_z , $t_{1/2}$, AUC_{∞} , % $AUC_{\infty,ex}$, CL/F , $AUC_{\infty}/\text{ratio}$, C_t/ratio per time point, unbound AUC_{∞} , unbound CL/F or unbound CL (if relevant), A_e (per collection interval and overall), A_e/dose , $Excr. Rate$, V_d , CR_R , CL_{GFR} , CL_{act} , CL_{act}/CL_R , $CL_{act}/(CL/F)$, CL_{CR} , and CL_{NR} .

[0054] Safety: Adverse events, clinical laboratory tests, including prolactin, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECGs) were analyzed to assess safety.

[0055] Statistical Methods:

[0056] Pharmacokinetics: Descriptive statistics were evaluated for the plasma concentrations at each sampling time, and for all pharmacokinetic parameters of paliperidone and its enantiomers for each hepatic function group. Graphical exploration of the paliperidone and enantiomer plasma concentrations and urine data, and the derived pharmacokinetic parameters, was performed. In addition, the enantiomer disposition was compared between the groups.

[0057] Log-transformed PK parameters were fit to a general linear model with hepatic function group as fixed effect.

[0058] Safety: All subjects were analyzed; statistical analyses were descriptive [? Does info need to be added here?].

[0059] Summary—Conclusions

[0060] Pharmacokinetic Results: The fraction of unbound paliperidone in plasma was higher in hepatically-impaired subjects compared with healthy subjects and averaged 0.353 and 0.279 respectively. The difference in plasma protein binding between the groups most likely results from the reduced α_1 -acid glycoprotein (α_1 -AGP) plasma concentration in hepatically-impaired subjects, since the fraction of unbound drug appears to be inversely related to the α_1 -AGP plasma concentration.

Predose Plasma Concentration of Albumin, α_1 -AGP, and Total Protein and Unbound Fraction for Paliperidone, (+)R078543, and (-)R078544

	Healthy Subjects (n = 10)	Hepatically-Impaired Subjects (n = 10)
Albumin (g/dL)	4.3 $\pm$ 0.2	3.3 $\pm$ 0.6
α_1 -AGP (mg/dL)	77.0 $\pm$ 18.8	46.6 $\pm$ 17.1
Total Protein (g/dL)	7.2 $\pm$ 0.2	6.9 $\pm$ 0.7
Unbound Fraction	0.215 $\pm$ 0.0469	0.306 $\pm$ 0.0687
(+) R078543		
Unbound Fraction	0.385 $\pm$ 0.0416	0.457 $\pm$ 0.0504
(-) R078544		
Unbound Fraction	0.279 $\pm$ 0.0492	0.353 $\pm$ 0.0564*
Paliperidone		

All values are mean (SD).

*Descriptive statistics based on n = 8, excluding Subjects 0005 and 0006.

[0061] Overall, hepatically-impaired subjects achieved lower total plasma concentrations than healthy subjects. AUC and C_{max} values of paliperidone and each of its enantiomers were lower for hepatically-impaired subjects than for healthy subjects: in each case, C_{max} was approximately 35% lower and AUC_{∞} approximately 27% lower. After correction for unbound fraction, the exposure was comparable between the groups. The median time to reach maximum plasma concentration was around 1 hour for both groups, although somewhat more variable among the hepatically-impaired subjects.

[0062] Paliperidone plasma concentration declined with a mean terminal half-life of 23.6 hours for healthy subjects and 26.5 hours for hepatically-impaired subjects.

[0063] The CL/F for paliperidone was about 35% higher in hepatically-impaired subjects compared with healthy subjects which is consistent with the lower AUC_{∞} . Moreover, hepatically-impaired subjects had 47% higher volumes of distribution for total Paliperidone compared with healthy subjects. Based on unbound concentrations, however, the clearance and volume of distribution were comparable between the groups.

[0064] Hepatically-impaired subjects showed more variable renal excretion profiles (i.e. larger % CV) than healthy subjects. There were no other apparent differences in urinary excretions parameters between the hepatic function groups. Approximately 50% of the dose was excreted unchanged into urine and did not differ between the groups. Renal clearance was not much different between the groups (67.4 vs. 51.2 ng/ml), which can be expected because the unbound plasma concentrations between the groups are comparable. Renal function, as determined by the creatinine clearance, was almost identical between the groups. Active renal clearance accounted on average for approximately 45% of the renal clearance in both groups.

AUC ration was comparable between healthy and hepatically-impaired subjects (i.e., 0.914 and 0.886, respectively).

[0067] Safety Results: The only adverse events that were reported in more than 1 subject in either group were hyperprolactinemia (see below) and dizziness (in 2 hepatically-impaired subjects only). Treatment-emergent increase in hepatic enzymes were noted in 1 hepatically-impaired and 1 healthy subject. These elevations were only slightly above the baseline value in the hepatically-impaired subject and less than twice the upper limit of normal in the healthy subject, and thus were not considered clinically important.

[0068] An increase in prolactin from the mean predose levels was seen in both hepatically-impaired and healthy subjects at 36 hours; thereafter mean levels decreased. Because the investigator was unblinded to the laboratory results, increases in prolactin levels were reported as adverse events in 8 hepatically-impaired and 6 healthy subjects; these adverse events were considered mild and very likely related to study drug by the investigator.

[0069] There were no unexpected findings in vital signs; no subject in either group met the criteria for orthostatic hypotension. Furthermore, no subjects had clinically important abnormal ECG values (including QT values).

Paliperidone								
Healthy Subjects				Hepatically-Impaired Subjects				
	n	Total	n	Unbound	n	Total	n	Unbound
C _{max} , ng/mL	10	7.14 ± 2.28	10	1.81 ± 0.292	10	4.57 ± 1.05	10	1.59 ± 0.318
AUC _∞ , ng · h/mL	10	176 ± 64.4	10	45.8 ± 8.72	9	128 ± 42.5	8	45.7 ± 12.6
t _{max} , h	10	1.00 (1.00–2.00)	10	1.25 (1.00–2.00)	10	1.25 (0.25–4.00)	10	1.25 (0.25–4.00)
t _{1/2} , h	10	23.6 ± 3.6		ND	10	26.5 ± 6.4		ND
CL/F, mL/min	10	105 ± 34.9	10	370 ± 67.1	9	143 ± 43.4	8	386 ± 99.3
V _{d,z} , L	10	211 ± 59.6	10	748 ± 144	9	311 ± 65.2	8	857 ± 146
CL _R , mL/min	10	51.2 ± 13.4		ND	9	67.4 ± 34.0		ND
CL _{NR} , mL/min	10	54.4 ± 23.7	10	188 ± 56.8	9	75.1 ± 16.2	8	205 ± 30.7
Ae, % dose	10	50.1 ± 7.94		ND	10	44.7 ± 10.62		ND

Mean $\pm$ SD; for t_{max} : median (range); ND: Not determined.

[0065] When the data from the two hepatic function groups were pooled, there was no apparent relationship between clearance of paliperidone or its enantiomers and most measures of hepatic function (i.e. albumin and bilirubin concentrations, prothrombin time, and Child-Pugh score); there was an inverse relationship between clearance of paliperidone or its separate enantiomers and α_1 -AGP concentration.

[0066] Exposure to both enantiomers was higher in healthy subjects compared with hepatically-impaired subjects; furthermore, in both groups, exposure to (+) R078543 was high than exposure to R078544. The (+)/(-) ration based on the AUC for the total plasma concentrations was somewhat larger in healthy subjects compared with hepatically-impaired subjects (i.e. 1.67 and 1.38 respectively). Based on unbound concentrations, however, the exposure to both enantiomers was within the same range, and the (+)/(-)

CONCLUSION

[0070] After oral administration of 1 mg paliperidone IR, hepatically impaired subjects had a lower mean C_{max} ($\approx$ 35%) and AUC_{∞} ($\approx$ 27%) for total paliperidone and its enantiomers than did healthy subjects.

[0071] The protein binding differed between the hepatic function groups. The unbound fraction of paliperidone was approximately 27% higher in hepatically-impaired subjects. Taking this difference in protein binding into account C_{max} and AUC_{∞} for the unbound fraction of paliperidone were comparable across the hepatic function groups. C_{max} was approximately 12% lower, and AUC_{∞} approximately 5% lower, in hepatically-impaired subjects compared with healthy subjects.

[0072] The mean terminal half-life for IR paliperidone and its enantiomers was between 23.6 and 25.0 hours for healthy subjects, and between 26.5 and 27.5 hours for hepatically-impaired subjects.

[0073] Paliperidone IR, 1 mg, was tolerated equally well by healthy and hepatically-impaired subjects.

We claim:

1. A method for the treatment of psychiatric patients having or at risk of hepatic impairment comprising administering a therapeutically effective amount of paliperidone its pharmaceutically acceptable acid addition salts, enantiomeric forms and esters thereof to such psychiatric patient in need thereof.

2. The method of claim 1 wherein the psychiatric patient is in need of treatment for psychosis.

3. The method of claim 2 wherein the psychiatric patient is in need of treatment for schizophrenia.

4. The method of claim 2 wherein the psychiatric patient is in need of treatment for bipolar disorder.

5. The method of claim 1 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder

(292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Dis-

order, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Other-

wise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

* * * * *

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°:

E.1.7.2.3.3

ASUNTO:

Radicación PCT N°	10-75713
Trámite	011
Evento	378
Actuación	440
Folios	008

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 Laboratorios Synthesis S.A.S., 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.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C).

04 NOV. 2011

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

2020 