



No. 10-002709-00005-0000

Fecha: 2011-09-16 12:06:33 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 39

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

Número del expediente: 10-002.709

Solicitante: OTSUKA PHARMACEUTICAL CO., LTD

SOLICITUD
PUBLICADA

Apoderado: HUMBERTO RUBIO CAMACHO

Título de la nueva creación o denominación del signo: "MÉTODOS PARA
PRODUCIR SUSPENSIÓN DE ARIPIRAZOLE Y UNA FORMULACIÓN LIOFILIZADA"

Gaceta: 629

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: LABORATORIOS SYNTHESIS S.A.S.	IDENTIFICACIÓN	
	Dirección: Carrera 44 N° 20 C 73 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BOGOTA Teléfono: 3692222 Fax: 3693542 E-mail:	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual Número 860.000.760-1	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 104 N°119-95 OF 104 Teléfono: 2131213 Fax: 6121979 E-mail: negocios@optimum-co.com	C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual Número 51.975.664 TP 83823	

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

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

⑤ Comprobante de pago No.

11-72051

Fecha

27-07-11

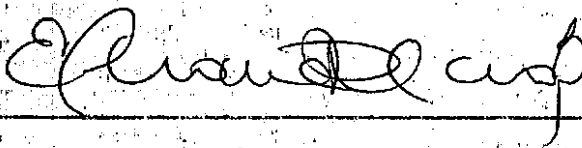
⑥ ANEXOS

- ☒ 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 BOHÓRQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 10 002.709
Asunto : Oposición a la solicitud de patente de Invención titulada
"MÉTODOS PARA PRODUCIR SUSPENSIÓN DE
ARIPRAZOLE Y UNA FORMULACIÓN LIOFILIZADA"
Solicitante : OTSUKA PHARMACEUTICAL CO., LTD
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 629 del 20 de junio 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 "MÉTODOS PARA PRODUCIR SUSPENSIÓN DE ARIPIRAZOLE Y UNA FORMULACIÓN LIOFILIZADA", cuyo titular es OTSUKA PHARMACEUTICAL CO., LTD, 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 aripiprazole. 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 13 de enero de 2010, reivindicando prioridad bajo la solicitud JP20070200088 del 2007-07-31; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 629 del 20 de junio de 2011, cuya publicación internacional corresponde a la WO2009017250 del 2009-02-05.

2.2. La solicitud colombiana 10 002.709 objeto de la presente oposición, se refiere a un método para producir una suspensión de aripiprazole que comprende los siguientes pasos: (a) combinar aripiprazole en cantidad y un vehículo para formar una suspensión primaria; (b) someter la suspensión primaria a una primera pulverización para formar una suspensión secundaria; y (c) someter la suspensión secundaria a una segunda pulverización para formar una suspensión final.

2.3. 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: WO2005041937 publicada el 12 de mayo de 2005.

2.4. Ahora bien, el documento D1, particularmente en la descripción revela una formulación de aripiprazole estéril liofilizado de liberación controlada. Particularmente, el documento D1 revela (ver página 2, línea 11 a página 4, línea 18; página 5, línea 25 a página 6, línea 25; página 9, líneas 11-22; página 10, línea 1



a página 11, línea 2; página 15, líneas 9-19; página 16, líneas 1-6; ejemplos 1 y 2; y, reclamaciones 25-29) un método para producir una suspensión de aripiprazol que comprende las etapas de a) la combinación de aripiprazol a granel y un vehículo para formar la suspensión primaria, b) someter la suspensión primaria a la pulverización con el tamaño de partícula deseado, preferiblemente 1-10 micrómetros y más preferiblemente de 2,5 micrómetros (ver página 5, línea 22 a página 6, línea 3). La pulverización es preferiblemente llevada a cabo por molienda húmeda aséptica (página 10, líneas 5-9; ejemplo 1), otras técnicas de reducción de tamaño de las partículas, que pueden ser empleados incluyen la cristalización asépticas controladas, la homogeneización de alta cizalladura, la homogeneización de alta presión, y microfluidización (página 5, líneas 22-25; ejemplo 2). Las suspensiones comprenden un agente de suspensión, que es preferentemente carboximetilcelulosa de sodio (Página 6, líneas 20-25; ejemplos y 2). D1 también da a conocer la liofilización de la suspensión aripiprazol, ya sea por enfriamiento a -40°C , y el secado a temperatura por debajo de 0°C , si el monohidrato se desea, o bien mediante un proceso de tres fases que comprende la etapa de refrigeración a -40°C , secado primario a una temperatura por debajo de 0°C , seguido de secado secundario a una temperatura superior a 0°C , si una forma anhidra de aripiprazol se desea. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

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

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 002.709 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.7.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.” A la fecha de prioridad, 31 de julio de 2007 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, método para producir una suspensión de aripiprazole, sobre el cual busca protección en el capítulo reivindicatorio.

2.8. 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 uno de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada “**MÉTODOS PARA PRODUCIR SUSPENSIÓN DE ARIPIPRAZOLE Y UNA FORMULACIÓN LIOFILIZADA**”, cuyo titular es OTSUKA PHARMACEUTICAL CO., LTD, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 629 del 20 de junio 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: WO2005041937 publicada el 12 de mayo de 2005.

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:
 - DI: WO2005041937 publicada el 12 de mayo de 2005.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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 director,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

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



RECIBO DE CAJA

No. 11 - 0072051

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	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

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

Responsable

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-002709-00005-0000

Fecha: 2011-09-16 12:06:33 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 39

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

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

Julio 27 de 2011 - 14:03:27

PODER ESPECIAL

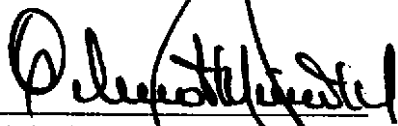
Yo, **ORLANDO MUÑOZ MARTINEZ**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad 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. 10 002.709, titulada "**MÉTODOS PARA PRODUCIR SUSPENSIÓN DE ARIPIRAZOLE Y UNA FORMULACIÓN LIOFILIZADA**", cuyo titular **OTSUKA PHARMACEUTICAL CO., LTD** publicada en la gaceta No. 629 del 20 de junio 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 15 días del mes de septiembre de 2011.

LABORATORIOS SYNTHESIS S.A.S.

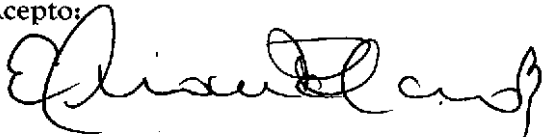


Cédula de Ciudadanía No. 8.317.044 de Medellín

NIT: 860.000.760-1

Subgerente

Acepto:



ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

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



28

DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá, D.C. Orlando Martinez

quien exhibió la C.C. 8317044

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

BOGOTÁ, D.C.

15 SEP 2011

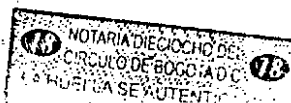
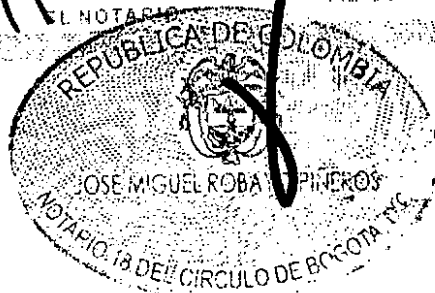
FIRMA

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EL NOTARIO



HUELLA DEL INDICE DERECHO



01

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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

5 DE SEPTIEMBRE DE 2011

HORA 15:51:44

R032482143

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 RE--- FORMAS.

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

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 CONDUCENTES 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 AQUEL.

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)



* 1 1 0 1 2 9 8 7 3

PAGINA: 3 de 5

* * * * *

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFIENDA LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE

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 CONDUCTENTES 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

5 DE SEPTIEMBRE DE 2011 HORA 15:51:44

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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

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011
ULTIMO AÑO RENOVADO : 2011

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011
ULTIMO AÑO RENOVADO : 2011

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011
ULTIMO AÑO RENOVADO : 2011

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011
ULTIMO AÑO RENOVADO : 2011

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993
RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011
ULTIMO AÑO RENOVADO : 2011

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

5 DE SEPTIEMBRE DE 2011 HORA 15:51:44

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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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/041937 A2

(51) International Patent Classification: A61K 9/19,
47/38, 47/26

MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(21) International Application Number:
PCT/US2004/034367

(22) International Filing Date: 18 October 2004 (18.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): AR, PO (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).

(30) Priority Data:
60/513,618 23 October 2003 (23.10.2003) US

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations 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, SI, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA,
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (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 patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

Published:

— without international search report and to be republished
upon receipt of that report

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

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NARINGREKAR, Vijay H. [US/US]; 12 Courtside Lane,
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(74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb
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4000 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BE, 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,

(54) Title: CONTROLLED RELEASE STERILE INJECTABLE ARIPIRAZOLE FORMULATION AND METHOD

(57) Abstract: A controlled release sterile freeze-dried aripiprazole formulation is provided which is formed of aripiprazole of a desired mean particle size and a vehicle therefor, which upon constitution with water and intramuscular injection releases aripiprazole over a period of at least about one week and up to about eight weeks. A method for preparing the controlled release freeze-dried aripiprazole formulation, and a method for treating schizophrenia employing the above formulation are also provided.

WO 2005/041937 A2

CONTROLLED RELEASE STERILE INJECTABLE ARIPIPAZOLE FORMULATION AND METHOD

FIELD OF THE INVENTION

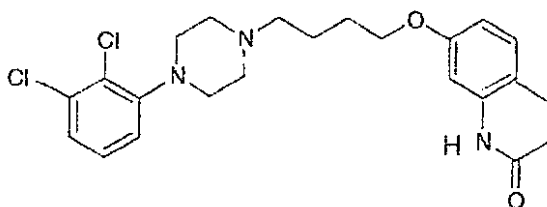
5 This application claims a benefit of priority from U.S. Provisional Application No. 60/513,618 the entire disclosure of which is herein incorporated by reference.

The present invention relates to a controlled release sterile freeze-dried aripiprazole formulation, an injectable formulation which contains the sterile freeze-dried aripiprazole and which releases aripiprazole over at least a one week period, a
10 method for preparing the above formulation, and a method for treating schizophrenia and related disorders employing the above formulation.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,006,528 to Oshiro et al. discloses 7-[(4-phenylpiperazino)-
15 butoxy] carbostyrils, which include aripiprazole, as dopaminergic neurotransmitter antagonists.

Aripiprazole which has the structure



20

is an atypical antipsychotic agent useful in treating schizophrenia. It has poor aqueous solubility (<1µg/mL at room temperature).

U.S. Patent No. 6,267,989 to Liversidge, et al. discloses a method for preventing crystal growth and particle aggregation in nanoparticulate compositions
25 wherein a nanoparticulate composition is reduced to an optimal effective average particle size employing aqueous milling techniques including ball milling.

U.S. Patent No. 5,314,506 to Midler, et al. relates to a process for the direct crystallization of a pharmaceutical having high surface area particles of high purity and stability wherein impinging jet streams are employed to achieve high intensity

micromixing of particles of the pharmaceutical followed by nucleation and direct production of small crystals.

5 A long-acting aripiprazole sterile injectionable formulation has merit as a drug dosage form in that it may increase the compliance of patients and thereby lower the rate of relapse in the treatment of schizophrenia. Examples of known long acting drug products for the treatment of schizophrenia include haloperidol decanoate and fluphenazine decanoate both of which have an ester compound of low water solubility dissolved in sesame oil. Microcapsules containing Risperidone (WO95/13814) and Olanzapine (WO99/12549) are also known.

10

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a sterile freeze-dried aripiprazole formulation which upon constitution with water for injection releases aripiprazole, in therapeutic amounts, over a period of at least about one week, and preferably over a period of two, three or four weeks and up to six weeks or more. 15 The freeze-dried aripiprazole formulation of the invention includes:

- (a) aripiprazole, and
- (b) a vehicle for the aripiprazole,

which formulation upon constitution with water forms an injectable suspension 20 which, upon injection, preferably intramuscularly, releases therapeutic amounts of aripiprazole over a period of at least one week, preferably two, three or four weeks, and up to six weeks or more.

The freeze-dried aripiprazole formulation of the invention will preferably include:

- 25 (a) aripiprazole,
- (b) one or more suspending agents,
- (c) optionally one or more bulking agents,
- (d) optionally one or more buffers, and
- (e) optionally one or more pH adjusting agents.

30 A mean particle size of the freeze-dried aripiprazole formulation within the range from about 1 to about 30 microns is essential in formulating an injectable which

releases aripiprazole over a period of at least about one week and up to six weeks or more, for example up to 8 weeks.

It has been found that the smaller the mean particle size of the freeze-dried aripiprazole, the shorter the period of extended release. Thus, in accordance with the present invention, when the mean particle size is about 1 micron, the aripiprazole will be released over a period of less than three weeks, preferably about two weeks. When the mean particle size is more than about 1 micron, the aripiprazole will be released over a period of at least two weeks, preferably about three to four weeks, and up to six weeks or more. Thus, in accordance with the present invention, the aripiprazole release duration can be modified by changing the particle size of the aripiprazole in the freeze-dried formation.

The term "mean particle size" refers to volume mean diameter as measured by laser-light scattering (LLS) methods. Particle size distribution is measured by LLS methods and mean particle size is calculated from the particle size distribution.

In addition, in accordance with the present invention, a controlled release sterile injectable aripiprazole formulation in the form of a sterile suspension, that is, the freeze-dried formulation of the invention suspended in water for injection, is provided which, upon injection, preferably intramuscularly, releases therapeutic amounts of aripiprazole over a period of at least one week, which includes:

- (a) aripiprazole,
- (b) a vehicle therefor, and
- (c) water for injection.

The controlled release sterile injectable formulation of the invention in the form of a sterile suspension allows for high drug loadings per unit volume of the formulation and therefore permits delivery of relatively high doses of aripiprazole in a small injection volume (0.1 – 600 mg of drug per 1 mL of suspension).

Further, in accordance with the present invention, a method is provided for preparing the sterile freeze-dried aripiprazole formulation described above which includes the steps of:

- (a) preparing sterile bulk aripiprazole, preferably having a desired particle size distribution and mean particle size within the range from about 5 to about 100 microns,

- 100
- (b) preparing a sterile vehicle for the sterile bulk aripiprazole,
 - (c) combining the sterile bulk aripiprazole and the sterile vehicle to form a sterile primary suspension,
 - (d) reducing the mean particle size of aripiprazole in the sterile primary suspension to within the range from about 1 to about 30 microns, to form a final sterile suspension, and
 - (e) freeze drying the final sterile suspension to form a sterile freeze-dried suspension of the aripiprazole of desired polymorphic form (anhydrous, monohydrate, or a mixture of both).

10 In carrying out the above method, the reduction of the mean particle size of the sterile primary suspension to the desired mean particle size is carried out employing an aseptic wet milling procedure, which preferably is aseptic wet ball milling. Aseptic wet milling is essential in forming a homogeneous and sterile aripiprazole formulation of desired mean particle size distribution.

15 In addition, in accordance with the present invention, a method for freeze drying the final sterile suspension of aripiprazole is provided which produces a sterile freeze-dried aripiprazole of desired polymorphic form, that is anhydrous, monohydrate, or a mixture of both.

20 Still further in accordance with the present invention, a method is provided for treating schizophrenia and related diseases which includes the step of administering to a patient in need of treatment therapeutic amounts of the above described controlled release injectable aripiprazole formulation.

25 As an unexpected observation, it has been discovered that a suspension of aripiprazole suspended in an aqueous solvent system will maintain a substantially constant aripiprazole drug plasma concentration when administered by injection; preferably as an intra-muscular injection. No large "burst phenomenon" is observed and it is considerably surprising that a constant aripiprazole drug plasma concentration can be maintained from one (1) to more than eight (8) weeks employing the aripiprazole suspension of the invention. The daily starting dose for an orally administered aripiprazole formulation is fifteen (15) milligrams. In order to administer a drug dose equivalent to one (1) to more than eight (8) weeks of the oral dosage quantity requires the administration of a very large amount of the drug as a

single dose. The aqueous aripiprazole injectable formulation of the invention may be administered to deliver large amounts of the drug without creating patient compliance problems.

The aripiprazole injectable formulation of the invention may include
5 anhydrous or monohydrate crystalline forms of aripiprazole or an admixture containing both. If the monohydrate is used, the maintenance of an extended drug plasma concentration is possible.

The aripiprazole injectable formulation of the invention can be administered as an aqueous ready-to-use suspension; however, by freeze-drying this suspension a
10 more useful drug product can be supplied.

BRIEF DESCRIPTION OF FIGURES

Figure 1 is a graph depicting mean plasma concentrations versus time profiles of the Example 1 formulation of the invention in rats;

15 Figure 2 is a graph depicting mean plasma concentrations versus time profiles of the Example 1 formulation of the invention in dogs; and

Figure 3 is a graph depicting mean plasma concentrations vs. time profiles of the Example 1 formulation of the invention in humans.

20 DETAILED DESCRIPTION OF THE INVENTION

The controlled release sterile injectable aripiprazole formulation of the invention will include aripiprazole in an amount within the range from about 1 to about 40%, preferably from about 5 to about 20%, and more preferably from about 8 to about 15% by weight based on the weight of the sterile injectable formulation.

25 As indicated, desired mean particle size of the aripiprazole is essential in producing an injectable formulation having the desired controlled release properties of the aripiprazole. Thus, to produce desired controlled release, the aripiprazole should have a mean particle size within the range from about 1 to about 30 microns, preferably from about 1 to about 20 microns, and more preferably for about 1 to about
30 10 to 15 microns.

Where the desired controlled release period is at least about two weeks, up to six weeks or more, preferably about three to about four weeks, the aripiprazole will

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have a mean particle size within the range from about 1 to about 20, preferably from about 1 to about 10 microns, more preferably from about 2 to about 4 microns, and most preferably about 2.5 microns. The aripiprazole having a mean particle size of about 2.5 microns will have a particle size distribution as follows:

5	<u>Preferred</u>	<u>More Preferred</u>
	95% < 20 microns	95% < 8 microns
	90% < 15 microns	90% < 6 microns
	50% < 10 microns	75% < 3 microns
	10% < 2 microns	50% < 1.5 microns
10		10% < 0.5 microns

The aripiprazole formulation of the invention will preferably be formed of:

- A. aripiprazole,
- B. a vehicle therefor, which includes:
 - (a) one or more suspending agents,
 - 15 (b) one or more bulking agents,
 - (c) one or more buffers, and
 - (d) optionally one or more pH adjusting agents.

The suspending agent will be present in an amount within the range from about 0.2 to about 10% by weight, preferably for about 0.5 to about 5% by weight based on the total weight of the sterile injectable formulation. Examples of suspending agents suitable for use include, but are not limited to, one, two or more of the following: sodium carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropylethyl cellulose, hydroxypropylmethyl cellulose, and polyvinylpyrrolidone, with sodium carboxymethyl cellulose and polyvinylpyrrolidone being preferred. Other suspending agents suitable for use in the vehicle for the aripiprazole include various polymers, low molecular weight oligomers, natural products, and surfactants, including nonionic and ionic surfactants, such as cetyl pyridinium chloride, gelatin, casein, lecithin (phosphatides), dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene

sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)); polyethylene glycols (e.g., Carbowax 3350® and 1450®, and Carbopol 934® (Union Carbide)), dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronic F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); a charged phospholipid such as dimyristoyl phosphatidyl glycerol, dioctylsulfosuccinate (DOSS); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (e.g., Aerosol OT®, which is a dioctyl ester of sodium sulfosuccinic acid (American Cyanamid)); Duponol P®, which is a sodium lauryl sulfate (DuPont); Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, Conn.); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)) - CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; and the like.

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Most of these suspending agents are known pharmaceutical excipients and 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 Society of Great Britain (The Pharmaceutical Press, 1986), specifically incorporated by reference. The suspending agents are commercially available and/or can be prepared by techniques known in the art.

Carboxymethyl cellulose or the sodium salt thereof is particularly preferred where the desired mean particle size is about 1 micron or above.

The bulking agent (also referred to as a cryogenic/lyophilize protecting agent) will be present in an amount within the range from about 1 to about 10% by weight, preferably from about 3 to about 8% by weight, more preferably from about 4 to about 5% by weight based on the total weight of the sterile injectable formulation. Examples of bulking agents suitable for use herein include, but are not limited to, one, two or more of the following: mannitol, sucrose, maltose, xylitol, glucose, starches, sorbitol, and the like, with mannitol being preferred for formulations where the mean particle size is about 1 micron or above. It has been found that xylitol and/or sorbitol enhances stability of the aripiprazole formulation by inhibiting crystal growth and agglomeration of drug particles so that desired particle size may be achieved and maintained.

The buffer will be employed in an amount to adjust pH of an aqueous suspension of the freeze-dried aripiprazole formulation to from about 6 to about 8, preferably about 7. To achieve such pH, usually the buffer, depending on type, will be employed in an amount within the range from about 0.02 to about 2% by weight, preferably from about 0.03 to about 1% by weight, and more preferably about 0.1% by weight based on the total weight of the sterile injectable formulation. Examples of buffers suitable for use herein include, but are not limited to, one, two or more of the following: sodium phosphate, potassium phosphate, or TRIS buffer, with sodium phosphate being preferred.

The freeze-dried formulation of the invention may optionally include a pH adjusting agent which is employed in an amount to adjust pH of the aqueous suspension of the freeze-dried aripiprazole within the range from about 6 to about 7.5, preferably about 7 and may be an acid or base depending upon whether the pH of the

aqueous suspension of the freeze-dried aripiprazole needs to be raised or lowered to reach the desired neutral pH of about 7. Thus, where the pH needs to be lowered, an acidic pH adjusting agent which as hydrochloric acid or acetic acid, preferably hydrochloric acid, may be employed. When the pH needs to be raised, a basic pH
5 adjusting agent will be employed such as sodium hydroxide, potassium hydroxide, calcium carbonate, magnesium oxide or magnesium hydroxide, preferably sodium hydroxide.

The freeze-dried aripiprazole formulations may be constituted with an amount of water for injection to provide from about 10 to about 400 mg of aripiprazole
10 delivered in a volume of 2.5 mL or less, preferably 2 mL for a two to six week dosage.

In carrying out the method for preparing the freeze-dried aripiprazole formulation of the invention, it is required that everything be sterile so that sterile aripiprazole and sterile vehicle are combined aseptically to form a sterile suspension and that the sterile suspension be freeze-dried in a manner to form sterile freeze-dried
15 powder or cake. Thus, an aseptic procedure is employed to produce sterile bulk aripiprazole of desired particle size distribution. The sterile bulk aripiprazole will have a mean particle size within the range from about 5 to about 100 microns, preferably from about 10 to about 90 microns.

Preferably, an impinging jet crystallization method is employed to produce
20 sterile aripiprazole of desired small particle size and a narrow size distribution, high surface area, high chemical purity, high stability due to improved crystal structure, while employing continuous processing.

The impinging jet crystallization utilizes two jet streams that strike each other head-on. One of the streams carries a solution rich in the aripiprazole and the other
25 carries an anti-solvent, such as water. The two streams strike each other which allows rapid homogeneous mixing and supersaturation due to high turbulence and high intensity of micromixing upon impact. This immediate achievement of supersaturation initiates rapid nucleation. In general, the average crystal size decreases with increasing supersaturation and decreasing temperature of the anti-
30 solvent. Therefore, in order to obtain the smallest particle size, it is advantageous to have the highest possible concentration of the rich solution and the lowest temperature of the anti-solvent.

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The vehicle for the sterile bulk aripiprazole including suspending agent, bulking agent, buffer, optional pH adjusting agent and water is prepared and subjected to sterilization. Thereafter, the sterile bulk aripiprazole and sterile vehicle are aseptically combined to form a sterile primary suspension and the particle size of the aripiprazole is reduced to a desired level. This is preferably carried out employing an aseptic wet milling procedure wherein sterile particles of aripiprazole dispersed in the sterile vehicle are subjected to grinding means in the presence of grinding media to reduce the particle size of the aripiprazole to within the range of about 1 to about 10 microns, depending upon desired controlled release period.

The aseptic wet milling procedure is preferably wet ball milling. When the desired mean particle size of the aripiprazole is above about 1 micron, the primary suspension (combined aripiprazole-vehicle) is passed through a wet ball mill a single time (single pass) at from about 5 to about 15 L/hr, preferably from about 8 to about 12 L/hr, and more preferably about 10 L/hr, to reduce mean particle size of the aripiprazole to within the desired range, for example, from about 1 to about 5 microns.

In addition to ball mills, such as Dyno mills, other low and high energy mills may be employed such as a roller mill, and high energy mills may be employed such as Netzsch mills, DC mills and Planetary mills. However, it is essential that the milling procedure and equipment employed be capable of producing sterile aripiprazole formulation of desired mean particle size.

Other techniques for particle size reduction which may be employed include aseptic controlled crystallization, high shear homogenization, high pressure homogenization and microfluidization to produce particles having a mean particle size ranging from about 1 to about 100 microns.

The resulting final suspension is aseptically filled into sterile vials and aseptically loaded into a sterilized freeze drier. It is essential that a carefully designed freeze drying cycle be applied in order to form and/or maintain the desired crystalline form of the aripiprazole, which is known to exist in monohydrate form (Aripiprazole Hydrate A) as well as in a number of anhydrous forms, namely Anhydride Crystals B, Anhydride Crystals C, Anhydride Crystals D, Anhydride Crystals E, Anhydride

Crystals F, and Anhydride Crystals G, all of which may be employed in the formulation of the invention.

The aripiprazole monohydrate (grains) or hydrate as referred to below employed in the present invention has the physicochemical properties given in (1)-(5) below. This aripiprazole hydrate is described hereinafter as "Aripiprazole Hydrate A".

(1) It has an endothermic curve characterized by the appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.

(2) It has an ¹H-NMR spectrum which has characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(3) It has a powder x-ray diffraction spectrum which has characteristic peaks at $2\theta = 12.6^\circ, 15.4^\circ, 17.3^\circ, 18.0^\circ, 18.6^\circ, 22.5^\circ$ and 24.8° .

(4) It has clear infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

(5) It has a mean grain size of 50 μm or less.

Aripiprazole Hydrate A is manufactured by milling conventional aripiprazole hydrate.

Conventional milling methods can be used to mill the aripiprazole hydrate. For example, the aripiprazole hydrate can be milled in a milling machine. A widely used milling machine can be used, such as an atomizer, pin mill, jet mill or ball mill. Of these, the atomizer is preferred.

Regarding the specific milling conditions when using an atomizer, a rotational speed of 5000-15000 rpm could be used for the main axis, for example, with a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

The mean grain size of the Aripiprazole Hydrate A obtained by milling should normally be 50 μm or less, preferably 30 μm or less. Mean grain size can be ascertained by the grain size measurement method described hereinafter.

Grain Size Measurement: 0.1 g of the grains to be measured were suspended in a 20 ml n-hexane solution of 0.5 g soy lecithin, and grain size was measured using a size distribution meter (Microtrack HRA, Microtrack Co.).

5 The aripiprazole anhydride crystals employed in the present invention have the physicochemical properties given in (6)-(10) below. These aripiprazole anhydride crystals are referred to hereinafter as "Aripiprazole Anhydride Crystals B".

(6) They have an ^1H -NMR spectrum which is substantially the same as the ^1H -NMR spectrum (DMSO- d_6 , TMS) shown in Figure 4. Specifically, they have characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, $J = 7.4$ Hz, 2H), 2.97 ppm (brt, $J = 4.6$ Hz, 4H), 3.92 ppm (t, $J = 6.3$ Hz, 2H), 6.43 ppm (d, $J = 2.4$ Hz, 1H), 6.49 ppm (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 7.04 ppm (d, $J = 8.1$ Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(7) They have a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they have characteristic peaks at $2\theta = 11.0^\circ$, 16.6° , 19.3° , 20.3° and 22.1° .

(8) They have clear infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

(9) They exhibit an endothermic peak near about 141.5°C in thermogravimetric/differential thermal analysis (heating rate $5^\circ\text{C}/\text{min}$).

(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate $5^\circ\text{C}/\text{min}$).

Aripiprazole Anhydride Crystals B employed in the present invention have low hygroscopicity. For example, Aripiprazole Anhydride Crystals B employed in the present invention maintain a water content of 0.4% or less after 24 hours inside a dessicator set at a temperature of 60°C and a humidity of 100%.

Well-known methods of measuring water content can be used as long as they are methods commonly used for measuring the water content of crystals. For example, a method such as the Karl Fischer method can be used.

30 The Aripiprazole Anhydride Crystals B employed in the present invention are prepared for example by heating the aforementioned Aripiprazole Hydrate A at 90-

125°C. The heating time is generally about 3-50 hours, depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of Aripiprazole Hydrate A is 100°C, the heating time should normally be 18 hours or more or preferably about 24 hours. If the heating temperature of Aripiprazole Hydrate A is 120°C, on the other hand, the heating time can be about 3 hours. The Aripiprazole Anhydride Crystals B of the present invention can be prepared with certainty by heating Aripiprazole Hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C.

Furthermore, the Aripiprazole Anhydride Crystals B employed in the present invention are prepared for example by heating conventional aripiprazole anhydride crystals at 90-125°C. The heating time is generally about 3-50 hours, depending on heating temperature. The heating time and heating temperature are inversely related, as described above. Specifically, if the heating temperature of the aripiprazole anhydride crystals is 100°C, the heating time can be about 4 hours, and if the heating temperature is 120°C the heating time can be about 3 hours.

The aripiprazole anhydride crystals which are the raw material for preparing the Aripiprazole Anhydride Crystals B employed in the present invention are prepared for example by Method a or b below.

Method a:

Aripiprazole Anhydride Crystals B are prepared by well-known methods, as by reacting 7-(4-bromobutoxy)-3,4-dihydrocarbostyryl with 1-(2,3-dichlorophenyl) piperidine and recrystallizing the resulting raw aripiprazole crystals with ethanol as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

Method b:

Aripiprazole Anhydride Crystals B are prepared by heating conventional aripiprazole hydrate at a temperature of at least 60°C and less than 90°C. The heating

time is generally about 1-30 hours, depending on heating temperature. The heating time and heating temperature are inversely related, as described above. Specifically, if the heating temperature of the aripiprazole hydrate is about 60°C, the heating time can be about 8 hours, while if the heating temperature is 80°C, the heating time can be about 4 hours.

Method b is described in the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996).

Furthermore, the Aripiprazole Anhydride Crystals B employed in the present invention are prepared for example by heating conventional aripiprazole hydrate at 90-125°C. The heating time is generally about 3-50 hours, depending on heating temperature. The heating time and heating temperature are inversely related. Specifically, if the heating temperature of the aripiprazole hydrate is 100°C, the heating time can be about 24 hours, while if the heating temperature is 120°C, the heating time can be about 3 hours.

The aripiprazole hydrate which is the raw material for preparing the Aripiprazole Anhydride Crystals B employed in the present invention is prepared for example by Method c below.

Method c:

Aripiprazole hydrate is obtained by dissolving the aripiprazole anhydride crystals obtained by Method a above in a hydrous solvent, and heating and then cooling the resulting solution. Using this method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

An organic solvent containing water is usually used as the hydrous solvent.

The organic solvent should be one which is miscible with water, such as for example an alcohol such as methanol, ethanol, propanol or isopropanol, a ketone such as acetone, an ether such as tetrahydrofuran, dimethylformamide, or a mixture thereof, with ethanol being particularly desirable. The amount of water in the hydrous solvent can be 10-25% by weight of the solvent, or preferably close to 20% by weight.

As mentioned above, the Aripiprazole Anhydride Crystals B employed in the present invention are prepared by heating at 90-125°C of the Aripiprazole Hydrate A,

conventional aripiprazole anhydride crystals or conventional aripiprazole hydrate, and the Aripiprazole Hydrate A, conventional aripiprazole anhydride crystals or conventional aripiprazole hydrate may be used either individually or in combination.

5 The above crystal forms and other crystal forms of aripiprazole and methods for making such crystal forms which may be employed herein include Hydrate A and Anhydride Crystals B as well as Anhydride Crystals C, Anhydride Crystals D, Anhydride Crystals E, Anhydride Crystals F, and Anhydride Crystals G, as disclosed in PCT WO 03/26659, published April 4, 2003.

10 If the monohydrate form of the aripiprazole in the freeze-dried formulation is desired then the freeze drying cycle should include cooling of the formulation to about -40°C at a suitable cooling rate. The primary drying should be performed at a temperature below around 0°C and a suitable vacuum and duration.

15 If the anhydrous form of the aripiprazole in the freeze-dried formulation is desired then the freeze drying cycle should include three phases: freezing, primary drying, and secondary drying. The freezing phase should include cooling of the formulation to about -40°C at a suitable cooling rate. The primary drying should be performed at a temperature below about 0°C and a suitable vacuum and duration. The secondary drying should be performed at a temperature above about 0°C and a suitable vacuum and duration.

20 The vials with the resulting freeze-dried aripiprazole suspension are aseptically stoppered under atmospheric pressure or partial vacuum and sealed.

Preferred injectable formulations in the form of aqueous suspensions are set out below:

Preferred Particle Size of About 1-10 Microns (Preferably About 2.5 Microns)

	Range % w/v	Preferred Range % w/v
(1) Sterile Aripiprazole – (mean particle size from about 1 to about 5 microns)	1 to 40	8 to 15
(2) Suspending Agent (preferably carboxymethyl cellulose Na salt)	0.2 to 10	0.5 to 5
(3) Bulking Agent (preferably mannitol)	1 to 10	4 to 5
(4) Buffer (preferably sodium phosphate) (adjust pH to about 6 to about 7.5)	0.02 to 2	0.03 to 1
(5) pH Adjusting Agent (preferably sodium hydroxide) (adjust pH to about 6 to about 7.5)	As needed	As needed
(6) Water for injection	As needed	As needed

The aripiprazole will be present in the aqueous injectable formulation in an amount within the range from about 1 to about 40% (w/v), preferably from about 5 to about 20 % (w/v), and more preferably from about 8 to about 15% (w/v), based on the total injectable formulation.

In preferred embodiments, the aripiprazole will be present in the aqueous injectable formulation to provide from about 50 to about 400 mg/2 mL of formulation, preferably from about 100 to about 200 mg/mL of formulation.

Preferred individual dose injectable formulations in accordance with the invention are as follows:

aripiprazole	100 mg	200 mg	400 mg
carboxymethyl cellulose	9 mg	9 mg	9 mg
mannitol	45 mg	45 mg	45 mg
Na phosphate	0.8 mg	0.8 mg	0.8 mg
sodium hydroxide	qs to adjust pH to 7	qs to adjust pH to 7	qs to adjust pH to 7
water for injection	qs to 1 mL	qs to 1 mL	qs to 1 mL

The aripiprazole formulations of the invention are used to treat schizophrenia and related disorders such as bipolar disorder and dementia in human patients. The preferred dosage employed for the injectable formulations of the invention will be a single injection or multiple injections containing from about 100 to about 400 mg

EXAMPLES**EXAMPLE 1**

An aripiprazole injectable (IM Depot) aqueous suspension (200 mg
5 aripiprazole/2 mL, 200 mg/vial) was prepared as follows.

ARIPIPAZOLE MICROSUSPENSION PREPARED BY MEDIA MILLING

A microparticulate dispersion of aripiprazole was prepared using a DYNO®-
MILL (Type KDL A, manufactured by Willy A. Bachoffen AG Maschinenfabrik,
10 Basel, Switzerland).

The following ingredients were added to a 3L glass jacketed vessel maintained
at 15°C (±5°C) to form a sterile primary suspension:

	Aripiprazole	100 g
	Carboxymethylcellulose, Sodium Salt 7L2P	9.0 g
15	Mannitol	45 g
	Sodium Phosphate, Monobasic	0.8 g
	Sodium Hydroxide Solution, 1N	q.s. to adjust pH to 7.0
	Water for Injection, USP	q.s. to 1040 g

The primary suspension was mixed at 500-1000 rpm for about 0.5 hour and
20 then at 300-500 rpm for an additional 1 hour under 20 "Hg (± 5"Hg) vacuum.

The media mill was prepared accordingly for the media milling process. The
grinding container was partially filled with zirconium oxide beads and the dispersion
was passed through the mill operating at the following conditions:

	Grinding container:	water jacketed 0.6 L stainless steel vessel
25	Coolant temperature:	15°C (±5°C)
	Agitation speed:	2500 rpm
	Grinding medium:	500 mL of very-high-density (VHD) zirconium oxide beads
	Suspension flow rate:	10 L/h
30	Milling time:	6 minutes

After a single pass milling, a sample of the processed suspension was removed and evaluated for particle size distribution using Horiba LA-910 Laser Scattering Particle Size Distribution Analyzer. The particles were determined to have a mean particle size of 2.5 microns (μ) and the following particle size distribution: 10% < 0.4 μ , 50% < 1.6 μ , 75% < 3.3 μ , 90% < 5.9 μ , and 95% < 7.6 μ .

2.5 mL of the above suspension were aseptically filled into sterilized vials which were then aseptically partially stoppered with sterilized stoppers. The vials were aseptically transferred to a freeze dryer and lyophilized according to the following cycle:

- (a) thermal treatment: freeze product at -40°C over 0.1-1 h and keep at -40°C for at least 3 h,
- (b) cool the condenser to -50°C or below,
- (c) primary drying: lower chamber pressure to approximately 100 microns Hg and increase product temperature to -5°C over approximately 2 h; continue primary drying at -5°C and 100 microns Hg for at least 48 h,
- (d) stopper the vials under atmospheric pressure or partial vacuum using sterile nitrogen or air and remove from the freeze dryer,
- (e) seal the vials with the appropriate seals and label.

20

EXAMPLE 2

An aripiprazole injectable (IM Depot) aqueous suspension (200 mg aripiprazole/2 mL, 200 mg/vial) was prepared as follows.

25

ARIPIRAZOLE MICROSUSPENSION PREPARED BY IMPINGING JET CRYSTALLIZATION

A microparticulate dispersion of aripiprazole was prepared using impinging jet crystallization.

The following procedure was employed to form a sterile bulk aripiprazole:

1. Suspend 100 g of aripiprazole in 2000 mL of 95% ethanol. Heat the suspension to 80°C until it becomes a clear solution.

2. Polish filter the aripiprazole solution into a holding vessel and maintain at 80° C.
3. Polish filter 2000 mL water to another holding vessel and heat to 80° C.
4. Pump the aripiprazole solution through a 0.02 inch diameter nozzle at 0.25 kg/min and impinge it with the 30° C water pumped at 0.25 kg/min through a 0.02 inch diameter nozzle to form a crystal slurry which is collected in an impingement vessel.
5. Agitate the newly formed crystal slurry in the impingement vessel while continuously transferring it to a receiver to maintain a constant volume in the impingement vessel.
6. At the end of impingement, cool the slurry in the receiver to room temperature.
7. Filter the slurry.
8. Dry the wet cake at 35° C under vacuum to yielding 100 g (96% recovery) of aripiprazole with reduced particle size (90% < 100 µm).

The following ingredients were added to a 3L glass jacketed vessel maintained at 15°C (±5°C) to form a sterile primary suspension:

	Aripiprazole (prepared by impinging jet crystallization):	100 g
20	Carboxymethylcellulose, Sodium Salt 7L2P	9.0 g
	Mannitol	45 g
	Sodium Phosphate, Monobasic	0.8 g
	Sodium Hydroxide Solution, 1N	q.s. to adjust pH to 7.0
	Water, USP	q.s. to 1040 g

- 25 The sterile suspension was mixed at 500-1000 rpm for about 0.5 hour and then at 300-500 rpm for an additional 1 hour under 20 "Hg (± 5"Hg) vacuum.

The sterile suspension was found to contain particles having mean particle size of 2.5 microns and the following particle size distribution:

	10%	<	0.4 μ
	50%	<	1.6 μ
5	75%	<	3.3 μ
	90%	<	5.9 μ
	95%	<	7.5 μ

2.5 mL of the above suspension were aseptically filled into sterilized vials which were then aseptically partially stoppered with sterilized stoppers. The vials were aseptically transferred to a freeze dryer and lyophilized according to the following cycle:

- (a) thermal treatment: freeze product at -40°C over 0.1-1 h and keep at -40°C for at least 6 h,
- (b) cool the condenser to -50°C or below,
- 15 (c) primary drying: lower chamber pressure to approximately 100 microns Hg and increase product temperature to -5°C over approximately 2 h; continue primary drying at -5°C and 100 microns Hg for at least 48 h,
- (d) stopper the vials under atmospheric pressure or partial vacuum using sterile nitrogen or air and remove from the freeze dryer,
- 20 (e) seal the vials with the appropriate seals and label.

EXAMPLE 3 (Animal PK Data)

A. Single-dose I.M. depot study in rats

25 Aripiprazole I.M. depot formulation prepared in Example 1 was injected into the thigh muscle of fifteen rats (M-males, F-females) at doses of 12.5, 25, and 50 mg/kg. Blood samples for the evaluation of systemic exposure after aripiprazole I.M. depot administration were collected on days 1 (6 h postdose), 2, 4, 7, 10, 15, 22, 28, 36, and 43 and analyzed for aripiprazole. Figure 1 shows mean plasma concentrations vs. time profiles of aripiprazole in rats.

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B. Single-dose I.M. depot study in dogs

The aripiprazole intramuscular (I.M.) depot formulation prepared in Example 1 was injected into the thigh muscle of five dogs (M-males, F-females) at doses of 100, 200, and 400 mg. Blood samples for the evaluation of systemic exposure after aripiprazole I.M. depot administration were collected on days 1 (10 and 30 minutes, and 1, 3, and 8 h postdose), 2, 4, 7, 10, 15, 22, 28, 36, and 42 and analyzed for aripiprazole. Figure 2 shows mean plasma concentrations vs. time profiles of aripiprazole in dogs.

PK profiles

Mean aripiprazole rats' serum concentration-time profiles are shown graphically in Fig. 1. Aripiprazole aqueous suspensions showed steady serum concentration for at least 4 weeks in the rats' model.

Mean aripiprazole dogs' serum concentration-time profiles are shown graphically in Fig. 2.

Aripiprazole aqueous suspensions showed steady serum concentration for 3-4 weeks in the dogs' model.

EXAMPLE 4 (Human PK Data)**Single-dose I.M. depot study in patients**

Aripiprazole I.M. depot formulation prepared in Example 1 was administered intramuscularly to patients diagnosed with chronic, stable schizophrenia or schizoaffective disorder at. The study design included administration of a 5-mg dose of aripiprazole solution to all subjects followed by a single dose of IM depot at 15, 50, and 100 mg per patient. Samples for PK analysis were collected until plasma concentrations of aripiprazole were less than the lower limit of quantification (LLQ) for 2 consecutive visits.

Figure 3 shows mean plasma concentrations vs. time profiles of aripiprazole in subjects 2 and 3 dosed with 15 mg of IM Depot, and subjects 4 and 5 who received 50 mg of IM Depot. In all cases aripiprazole plasma levels showed a fast onset of release and sustained release for at least 30 days.

18. The freeze-dried formulation as defined in Claim 17 having a mean particle size within the range from about 1 to about 10 microns which upon constitution with water for injection releases aripiprazole over a period of at least about three weeks.

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19. The freeze-dried formulation as defined in Claim 18 having a mean particle size of about 2.5 microns.

20. The freeze-dried formulation as defined in Claim 17 wherein said
10 vehicle comprises:

- (a) one or more suspending agents,
- (b) one or more bulking agents, and
- (c) one or more buffering agents.

15 21. The freeze-dried formulation as defined in Claim 20 further including a pH adjusting agent.

22. The freeze-dried formulation as defined in Claim 20, which upon
constitution with water and injection releases aripiprazole over at least about a three
20 week period, comprising:

- (a) aripiprazole,
- (b) carboxymethyl cellulose or its sodium salt,
- (c) mannitol,
- (d) sodium phosphate to adjust pH to about 7, and
- 25 (e) optionally sodium hydroxide to adjust pH to about 7.

23. The freeze-dried formulation as defined in Claim 22 which upon
reconstitution with water and injection releases aripiprazole over about a four week
period.

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24. The freeze-dried formulation as defined in Claim 23 wherein the aripiprazole is the form of anhydrous crystals or is in the form of a monohydrate.

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25. A method for preparing the sterile freeze-dried formulation as defined in Claim 17 which comprises the steps of:

- 5 (a) preparing sterile bulk aripiprazole having a desired particle size distribution,
- (b) preparing a sterile vehicle for the sterile bulk aripiprazole,
- (c) combining said sterile aripiprazole and said sterile vehicle to form a sterile primary suspension which includes a sterile mixture of solids,
- 10 (d) reducing the mean particle size of said sterile mixture of solids in said sterile primary suspension to within the range from about 1 to about 10 microns to form a sterile final suspension, and
- (e) freeze drying said sterile final suspension to form the freeze-dried formulation.

- 15 26. The method as defined in Claim 25 wherein the step of reducing the mean particle size of the sterile mixture of solids in said sterile primary suspension is carried out employing wet milling.

- 20 27. The method as defined in Claim 26 wherein the wet milling comprises wet ball milling.

- 25 28. The method as defined in Claim 25 wherein said freeze drying step is carried out by cooling the sterile final suspension to about -40° and drying said cooled sterile final suspension at below about 0° C, to form freeze-dried aripiprazole in the form of its monohydrate.

- 30 29. The method as defined in Claim 25 where the freeze drying step of the sterile final suspension is carried out in three phases: (1) a freezing phase which includes cooling of the sterile final suspension at about -40° C, (2) a primary drying phase which is performed at below about 0° C, and (3) a secondary drying phase which is performed at above about 0° C, to form aripiprazole in anhydrous form.