

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 12 018.250

Solicitante: SUPERNUS PHARMACEUTICALS, INC

Apoderado: LUZ CLEMENCIA DE PAEZ

Título de la Nueva Creación: UN MÉTODO DE TRATAMIENTO DE UN TRANSTORNO NEUROLÓGICO

Gaceta: 642

2. Datos del Opositor

☐ Persona Natural ☐ Persona Jurídica
SYNTHESIS S.A.S.

Nombre o denominación /Razón social completa

LUIS PALACIOS ARAGON

Nombre del representante legal

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☐ Otro ☐ Cuál _____

Número 860000760-1 _____

Dirección. CRA 44 20C 73 _____ Ciudad BOGOTA

Teléfono 3692222 Fax: _____ Correo electrónico _____

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

MORENO BOHORQUEZ ELIANA ISaura

51.975.664

83823

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

CRA 13 119-95 OFICINA 104

Dirección electrónica
negocios@optimum-co.com

No. Fax
(571)6121979

Número telefónico
(571)2131213

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general:

4. Fundamentos de la oposición

Causal: Art14, 16, 18,20 y 30 de la decisión 486 de la CAN no cumple con los requisitos De patentabilidad.

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

Prórroga:

SI

☐

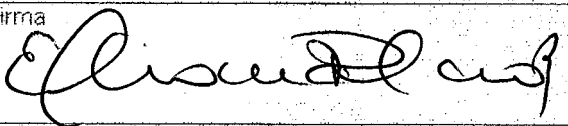
NO

☐

5. Anexos

- ☒ Comprobante de pago de la tasa.
- ☒ Poder, si fuera el caso.
- ☒ Fundamentos de la oposición. Se anexan 37 folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan 8 folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma

Nombre del Firmante	Firma
ELIANA ISAURO MORENO BOHORQUEZ	
CC. 51.975.664	Tarjeta Profesional: 83823

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

Referencia : Expediente N° 12 018.250
Asunto : Oposición a la solicitud de patente de Invención titulada
"UN MÉTODO DE TRATAMIENTO DE UN
TRANSTORNO NEUROLÓGICO"
Solicitante : SUPERNUS PHARMACEUTICALS, INC.
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial
N° 642 del 16 de abril de 2012

Yo, **ELIANA ISAURA MORENO BOHÓRQUEZ**, 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 "**UN MÉTODO DE TRATAMIENTO DE UN TRANSTORNO NEUROLÓGICO**", cuyo titular es **SUPERNUS PHARMACEUTICALS, INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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 PRAMIPEXOL. 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 2 de febrero de 2012, reivindicando prioridad bajo la solicitud US20090222684P del 2009-07-02; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 642 del 16 de abril de 2012, cuya publicación internacional corresponde a la WO2008/077623 del 2006-12-21.

2.2. La solicitud colombiana 12 018.250 objeto de la presente oposición, se refiere a un método para tratar padecimientos neurológicos, tales como enfermedad de Parkinson y Síndrome de Piernas Inquietas, en un sujeto mamífero. El método

comprende la administración de una formulación de liberación controlada una vez al día de pramipexol, cuya formulación proporciona un perfil de PK que asciende consistentemente durante las horas de sueño.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al a un método de tratamiento de padecimientos neurológicos y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

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

- D1: US2005175691 publicada el 11 de agosto de 2005.

2.5. Ahora bien, además que la materia no es objeto de protección por patente por no implicar una aplicación industrial por referirse a un método de tratamiento, el uso de pramipexol es conocido a la fecha de prioridad, como lo indica el documento D1, que particularmente en la descripción revela una composición farmacéutica oral que comprende una cantidad terapéuticamente eficaz de pramipexol o una sal farmacéuticamente aceptable del mismo y por lo menos un excipiente farmacéuticamente aceptable, dicha composición exhibe al menos uno de (a) una en la que perfil de liberación in vitro en promedio no más de aproximadamente 20% del pramipexol se disuelve dentro de 2 horas después de la colocación de la composición en un ensayo de disolución estándar, y (b) un perfil in vivo tras la administración de absorción pramipexol sola dosis para humanos adultos sanos en el que el tiempo para alcanzar una media de 20% de absorción es mayor de aproximadamente 2 horas y // o el tiempo para alcanzar una media de 40% de absorción es mayor que aproximadamente 4 horas. La composición es útil para la administración oral, no más de una vez al día, a un sujeto que tiene una condición o trastorno para el que está indicado un agonista del receptor de dopamina. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud además no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

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

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 12 018.250 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. **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, 2 de julio de 2009 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método que comprende la administración de una formulación de liberación controlada una vez al día de pramipexol, sobre el cual busca protección en el capítulo reivindicatorio.

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

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79

E-mail: negocios@optimum-co.com - www.optimum-co.com

Bogotá Colombia

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 ***“UN MÉTODO DE TRATAMIENTO DE UN TRANSTORNO NEUROLÓGICO”***, cuyo titular es SUPERNUS PHARMACEUTICALS, INC, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 642 del 16 de abril de 2012.

3. PRUEBAS

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

- D1: US2005175691 publicada el 11 de agosto 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:
 - D1: US2005175691 publicada el 11 de agosto 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 Superintendente,

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

ANEXO



US 20050175691A1

(19) **United States**
 (12) **Patent Application Publication** (10) **Pub. No.: US 2005/0175691 A1**
 Lee et al. (43) **Pub. Date: Aug. 11, 2005**

(54) **PRAMIPEXOLE ONCE-DAILY DOSAGE FORM**

Publication Classification

(76) **Inventors** Ernest J. Lee, Kalamazoo, MI (US);
 Gerard M. Bredael, Portage, MI (US);
 John R. Baldwin, Kalamazoo, MI
 (US); Steven R. Cox, Schwaaberville, MI
 (US); Mark J. Heintz, Portage, MI
 (US)

(51) **Int. Cl.⁷** **A61K 9/20**
 (52) **U.S. Cl.** **424/465**

(57) **ABSTRACT**

Correspondence Address:
PFIZER INC
150 EAST 42ND STREET
5TH FLOOR - STOP 49
NEW YORK, NY 10017-5612 (US)

(21) **Appl. No.:** 10/626,275
 (22) **Filed:** Jul. 24, 2003

Related U.S. Application Data

(60) Provisional application No. 60/398,427, filed on Jul. 25, 2002. Provisional application No. 60/398,447, filed on Jul. 25, 2002. Provisional application No. 60/479,514, filed on Jun. 18, 2003.

An orally deliverable pharmaceutical composition comprises a therapeutically effective amount of pramipexole or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, said composition exhibiting at least one of (a) an in vitro release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and (b) an in vivo pramipexole absorption profile following single dose administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours. The composition is useful for oral administration, not more than once daily, to a subject having a condition or disorder for which a dopamine receptor agonist is indicated.

PRAMIPEXOLE ONCE DAILY DOSAGE FORM

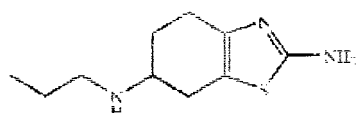
[0001] This application claims priority of U.S. provisional application Ser. No. 60/398,427 filed on Jul. 25, 2002; U.S. provisional application Ser. No. 60/398,441 filed on Jul. 25, 2002; and U.S. provisional application Ser. No. 60/419,514 filed on Jun. 18, 2003.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical formulations of the dopamine receptor agonist, pramipexole, and more particularly to sustained-release dosage forms suitable for once-daily administration of pramipexole.

BACKGROUND OF THE INVENTION

[0003] Pramipexole (1) is a dopamine D₂ receptor agonist useful in treatment of Parkinson's disease. Pramipexole as its dihydrochloride salt is commercially available as Mirapex® tablets of Pharmacia & Upjohn. These are immediate-release tablets in 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 1.5 mg strengths, designed for oral administration of a single tablet three times per day to provide a daily dose of 0.375 to 4.5 mg. See *Physicians' Desk Reference* 57th edition (2003), 2768-2772. Doses herein are expressed in amounts of pramipexole dihydrochloride monohydrate unless otherwise specified. 1.0 mg pramipexole dihydrochloride monohydrate is equivalent to about 0.7 mg pramipexole base.



[0004] A three times daily dosing regimen for immediate-release pramipexole dihydrochloride tablets is well tolerated, but patient compliance would be much improved if a once-daily regimen were possible. In this regard, it was noted that the primary indication for the drug, Parkinson's disease, is an affliction that becomes more prevalent with advancing age and is often accompanied by decline in memory. A once-daily regimen would be especially useful in enhancing compliance among elderly patients.

[0005] In common with other anti-Parkinson's disease drugs, pramipexole has potential to cause undesirable side effects. Side effects of pramipexole have been reported to include orthostatic hypotension, the incidence of which is dose-related. There are also reports of subjects on pramipexole medication experiencing increased somnolence, in particular "sleep attacks". Such attacks involve a person falling asleep while engaged in activities of daily living, including operation of a motor vehicle, sometimes resulting in accidents. Development of a new once-daily dosage form of pramipexole must take into account the potential to cause such side effects, so that the new dosage form, administered once daily, can be tolerated at least as well as the present immediate-release tablet formulation, administered three times daily.

[0006] It is an object of the present invention to provide a once-daily dosage form of pramipexole suitable for oral

administration. It is a further object to provide such a dosage form having potential for side effects no greater than a three times daily regimen of pramipexole immediate release tablets. It is a still further object to identify an in vitro release profile that would be characteristic of a well tolerated once-daily dosage form of pramipexole. It is a still further object to identify an in vivo pharmacokinetic (PK) profile that would be consistent with good therapeutic efficacy while not causing an unacceptable incidence or severity of side effects. It is a still further object to provide exemplary dosage forms exhibiting such an in vitro release and/or in vivo PK profile.

[0007] Sustained release formulations of many drugs have been described in the literature. For example, U.S. Pat. No. 6,197,339 discloses a sustained-release tablet comprising (R)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-b]quinolin-2(1H)-one (Z)-2-butenediate (1:1) (the dopamine D₂ receptor agonist sumanirole maleate) in a matrix comprising hydroxypropylmethylcellulose (HPMC) and starch. The tablet is disclosed to be useful in treatment of Parkinson's disease. Starches disclosed to be suitable therein include pregelatinized starch.

[0008] U.S. Pat. No. 5,458,887 discloses a controlled-release tablet comprising an osmotic core that consists of a drug in admixture with a water-swellaable component such as HPMC or polyethylene oxide, and a coating that comprises a water-resistant polymer and a minor amount of a water-soluble compound that acts as a pore-former. Upon formation of pores in the coating by dissolution of the water-soluble compound, the water-swellaable agent is said to expand the core and provide a drug-rich surface in contact with gastrointestinal fluid.

[0009] U.S. Pat. No. 5,656,296 discloses a dual control sustained-release formulation comprising a core that comprises a drug and a low melting point excipient, and a coating layer over the core that comprises a pH-independent water-insoluble polymer and a water-soluble film-forming polymer.

[0010] European Patent Application No. EP 0 933 079 discloses a starch said to be suitable for preparing tablets having high hardness yet being capable of rapid disintegration in an aqueous medium. Tensile strength of the finished tablets is calculated from the hardness.

[0011] Hubble et al. (1995), *Clinical Neuropharmacology* 18(4), 338-347, described efficacy, safety, tolerability and pharmacokinetics of pramipexole administered three times a day in patients with early Parkinson's disease. A review of pramipexole use in management of early and advanced Parkinson's disease has been published by Dooley & Markham (1998), *Drugs & Aging* 12(6), 495-514. No disclosure is made therein of once-daily administration or sustained-release formulation of pramipexole.

[0012] More recently, Biglan & Holloway (2002), *Expert Opinion on Pharmacotherapy* 3(2), 197-210, reviewed pramipexole and its clinical utility in Parkinson's disease and noted that daily dosing with Mirapex® tablets is recommended in patients with impaired renal function, as evidenced by creatine clearance of 15-34 ml/minute. They also indicated that while dopamine receptor agonists generally have been associated with orthostatic hypotension, pramipexole does not appear to cause this complication any

more than placebo in randomized controlled trials. It is reported therein, however, that evidence from such trials supports increased incidence of somnolence in patients receiving pramipexole in early Parkinson's disease.

[0013] Steady-state PK properties of pramipexole, administered three times a day in the form of pramipexole dihydrochloride tablets, were reported by Wright et al. (1997), *Journal of Clinical Pharmacology* 37, 520-525, who concluded that steady-state PK characteristics were linear up to a daily dose of 4.5 mg, for both men and women.

[0014] Patents and publications cited above are incorporated herein by reference.

SUMMARY OF THE INVENTION

[0015] There is now provided an orally deliverable pharmaceutical composition comprising a therapeutically effective amount of pramipexole or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, said composition exhibiting at least one of (a) an in vitro release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and (b) an in vivo pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

[0016] There is further provided a method of treatment of a subject having a condition or disorder for which a dopamine receptor agonist is indicated, the method comprising orally administering to the subject, not more than once daily, an orally deliverable pharmaceutical composition comprising a therapeutically effective amount of pramipexole or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, said composition exhibiting at least one of (a) an in vitro release profile wherein no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and (b) an in vivo pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

[0017] There is still further provided a process for selecting a formulation of pramipexole or a pharmaceutically acceptable salt thereof suitable for sustained-release oral delivery of pramipexole. According to a first embodiment, the process comprises placing a candidate formulation in a dissolution medium under conditions of a standard in vitro dissolution test, wherein if on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the candidate formulation in the dissolution medium, the candidate formulation is deemed suitable for selection. According to a second embodiment, the process comprises conducting a standard pharmacokinetic study following single dose oral administration of a candidate formulation to healthy adult humans and deriving an in vivo pramipexole absorption profile from said study, wherein if the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40%

absorption is greater than about 4 hours, the candidate formulation is deemed suitable for selection.

[0018] The term "orally deliverable" herein means suitable for oral, including peroral and intra-oral (e.g., sublingual or buccal) administration, but compositions of the present invention are adapted primarily for peroral administration, i.e., for swallowing. Where the composition is in the form of a discrete solid article such as a tablet or capsule, it is typically swallowed whole or broken, with the aid of water or other drinkable fluid.

[0019] A "therapeutically effective amount" of pramipexole herein is a daily dosage amount that, when administered as part of a regimen, provides therapeutic benefit in treatment of a condition or disorder for which a dopamine receptor agonist is indicated. Suitable amounts per dose are likely to be found in a range from about 0.1 to about 10 mg, preferably about 0.3 to about 5 mg, for example about 0.375, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0 or 4.5 mg, expressed as pramipexole dihydrochloride monohydrate equivalent.

[0020] A "standard dissolution test" herein is a test conducted according to *United States Pharmacopeia* 24th edition (2000) (USP 24), pp. 1941-1943, using Apparatus 1 described therein at a spindle rotation speed of 100 rpm and a dissolution medium of 0.05M phosphate buffer, pH 6.8, at 37° C., or other test conditions substantially equivalent thereto.

[0021] In vivo "absorption" herein refers to the percentage of pramipexole that enters the bloodstream, as conventionally calculated from data of a standard PK study involving oral administration of a single dose of pramipexole. It will be understood that PK data are subject to the usual variation seen in biological data, thus the absorption percentages specified above are means from a population, typically at least about 8 in number, of individual healthy adults in accordance with standard statistical practice.

[0022] A "subject" herein is an animal of any species, preferably mammalian, most preferably human. Conditions and disorders in a subject for which a dopamine receptor agonist is said herein to be "indicated" are not restricted to conditions and disorders for which a dopamine receptor agonist has been expressly approved by a regulatory authority, but also include other conditions and disorders known or believed by a physician to be amenable to treatment with a dopamine receptor agonist. "Treatment" herein embraces prophylactic treatment unless the context requires otherwise.

[0023] Compositions of the invention exhibit a number of surprising and unexpected features and benefits.

[0024] First, sustained-release dosage forms are typically sought where it is desired to enable longer time intervals between dosing of a drug having a short half-life in plasma, due for example to rapid metabolism, excretion or other routes of depletion. Among drugs used to treat Parkinson's disease, levodopa is a well-known example, having a short elimination half-life ($t_{1/2}$) of about 1.5 hours. See Ceballos & De Michele (1999), *European Journal of Neurology* 6(1), 1-21. By contrast, pramipexole has a $t_{1/2}$ of about 9 to about 14 hours, depending on the particular study, and would not on this ground be expected to require special attention to formulation to enable once-daily dosing.

[0025] Second, pramipexole, at least in the form of its dihydrochloride salt, has high solubility in water (about 200

mg/ml at 20-25° C.). Highly water-soluble drugs are typically difficult to formulate in sustained-release form because of the tendency of the drug to rapidly leach out of the dosage form upon exposure to an aqueous medium such as gastrointestinal fluid.

[0026] Third, as demonstrated herein, pramipexole dosage forms having very similar *in vitro* release profiles, as characterized by standard parameters such as time to reach 50% or 80% dissolution, can, as demonstrated herein, have *in vivo* PK profiles that differ in very meaningful ways. Differences in PK profile between dosage forms having similar 50% and 80% dissolution times in an *in vitro* test can define the difference between a dosage form that meets the criteria of the present invention and one that does not.

[0027] This last finding is especially unexpected in light of a close *in vitro/in vivo* correlation that is evident for individual dosage forms, as demonstrated herein. It is surprisingly found that data for early time points (up to about 2 hours) and/or initial dissolution rates (up to about 20% dissolution) in the *in vitro* test described herein are indicative of a PK profile consistent with the present invention. Thus a pramipexole composition exhibiting no more than about 20% dissolution at a 2-hour time point in the *in vitro* test is strongly indicative of a desirable *in vivo* PK profile, whereas one exhibiting faster early dissolution, even if 50% and 80% dissolution times are no different, is not so indicative.

[0028] These and other features, benefits and advantages of the invention will be apparent from the disclosure that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. 1 is a graph showing *in vitro* dissolution profiles of three different 0.375 mg sustained-release tablet formulations of pramipexole dihydrochloride monohydrate, as more fully described in Example 6.

[0030] FIG. 2 is a graph from a human PK study showing time course of mean plasma pramipexole concentration following oral administration of 0.375 mg pramipexole dihydrochloride monohydrate, either as a 0.125 mg immediate-release tablets administered three times at 8-hour intervals or as a single 0.375 mg dose of each of three different sustained-release tablets, as more fully described in Example 7.

[0031] FIG. 3 shows *in vitro/in vivo* correlation for the pramipexole dihydrochloride tablets of Example 1.

[0032] FIG. 4 shows *in vitro/in vivo* correlation for the pramipexole dihydrochloride tablets of Example 2.

[0033] FIG. 5 shows *in vitro/in vivo* correlation for the pramipexole dihydrochloride tablets of Example 5.

DETAILED DESCRIPTION OF THE INVENTION

[0034] In one embodiment, a pramipexole composition of the invention exhibits at least one of the following:

[0035] (a) an *in vitro* release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and

[0036] (b) an *in vivo* pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

[0037] Accordingly, in a particular embodiment the composition satisfies at least the *in vitro* test set forth in (a) above.

[0038] In another particular embodiment the composition satisfies at least the *in vivo* test set forth in (b) above.

[0039] To satisfy the *in vitro* test, on average no more than about 20% of the pramipexole initially contained in the composition must dissolve within 2 hours after placement in a dissolution test conducted according to USP 24 using Apparatus 1 at a spindle rotation speed of 100 rpm and a dissolution medium of 0.05M phosphate buffer, pH 6.8, at 37° C., or in a substantially equivalent test. Preferably no more than about 12% of the pramipexole dissolves within 1 hour in such a test. Time to reach 50% dissolution is preferably at least about 4 hours, more preferably at least about 6 hours. Time to reach 80% dissolution is preferably at least about 8 hours, more preferably at least about 12 hours.

[0040] To satisfy the *in vivo* test, a single-dose PK study in healthy adult human subjects must provide data consistent with an absorption profile wherein, at a time point about 2 hours after administration, mean absorption has not yet reached 20%, and/or at a time point about 4 hours after administration, mean absorption has not yet reached 40%. Preferably the time to reach a mean of 40% absorption is at least about 5 hours, more preferably at least about 6 hours.

[0041] It is preferred that the composition, when administered once daily, exhibit a bioavailability, as expressed conventionally by AUC_{0-18} or $AUC_{0-\infty}$, that is substantially equivalent to the same daily dose of an immediate-release pramipexole dihydrochloride reference formulation, for example Mirapex® tablets, administered three times a day. In the present context, "substantially equivalent" means that the bioavailability of such a preferred composition is about 0.8 to about 1.25 times that of the reference formulation.

[0042] It is preferred that the composition, following single dose administration of 0.375 mg (expressed as pramipexole dihydrochloride monohydrate equivalent), exhibit a maximum plasma concentration (C_{max}) of pramipexole that is not greater than about 0.3 ng/ml. Where a higher dose is administered, the preferred upper limit of C_{max} is proportionately greater, it being known that pharmacokinetics of pramipexole are substantially linearly dose-related up to a daily dose of 4.5 mg. Wright et al. (1997), *op. cit.*

[0043] It is preferred that the composition, following single dose administration, exhibit a time to reach maximum plasma concentration (T_{max}) of pramipexole that is at least about 6 hours, preferably at least about 8 hours.

[0044] It is especially preferred that the composition exhibit a PK profile consistent with steady-state plasma concentrations having a fluctuation ratio that is not substantially greater than that of the reference formulation as defined above. Fluctuation ratio (FR) is defined by the following equation:

$$FR = (C_{max} - C_{min}) / C_{avg}$$

[0045] where C_{max} , C_{min} and C_{avg} are maximum, minimum and average plasma concentrations respectively.

[0046] Preferably the PK study used to generate the parameters specified above for a candidate composition is conducted according to a protocol that is generally accepted in the art. Preferably at least 6, more preferably at least 8, most preferably at least 10 subjects are enrolled in the study and receive the candidate composition.

[0047] A composition having the in vitro release and/or in vivo PK parameters specified above is advantageous in having reduced potential to cause undesirable side effects that may be related to a combination of high C_{max} and short T_{max} by comparison with other once-daily dosage forms. Preferably the incidence of side effects is no greater than with an immediate-release dosage form such as Mirapex® tablets administered in a three times daily regimen. More preferably, the incidence of side effects is even lower than with such an immediate-release regimen. It is contemplated that these advantages become more pronounced with increase in daily dosage.

[0048] A composition of the invention comprises pramipexole or a pharmaceutically acceptable salt thereof, in a therapeutically effective daily dosage amount. It will be understood that mention of pramipexole or another active pharmaceutical agent herein embraces racemates, enantiomers, polymorphs, hydrates and solvates thereof. Pramipexole is used preferably in the form of its S-enantiomer, (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole.

[0049] It is preferred to use a salt of pramipexole, especially a salt exhibiting moderate to high solubility in water. Illustrative salts include those prepared using the following acids: hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, methanesulfonic acid, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, p-hydroxybenzoic, toluenesulfonic, formic, acetic, propionic, benzoic, anthranilic, tartaric, malic, malic, citric, isocitric, succinic, ascorbic, lactic, glycolic, gluconic, glucuronic, pyruvic, oxaloacetic, fumaric, aspartic, glutamic, stearic, salicylic, phenylacetic, mandelic, pantoic, pantothenic, sulfanilic, cyclohexylaminosulfonic, alginate, β hydroxybutyric, galactaric and galacturonic acids.

[0050] A preferred salt of pramipexole is the dihydrochloride salt, most preferably in the form of the monohydrate.

[0051] Pramipexole and salts thereof, including the dihydrochloride salt, useful herein can be prepared by processes known per se, including processes disclosed in patents and other literature pertaining to pramipexole.

[0052] The composition can take any form suitable for oral administration, but is typically formulated as a discrete solid dosage unit such as a tablet or capsule, wherein the pramipexole or salt thereof is present as solid particles, and is formulated together with one or more pharmaceutically acceptable excipients. The excipients are selected in part to provide a release profile and/or PK profile consistent with those defined above.

[0053] The amount of pramipexole present in a composition of the invention is sufficient to provide a daily dose in one to a small plurality, for example one to about 4, of dosage units to be administered at one time. Preferably the

full daily dose is delivered in a single dosage unit. An amount of about 0.1 to about 10 mg per dosage unit, or about 0.05% to about 5% by weight of the composition, will generally be suitable. Preferably an amount of about 0.2 to about 6 mg, more preferably an amount of about 0.3 to about 5 mg, pramipexole per dosage unit is present. Specific amounts per tablet contemplated herein include 0.375, 0.5, 0.75, 1.0, 1.5, 3.0 and 4.5 mg pramipexole dihydrochloride monohydrate.

[0054] The particular formulation selected for the pramipexole is not critical so long as it achieves a release and/or PK profile as defined herein. Such a profile can be achieved using one or more release-modifying means. Illustratively, release-modifying means suitable for use in a composition of the invention include a polymer matrix wherein the pramipexole is dispersed; a release-controlling layer or coating surrounding the whole dosage unit or pramipexole-containing particles, granules, beads or zones within the dosage unit; and an osmotic pump.

[0055] In one embodiment, the composition takes the form of a tablet comprising pramipexole or a salt thereof, dispersed in a matrix comprising a hydrophilic polymer and starch. Preferably the starch has a tensile strength of at least about 0.15 kN cm⁻² at a solid fraction representative of the tablet, for example about 0.75 to about 0.85, illustratively 0.8.

[0056] Hydrophilic polymers useful according to the present embodiment are pharmaceutically acceptable polymeric materials having a sufficient number and distribution of hydrophilic substituents such as hydroxy and carboxy groups to impart hydrophilic properties to the polymer as a whole. Suitable hydrophilic polymers include, without limitation, methylcellulose, HPMC (hypromellose), carmellose sodium (sodium carboxymethylcellulose) and carboxer (polyacrylic acid). More than one such polymer can optionally be used.

[0057] HPMC is a preferred hydrophilic polymer. Various types and grades of HPMC are available. In one embodiment HPMC type 2208, preferably meeting specifications set forth in a standard pharmacopeia such as USP 24, is used. HPMC type 2208 contains 19-24% by weight methoxy and 4-12% by weight hydroxypropoxy substituents. Especially suitable HPMCs have nominal viscosity ranging from about 100 to about 10,000 mPa s; illustratively a suitable HPMC type 2208 is one having a nominal viscosity of about 4,000, with a measured viscosity of about 3,000 to about 5,600 mPa s. Such an HPMC is available, for example, as Methocel® K4 MP from Dow Chemical Co., and substantially equivalent products are available from other manufacturers.

[0058] The amount of hydrophilic polymer in the composition depends on the particular polymer selected, on the active pharmaceutical agent and on the desired sustained release profile. Typically, however, the hydrophilic polymer is included in an amount of about 20% to about 70%, preferably about 30% to about 60% and more preferably about 35% to about 50%, by weight of the composition. In the illustrative case of HPMC type 2208, a suitable amount will generally be found in the range from about 30% to about 60%, preferably about 35% to about 50%, for example about 40%, by weight of the composition.

[0059] It is believed, without being bound by theory, that the hydrophilic polymer functions to provide extended or

sustained release of the pramipexole, for example by gradual dissolution or erosion of the polymer in the gastrointestinal tract.

[0060] Starches useful herein include starches from any suitable botanical source, for example corn, wheat, rice, tapioca, potato, etc. Preferred starches have a relatively high ratio of amylose to amylopectin, containing for example at least about 20%, more preferably at least about 25%, amylose. Especially preferred is pregelatinized starch, which is a type of modified starch that has been processed to render the starch more flowable and directly compressible. Partially or wholly pregelatinized starches can be used.

[0061] It is believed, without being bound by theory, that the primary function of the starch in a composition of the present embodiment is as a binding agent. A starch meeting the preferred tensile strength criterion defined herein is sometimes referred to herein as a "super binder".

[0062] The amount of starch in a composition of the present embodiment is typically higher than is conventionally present as a binder in tablet formulations. Suitable amounts will generally be found in the range of about 25% to about 75% by weight. Preferably the amount of starch is about 40% to about 70%, more preferably about 45% to about 65%, for example about 50%, by weight of the composition.

[0063] Tensile strength of a starch sample can be measured by any suitable test. Illustrative test procedures are described by Hiestand & Smith (1984), *Powder Technology* 38, 145-159, and by Hiestand & Smith (1991), *International Journal of Pharmaceutics* 67, 231-246, these articles being incorporated herein by reference.

[0064] An example of a tensile strength test that can be used (herein referred to as a "uniaxial tensile strength test") requires preparation of a series of compacts of the starch sample, followed by determination of tensile strength of the compacts using a computerized multifunction tablet tester (MTT). The compacts are prepared with various degrees of compression force to provide compacts having a range of solid fraction. As a sustained release tablet formulation typically has a solid fraction of about 0.8, it is useful to prepare compacts approximating such a solid fraction.

[0065] Absolute density of the starch sample can be determined using a helium-air pycnometer.

[0066] A computer-controlled uniaxial tablet press is used to prepare the compacts. Voltage output from the punch and die load cells of the tablet press are first zeroed. The punch and die are lubricated with magnesium stearate powder and the die assembly is placed in the press. Compression and decompression parameters are selected on the computer. The desired amount of starch to be compacted is weighed and poured into the die cavity. The resulting powder bed is leveled with a spatula. The punch is inserted into the die and the computer-controlled compression/decompression cycle is started.

[0067] Just prior to the end of the compression phase, thickness of the compact as measured by LVDT is recorded. At the end of the compression phase, the final compression force as measured by voltage of the punch load cell is recorded.

[0068] At the end of the decompression phase, the punch and die rams are retracted. The compact is removed from the die and inspected for defects, such as cracking or sticking. Cracking can be reduced by increasing decompression time. If the compact is free of defects, its length, width, thickness and weight are measured to enable calculation of apparent density. Solid fraction is calculated by dividing absolute density by apparent density.

[0069] In preparation of the MTT for tensile strength determination, a suitable software program is run. The platen is screwed to the load cell of the MTT and the tensile strength assembly is slid into the MTT opposite the platen. The load cell signal is monitored via the computer and the zero offset on the signal conditioner is adjusted to provide a positive baseline voltage as close as possible to zero. A forward velocity is selected that will generate a time constant of approximately 15 seconds (usually the velocity selected will be about 0.8 to about 1.2 mm s⁻¹).

[0070] The compact to be tested is placed in the holder of the tensile strength assembly. The motor is initiated via the computer, driving the platen toward the compact until the surface of the compact is detected, and stopping the platen a few millimeters from the compact. The oscilloscope is triggered, to record the force applied to the compact, and the motor is restarted. The platen is driven into the compact until a crack is detected, either by sight or by sound, and the motor is immediately reversed.

[0071] Peak force is recorded from the oscilloscope trace. Tensile strength is calculated from the peak force using appropriate computer software.

[0072] From several runs using compacts at a range of solid fractions around 0.8, data are plotted and tensile strength at a solid fraction of 0.8 is estimated. If the tensile strength at a solid fraction of 0.8 is about 0.15 kN cm⁻² or greater, the starch sample is deemed to be suitable for use in preparing a composition according to the present embodiment of the invention.

[0073] It has now surprisingly been discovered that a much simpler test, one that is more amenable to implementation in a manufacturing setting, can be used to estimate tensile strength of a starch sample, in particular to determine whether the starch sample has a tensile strength of at least about 0.15 kN cm⁻² at a solid fraction representative of a desired sustained-release tablet.

[0074] According to this test, compacts of the starch sample are prepared on a standard automated tablet press under a range of compression forces. For example, a Carver press (e.g., Model 3888.11/10000) fitted with flat-faced tooling of suitable diameter (e.g., 1½ inch or about 0.7 cm for a 300 mg compact), operated at compression forces of about 4 to about 16 kN (about 900 to about 3600 lbf) for a dwell time of at least about 4 seconds has been found to give satisfactory results. Illustratively, such compacts can be prepared at 1000, 1500, 2000 and 3000 lbf (4.45, 6.67, 8.90 and 13.34 kN). Preferably a dwell time of at least about 10 seconds, more preferably at least about 30 seconds, still more preferably at least about 60 seconds, is used. Illustratively, a dwell time of 90 seconds has been found to give satisfactory results. Weight, diameter and thickness of each compact are measured accurately (alternatively, diameter can be assumed to equal that of the tooling) to enable

calculation of apparent density and hence solid fraction, absolute density having been measured as described above, for example by helium-air pycnometry.

[0075] Hardness of each compact thus prepared is then determined by any suitable tablet hardness test, for example using a Key III 500 hardness tester. Hardness is a measure of the force required to cause crushing of the compact, and is typically expressed in units such as kilopounds (kp) or Strong-Cobb units (SCU). A hardness of about 10.2 kp or about 14.4 SCU corresponds to a force of 0.1 kN.

[0076] For present purposes it is considered that crushing strength of the compact is equivalent to tensile strength. Thus tensile strength (σ_t , in kN cm^{-2}) can be calculated from the equation

$$\sigma_t = 2F/\pi D H$$

[0077] where F is the force required to cause crushing (in kN), D is diameter of the compact (in cm) and H is thickness of the compact (in cm). For example, a compact of diameter 0.7 cm and thickness 0.4 cm having a hardness of 20 SCU (equivalent to a force of 2.139 kN) has a calculated tensile strength of 0.316 kN cm^{-2} .

[0078] The relationship between tensile strength and solid fraction is next established for the starch sample. This can be done by plotting data for tensile strength and solid fraction on a graph (solid fraction tends to increase with increasing compression force during preparation of the compact) or by performing a regression analysis. From that relationship, tensile strength at a standardized value of solid fraction can be estimated. The standardized value selected is one that is representative of the solid fraction of a desired sustained-release tablet, e.g., 0.8.

[0079] Where the material of the compact is pregelatinized starch, it has been found that tensile strength as determined in a simple test as described immediately above is surprisingly close to a "true" tensile strength measurement as determined by the triaxial tensile strength test method previously described, which in turn is essentially similar to methods known in the art such as that disclosed by Lifesund & Smith (1984), *op. cit.*

[0080] It has also been found that a longer dwell time (e.g., 90 seconds) in the test method of the present invention gives a better correlation with triaxial tensile strength than a very short dwell time (e.g., 4 seconds). See Example 1 below and FIGS. 1 and 2.

[0081] An especially preferred starch has a tensile strength of at least about 0.175 kN cm^{-2} , even more preferably at least about 0.2 kN cm^{-2} , at a solid fraction representative of a desired sustained-release tablet.

[0082] Even among commercially available pregelatinized starches, the preferred type of starch for use in a composition of the present embodiment, considerable variation exists in tensile strength. Pregelatinized starches not meeting the tensile strength criterion established herein are not readily identified without testing, for example by a method as disclosed above. Such pregelatinized starches are generally unsuitable for commercial-scale manufacture of a sustained-release matrix tablet formulation of pramipexole, because of a problem as set forth immediately below.

[0083] An uncoated tablet, or a tablet core prior to coating, comprising starch and a hydrophilic polymer acting as a

matrix for a water-soluble drug or prodrug requires to have a certain minimum hardness in order to be able to resist breakage and/or attrition due to mechanical stresses imposed during a high-speed tableting operation (including all steps up to and including filling of the tablets into containers). The minimum acceptable hardness will depend on a number of factors, including the severity of the mechanical stresses, but is typically at least about 20 SCU, preferably at least about 22 SCU, more preferably at least about 24 SCU (about 17 kp).

[0084] Hardness can be increased by increasing the compression force applied by the tablet press, but only up to a certain level. At least in the case of tablets as described herein, above a certain compression force, further increases in compression force give little or no further increase in tablet hardness. There is, in other words, a maximum hardness achievable by compression of a particular starch/hydrophilic polymer/active agent composition. A starch providing a maximum hardness inadequate to withstand the mechanical stresses of a high-speed tableting operation is unsuitable for the present purpose. As shown in FIG. 3, certain pregelatinized starches have been found to provide a maximum hardness of 20 SCU or less; these are now identified as starches having low tensile strength (0.1 kN cm^{-2} or less according to the test method of the invention utilizing a dwell time of 90 seconds).

[0085] Even if a maximum hardness of at least about 20 SCU is achievable, with a starch of low tensile strength it may be achievable only by use of extremely high compression forces. A requirement for such forces reduces speed and efficiency and increases cost of a tableting operation and is undesirable for these reasons.

[0086] Where tablets are to be subjected to an additional process step after compression, in particular a coating step, exposure to mechanical stresses is greatly increased. According to a preferred embodiment, therefore, the sustained-release tablet of the invention further comprises a coating.

[0087] Particularly for a highly water-soluble salt such as pramipexole dihydrochloride, a hydrophilic polymer matrix is often inadequate to provide sustained release of sufficiently long duration to permit once daily administration. It is believed that such a salt is readily leached out of the hydrophilic matrix when contacted by an aqueous medium such as gastrointestinal fluid. It is therefore desirable to further slow the process of drug release by providing a release-controlling coating around the tablet. Such a coating typically comprises a hydrophobic or water-insoluble polymer component such as ethylcellulose together with a hydrophilic or water-soluble pore-forming component such as HPMC.

[0088] Where a starch is used having a tensile strength of at least about 0.15 kN cm^{-2} , preferably at least about 0.175 kN cm^{-2} , more preferably at least about 0.2 kN cm^{-2} , at a solid fraction representative of the tablet (e.g., about 0.75 to about 0.85), the composition is found to be especially suited to a high-speed tableting operation that includes a step of coating the tablet with a release-controlling layer.

[0089] Alternatives to ethylcellulose and HPMC as components of a release coating layer include other cellulosic polymers (e.g., methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, carboxymethylcellulose esters such as cellulose acetate, etc.), polyvinyl acetate, polyvinyl pyrrolidone, polymers and copolymers of acrylic acid and methacrylic acid and esters thereof, polyethylene glycol, carrageenan and other gums, and the like.

[0090] A release-controlling layer, if present, typically constitutes about 1% to about 15%, preferably about 2.5% to about 10%, by weight of the tablet as a whole. The hydrophobic or water-insoluble component, preferably comprising ethylcellulose, typically constitutes about 1% to about 10%, preferably about 2% to about 3%, by weight of the tablet as a whole. The pore-forming component, preferably comprising HPMC, is typically present in an amount of about 5% to about 50%, preferably about 20% to about 40%, by weight of the water-insoluble or hydrophobic component.

[0091] The coating, if present, can optionally contain additional pharmaceutically acceptable excipients such as plasticizers, dyes, etc.

[0092] Illustratively, a release-controlling layer, in an amount of about 2.5% to about 5% by weight of the tablet core (i.e., the tablet weight excluding the coating) comprises an ethylcellulose-based material (e.g., Surelease® of Celcon) and an HPMC-based pore-forming material (e.g., Opadry® of Colorcon) in a weight ratio of about 3:1 to about 4:1.

[0093] A release-controlling layer or coating should be applied at as uniform a thickness as possible to provide optimum control of release rate of the pramipexole.

[0094] Alternatively or in addition, the sustained-release tablet of the invention comprises a nonfunctional coating. A nonfunctional coating can comprise a polymer component, for example HPMC, optionally with other ingredients, for example one or more plasticizers, colorants, etc. The term "nonfunctional" in the present context means having substantially no effect on release properties of the tablet, and should not be read to imply that the coating serves no useful purpose. For example, such a coating can impart a distinctive appearance to the tablet, provide protection against attrition during packaging and transportation, improve ease of swallowing, and/or have other benefits. A nonfunctional coating should be applied in an amount sufficient to provide complete coverage of the tablet, typically an amount of about 1% to about 10%, more typically an amount of about 2.5% to about 5%, by weight of the tablet as a whole, will be found suitable.

[0095] Uncoated tablets and cores of coated tablets of the present embodiment can optionally contain one or more pharmaceutically acceptable excipients in addition to the starch and hydrophilic polymer components described above. Such excipients include without limitation fillers and lubricants. Other conventional excipients known in the art can also be included.

[0096] A glidant can be used to improve powder flow properties prior to and during tableting and to reduce caking.

Suitable glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium phosphate and the like. In one embodiment, colloidal silicon dioxide is included as a glidant in an amount up to about 2%, preferably about 0.2% to about 0.6%, by weight of the tablet.

[0097] A lubricant can be used to enhance release of a tablet from apparatus on which it is formed, for example by preventing adherence to the face of an upper punch ("picking") or lower punch ("sticking"). Suitable lubricants include magnesium stearate, calcium stearate, canola oil, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, mineral oil, poloxamer, polyethylene glycol, polyvinyl alcohol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, hydrogenated vegetable oil, zinc stearate and the like. In one embodiment, magnesium stearate is included as a lubricant in an amount of about 0.1% to about 1.5%, preferably about 0.3% to about 1%, by weight of the tablet.

[0098] Tablets can be of any suitable size and shape, for example round, oval, polygonal or pillow-shaped, and optionally bear nonfunctional surface markings. Especially in the case of coated tablets they are preferably designed to be swallowed whole and are therefore typically not provided with a breaking score. Dosage unit compositions of the invention can be packaged in a container, accompanied by a package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions and adverse reactions.

[0099] There is also provided a method of treatment of a subject having a condition or disorder for which a dopamine D₂ receptor agonist is indicated, the method comprising orally administering to the subject, not more than once daily, an orally deliverable pharmaceutical composition comprising a therapeutically effective amount of pramipexole or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, said composition exhibiting at least one of:

[0100] (a) an in vitro release profile wherein no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test as defined herein; and

[0101] (b) an in vivo pramipexole absorption profile following single dose administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

[0102] The method is particularly useful where the condition or disorder is Parkinson's disease or a complication associated therewith.

[0103] Suitable daily dosage amounts of pramipexole include 0.375, 0.5, 0.75, 1.0, 1.5, 3.0 and 4.5 mg, expressed as pramipexole dihydrochloride monohydrate.

EXAMPLES

Example 1

[0104] Pramipexole dihydrochloride sustained-release tablets were prepared having the compositions shown in Table 1.

Coated tablets were cured using a 12 inch (about 30 cm) Vector 1 CDS or 24 inch (about 60 cm) Thomas Accela-Coats coating pan for about 15 minutes at a bed temperature of at least about 70° C. After curing, temperature was ramped down over a period of about 8 minutes to an exhaust temperature of about 45° C.

TABLE 1

Composition of pramipexole dihydrochloride tablets of Example 1								
Ingredient	Amount (mg)							
pramipexole dihydrochloride monohydrate	0.575	0.575	1.15	3.01	4.57	0.575	0.575	4.57
HPMC (type 2208, 4000 mPa.s)	140.0	140.0	140.0	140.0	140.0	70.0	157.5	157.5
pregelatinized starch	206.5	206.5	206.5	206.5	206.5	103.25	189.0	189.0
colloidal silica dioxide	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
magnesium stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
total	350	350	350	350	350	175	350	350

[0105] All ingredients except the lubricant (magnesium stearate) were screened to remove lumps and were blended thoroughly in a low-shear mixer operating at 24 rpm for 10-30 minutes. The lubricant was then screened into the mixer and the materials were blended for a further 2-5 minutes. The resulting lubricated mixture was compressed into 350 mg pillow-shaped tablets using a Kilian S100 tableting machine.

Example 2

[0109] Coated sustained-release tablets of pramipexole dihydrochloride were prepared having the composition shown in Table 2.

TABLE 2

Composition of coated tablets of Example 2	
Ingredient	Amount (mg)
pramipexole dihydrochloride monohydrate	0.575
HPMC (type 2208, 4000 mPa.s)	140.0
pregelatinized starch	206.5
colloidal silica dioxide	1.4
magnesium stearate	1.75
total core	350
ethylcellulose-based coating material (Surelease®)	8.4
HPMC-based coating material (Opadry®)	2.1
total coating	10.5

Example 3

[0106] Coated sustained-release tablets of pramipexole dihydrochloride were prepared having the composition shown in Table 2.

TABLE 2

Composition of coated tablets of Example 3	
Ingredient	Amount (mg)
pramipexole dihydrochloride monohydrate	0.575
HPMC (type 2208, 4000 mPa.s)	140.0
pregelatinized starch	206.5
colloidal silica dioxide	1.4
magnesium stearate	1.75
total core	350
ethylcellulose-based coating material (Surelease®)	8.4
HPMC-based coating material (Opadry®)	2.1
total coating	10.5

[0107] Tablet cores were prepared exactly as in Example 1. A coating solution was prepared as follows. Opadry® HPMC-based material in an amount of 4.801 g was added to 103.041 g water and mixed for 45 minutes to provide an HPMC mixture. Next, 76.819 g Surelease® ethylcellulose-based material was added to the HPMC mixture and mixed for an additional 30 minutes to provide a coating solution.

[0110] Tablet cores were prepared exactly as in Example 1. A coating solution was prepared as follows. Opadry® HPMC-based material in an amount of 4.801 g was added to 103.041 g water and mixed for 45 minutes to provide an HPMC mixture. Next, 76.819 g Surelease® ethylcellulose-based material was added to the HPMC mixture and mixed for an additional 30 minutes to provide a coating solution.

[0111] Coating to a 3% weight gain and curing of the coated tablets were performed exactly as in Example 2.

Example 4

[0112] Coat sustained-release tablets of pramipexole dihydrochloride were prepared having the composition shown in Table 4.

[0108] The coating solution was applied to the tablet cores in an amount providing a 3% weight gain. The resulting

TABLE 4

Composition of coated tablets of Example 1	
Ingredient	Amount (mg)
pramipexole dihydrochloride monohydrate	0.375
HPMC (type 2208, 4000 mPa.s)	140.0
pregelatinized starch	206.5
colloidal silicon dioxide	1.4
magnesium stearate	1.75
total core	350
ethylcellulose-based coating material (Surelease®)	17.12
HPMC-based coating material (Opadry®)	4.35
total coating	17.5

[0113] Tablet cores were prepared exactly as in Example 1. A coating solution was prepared as follows: Opadry® HPMC-based material in an amount of 10.003 g was added to 177.737 g water and mixed for 45 minutes to provide an HPMC mixture. Next, 120.03 g Surelease® ethylcellulose-based material was added to the HPMC mixture and mixed for an additional 30 minutes to provide a coating solution.

[0114] Coating to a 3% weight gain and curing of the coated tablets were performed exactly as in Example 2. After this first curing step, coating was repeated to provide a total tablet weight gain of about 5%, followed by curing for about 15 minutes at a bed temperature of at least about 70° C. After curing, temperature was ramped down over a period of about 8 minutes to an exhaust for temperature of about 45° C.

Example 5

[0115] Coated sustained-release tablets of pramipexole dihydrochloride were prepared having the composition shown in Table 5.

TABLE 5

Composition of coated tablets of Example 5	
Ingredient	Amount (mg)
pramipexole dihydrochloride monohydrate	0.375
HPMC (type 2208, 4000 mPa.s)	140.0
pregelatinized starch	206.5
colloidal silicon dioxide	1.4
magnesium stearate	1.75
total core	350
ethylcellulose-based coating material (Surelease®)	14.0
HPMC-based coating material (Opadry®)	2.5
total coating	17.5

[0116] Tablet cores were prepared exactly as in Example 1. A coating solution was prepared as follows: Opadry® HPMC-based material in an amount of 8.002 g was added to 171.735 g water and mixed for 45 minutes to provide an HPMC mixture. Next, 128.032 g Surelease® ethylcellulose-based material was added to the HPMC mixture and mixed for an additional 30 minutes to provide a coating solution.

[0117] Coating to a 5% total weight gain and curing of the coated tablets were performed exactly as in Example 2.

Example 6

[0118] Dissolution profiles of the pramipexole dihydrochloride tablets of each of Examples 1, 2 and 5 were evaluated in a standard in vitro USP dissolution assay under the following conditions. USP apparatus 1 was used to stir a dissolution medium (900 ml of 0.05M phosphate buffer at a pH of 6.8) at a spindle rotation speed of 100 rpm and a temperature of 37° C.

[0119] Data are shown in FIG. 1. The uncoated tablet of Example 1 and the tablet of Example 2 having a 3% coating comprising 25% pore-former exhibited very similar overall dissolution profiles. On close inspection, however, it will be noticed that the uncoated tablet of Example 1 showed faster initial dissolution, such that at 1 hour and 2 hour sampling times the percent dissolved was greater, than in the case of the coated tablet of Example 2. For example, at 1 hour, the coated tablet of Example 2 showed only 11% dissolution, while the uncoated tablet of Example 1 showed 15% dissolution. Similarly, at 2 hours, the coated tablet of Example 2 showed no more than 20% dissolution, while the uncoated tablet of Example 1 showed 24% dissolution.

[0120] Dissolution of the tablet of Example 5 having a 5% coating comprising 20% pore-former exhibited a dissolution profile much slower than either the tablet of Example 1 or the tablet of Example 2.

Example 7

[0121] An in vivo study was conducted in healthy human volunteers to assess bioavailability of pramipexole formulated as the sustained-release or extended-release (XR) tablets of Examples 1, 2 and 5 by comparison with a reference treatment with immediate-release (IR) pramipexole dihydrochloride tablets, and to evaluate safety of pramipexole when its absorption profile is altered as in these extended-release tablets.

[0122] Method

[0123] The study followed an open-label, 4-way, randomized crossover design and was conducted in healthy male and female subjects ranging from 18 to 55 years of age. The subjects received each of the four treatments during the course of the study, which was conducted at a single center. A total of 12 subjects were enrolled. The subjects were fasted overnight and then given a 0.375 mg oral dose of pramipexole dihydrochloride monohydrate. In the case of the IR formulation, which was provided as Mirapex® tablets, three equally divided doses of 0.125 mg each were given at 8-hour intervals, beginning in the morning. In the case of the XR formulations of Examples 1, 2 and 5, a single 0.375 mg tablet was given in the morning. Serial blood samples were taken over a 48-hour period for PK assessment. Adverse events were recorded during the same 48-hour period.

[0124] Plasma pramipexole concentrations were quantitated by an HPLC-MS/MS method, validated over the assay range 0.05-15 ng/ml. All runs met bioanalytical acceptance criteria for calibration standards and quality control. Samples were not diluted prior to analysis as all sample concentrations were within the limits of quantitation.

[0125] PK parameters for pramipexole were estimated by non-compartmental methods, using the nonlinear regression program Kinetica of Innaphas. Individual plasma concentration data and the actual time-points of blood sampling from each subject were used in the analysis. Plasma concentrations below the lower limit of quantitation at early time-points were set to zero, whereas those in the terminal phase were excluded from the analysis.

[0126] In vivo pramipexole absorption data were derived by a deconvolution routine employing the Kinetica program. To perform this analysis, a fit of the pramipexole data from the reference treatment was first made to a one-compartment open PK disposition model with first order absorption. Based on this fit, plasma pramipexole concentrations were simulated for a 0.575 mg intravenous bolus dose of pramipexole. These simulated pramipexole concentrations were used in the deconvolution routine.

[0127] In vitro/in vivo correlations for each of the pramipexole XR formulations were examined by evaluating a linear relationship of in vivo absorption as a function of in vitro dissolution.

[0128] Prediction of mean steady-state concentrations arising from repeated daily dosing was performed by interpolation of hourly concentrations from individual subjects' observed concentration/time data and then by the principle of superposition, estimating the concentrations during the 6th day of dosing. Estimates of half-life obtained from this study, which were consistent with values reported previously, indicate that steady state would be achieved by the 4th day. The steady-state parameters (T_{max} , C_{max} , C_{min} , AUC_{0-24} , C_{avg}) (calculated as AUC_{0-24}/τ) and IR (fluctuation ratio, calculated as $(C_{max}-C_{min})/C_{avg}$) were also estimated during this exercise.

[0129] Results

[0130] Of the 12 subjects enrolled, 10 completed the study. Two subjects were dropped prior to receiving the reference treatment, therefore their data were not included in the PK analysis.

[0131] Mean plasma pramipexole concentrations over the 48-hour assessment period are shown in FIG. 2. PK estimates derived from the individual subject data are provided in Table 6.

TABLE 6

PK parameters (mean $\pm$ standard deviation)				
Parameter	IR tablet	XR tablets		
	(Mimpex®)	Example 1	Example 2	Example 5
AUC_{0-24} (ng·h/mL)	9.93 $\pm$ 2.05	9.05 $\pm$ 3.24	8.66 $\pm$ 2.61	8.91 $\pm$ 4.15
AUC_{0-48} (ng·h/mL)	8.60 $\pm$ 2.33	7.75 $\pm$ 2.83	7.60 $\pm$ 2.11	7.97 $\pm$ 2.77
C_{max} (ng/mL)	11.33 $\pm$ 0.88*	10.82 $\pm$ 0.76	10.82 $\pm$ 0.66	11.42 $\pm$ 0.65
T_{max} (h)	15.9 $\pm$ 2.4*	12.1 $\pm$ 2.1	12.0 $\pm$ 5.3	15.0 $\pm$ 6.5
$T_{1/2}$ (h)	9.1 $\pm$ 2.5	11.4 $\pm$ 4.1	12.9 $\pm$ 2.8	12.1 $\pm$ 9.0

*assessed after third 0.125 mg tablet.

[0132] Mean cumulative absorption data (up to 24 hours) for the XR tablets are shown in Table 7, together with corresponding in vitro dissolution data from Example 6.

TABLE 7

In vitro dissolution and in vivo absorption data for XR tablets						
Time (h)	Example 1		Example 2		Example 5	
	% diss. (in vitro)	% abs. (in vivo)	% diss. (in vitro)	% abs. (in vivo)	% diss. (in vitro)	% abs. (in vivo)
0	0	0.0	0	0.0	0	0.0
1	15	0.6	11	3.3	2	0.0
2	24	21.1	20	13.2	7	0.5
4	56	43.2	74	56.0	20	15.0
6	47	52.5	46	39.4	31	23.9
8	55	57.8	55	45.6	41	29.6
12	69	68.6	70	57.1	56	41.6
16	79	75.5	80	67.4	90	51.1
24	90	83.6	87	83.0	85	64.8

[0133] In vitro/in vivo correlation plots derived from the data of Table 7 are shown in FIGS. 3-5 for the XR tablets of Examples 1, 2 and 5 respectively.

[0134] Estimated PK parameters calculated from predicted steady-state concentrations are given in Table 8

TABLE 8

Predicted steady state PK parameters (mean $\pm$ standard deviation)				
Parameter	IR tablet	XR tablets		
	(Mimpex®)	Example 1	Example 2	Example 5
T_{max} (h)		5.4 $\pm$ 1.9	5.0 $\pm$ 1.3	5.0 $\pm$ 2.8
C_{max} (ng/mL)	0.53 $\pm$ 0.13	0.48 $\pm$ 0.15	0.48 $\pm$ 0.14	0.41 $\pm$ 0.14
C_{min} (ng/mL)	0.29 $\pm$ 0.14	0.22 $\pm$ 0.12	0.27 $\pm$ 0.11	0.25 $\pm$ 0.15
C_{avg} (ng/mL)	0.40 $\pm$ 0.13	0.36 $\pm$ 0.14	0.38 $\pm$ 0.12	0.34 $\pm$ 0.15
AUC_{0-24} (ng·h/mL)	9.63 $\pm$ 3.12	8.56 $\pm$ 3.29	9.00 $\pm$ 2.92	8.06 $\pm$ 3.52
IR	0.66 $\pm$ 0.22	0.67 $\pm$ 0.31	0.61 $\pm$ 0.18	0.62 $\pm$ 0.45

[0135] The subjects dropped from the study experienced a non-serious adverse event, orthostatic hypotension. Both subjects were receiving treatment with the XR tablet of Example 1 when this adverse event occurred.

[0136] No serious adverse events were reported in the study. The most frequently reported event was orthostatic

hypotension, all but two of which were considered transient in nature. The numbers of individual non-serious adverse events reported for each treatment are given in Table 9.

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 Representante Legal 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. **12 018.250**, titulada **"UN METODO DE TRATAMIENTO DE UN TRANSTORNO NEUROLÓGICO"**, cuyo titular **SUPERNUS PHARMACEUTICALS, INC.** publicada en la gaceta No. 642 del 16 de abril de 2012.

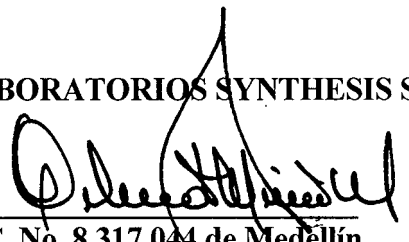
Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados.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

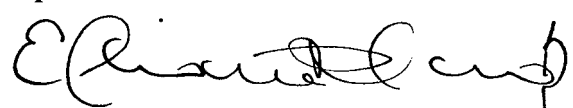
Dado y Firmado en Bogotá (Colombia) a los 06 días del mes de julio de 2012.

LABORATORIOS SYNTHESIS S.A.S.




C.C. No. 8.317.044 de Medellín
NIT: 860.000.760-1
Representante Legal

Acepto:


ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51.975.664
T.P. 83823 del C.S.J

ARGAS FALLO

48

DECLARACION DE...

Mexico Orlando
MARTINEZ
8317044
Medellin

09 JUL 2012



[Signature]
[Large handwritten 'R' mark]





01



* 1 1 7 5 7 4 1 9 6 *



CAMARA DE COMERCIO DE BOGOTA

SEDE KENNEDY

14 DE JUNIO DE 2012

HORA 08:52:40

R035032303

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:

RENOVACION DE LA MATRICULA :29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO: 2012

ACTIVO TOTAL REPORTADO:\$78,678,599,000

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

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

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : lmbautista@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

09533 (07) M2411461

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 NUMERO 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 SNTAFE 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 SNTAFE 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



01



CAMARA DE COMERCIO DE BOGOTA

SEDE KENNEDY

14 DE JUNIO DE 2012 HORA 08:52:40

R035032303

PAGINA: 2 de 5

* * * * *

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
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
146	2011/10/24	0000	BOGOTA D.C.	2011/11/30	01531828

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 ADELANTAR 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 : \$22,000,000,000.00
NO. DE ACCIONES : 22,000,000.00
VALOR NOMINAL : \$1,000.00

** CAPITAL SUSCRITO **

VALOR : \$20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
VALOR NOMINAL : \$1,000.00

** CAPITAL PAGADO **

VALOR : \$20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
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	C.E. 00000000E399661
---------------------------------	----------------------

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A



01

* 1 1 7 5 7 4 1 9 8 *



CAMARA DE COMERCIO DE BOGOTA

SEDE KENNEDY

14 DE JUNIO DE 2012 HORA 08:52:40

R035032303

PAGINA: 3 de 5

* * * * *

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) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

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 BOGOTÁ, 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

10028-101E MY41846

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 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 CERTIFICACION DE REVISOR FISCAL DEL 4 DE OCTUBRE DE 2011, INSCRITA EL 10 DE OCTUBRE DE 2011 BAJO EL NUMERO 01519171 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	

ARCILA SABOGAL DIANA YAMILE	C.C. 000000052828052
-----------------------------	----------------------

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 6 DE FEBRERO DE 2012, INSCRITA EL 8 DE FEBRERO DE 2012 BAJO EL NUMERO 01605220 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL SUPLENTE	

VILLATE AVENDAÑO MARIA PILAR	C.C. 000001053605913
------------------------------	----------------------

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):



01



* 1 1 7 5 7 4 1 9 9 *

28



CAMARA DE COMERCIO DE BOGOTA

SEDE KENNEDY

14 DE JUNIO DE 2012

HORA 08:52:40

R035032303

PAGINA: 4 de 5

* * * * *

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.

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 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

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 \$U 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,



01

* 1 1 7 5 7 4 2 0 0 *



CAMARA DE COMERCIO DE BOGOTA

SEDE KENNEDY

14 DE JUNIO DE 2012

HORA 08:52:40

R035032303

PAGINA: 5 de 5

* * * * *

VALOR : \$ 4,000
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

