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Tra. 2 PATENTES
Act. 400 OPOSIOBSERV

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Folios: 103

FORMULARIO UNICO DE OPOSICION
2000-12

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OPOSICION A:

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

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**SOLICITUD
PUBLICADA**

Número del expediente: 06 042.169

Solicitante: PROCAPS.

Apoderado: REINALDO PINILLA MORENO

Título de la nueva creación o denominación del signo:

"UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN
TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO
PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN
SOLUCIÓN TRANSPARENTE."

Gaceta: 576 de 31 De Mayo de 2007 Número de Publicación 71

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.26.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

124 30

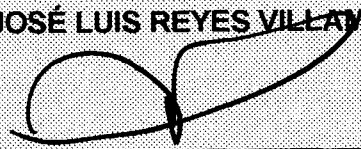
5 Comprobante de pago No 07-65,183 (Oposición) Fecha Agosto 13 de 2003
07-64,378 (Prórroga) Fecha Agosto 10 de 2003

6 Anexos:

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

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

12531

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 06-042-169

TÍTULO SOLICITADO: "UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE."

PUBLICACIÓN:

GACETA No. 576 de 31 de Mayo de 2007, número de publicación 71.

SOLICITANTE:

PROCAPS S.A.

APODERADO:

REINALDO PINILLA MORENO

TRÁMITE:

PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-042-169**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUIMICAS S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

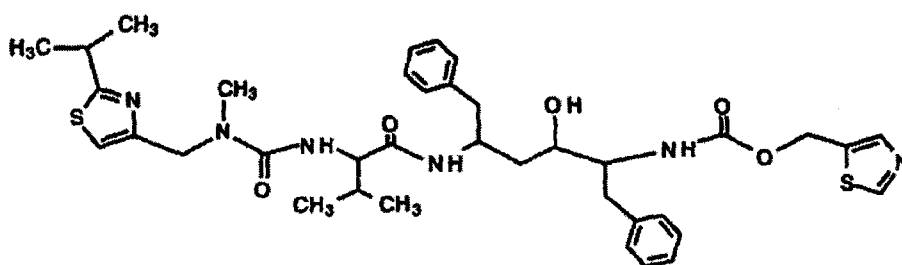
La solicitud Colombiana 06-042-169 en trámite que se refiere a una formulación farmacéutica en solución transparente que contiene ritonavir entre el 1 y 90% del peso total de la formulación, y el proceso de elaboración de la misma para ser depositada finalmente en cápsulas de gelatina, carece de novedad y de nivel inventivo como se argumenta a continuación:

- La publicación internacional WO 95/07696 publicada el 23 de Marzo de 1995 y titulada "PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS" revela una composición farmacéutica que comprende una solución de un compuesto inhibidor de proteasa HIV en un solvente orgánico farmacéuticamente aceptable, que comprende un alcohol farmacéuticamente aceptable; la composición puede opcionalmente comprender un ácido o una combinación de ácidos farmacéuticamente aceptables; adicionalmente, la solución puede ser encapsulada en cápsulas de gelatina dura o de gelatina blanda.

Adicionalmente describe:

In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.



II

(Ritonavir)

(...)

acceptable surfactant or a mixture of pharmaceutically acceptable surfactants. In addition, the solution composition of the invention can comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability. Solutions encapsulated in a SEC may also comprise glycerin for physical stability.

(...)

The term "pharmaceutically acceptable organic solvent" as used herein refers to polypropylene glycol; polyethylene glycol (for example, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 540, polyethylene glycol 1450, polyethylene glycol 6000, polyethylene glycol 8000 (all available from Union Carbide) and the like); pharmaceutically acceptable alcohols which are liquids at about room temperature, approximately 20°C, (for example, propylene glycol, ethanol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like); polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil) or

(...)

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated

(...)

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Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

(...)

A preferred pharmaceutically acceptable solvent is propylene glycol or a mixture of propylene glycol (about 80% v/v) and ethanol (about 20% v/v) or a mixture of propylene glycol (from about 80% to about 90% v/v), ethanol (from about 5% to about 10% v/v) and water (from about 5% to about 10% v/v).

Yet another preferred composition of the invention comprises a solution of
(1) a compound of the formula II in the amount of from about 2% to about 30%
(preferably, from about 4% to about 30%) by weight of the total solution; and

(...)

Lo anterior demuestra que en el estado del arte se encuentran composiciones farmacéuticas de Ritonavir como un agente inhibidor de la proteasa VIH en uno o más solventes orgánicos farmacéuticamente aceptables, junto con antioxidantes adecuados, incluso, puede contener Propilenglicol monolaurato entre sus excipientes, su forma farmacéutica puede ser cápsulas de gelatina blanda y los porcentajes o rangos se encuentran dentro de lo revelado en la solicitud colombiana en trámite.

Para complementar lo consignado, podemos ver que las reivindicaciones de la solicitud internacional describen:

1. A pharmaceutical composition comprising a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.
2. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
4. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.
10. The composition of Claim 9 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

-

(a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or



(Ritonavir)

- (c) a pharmaceutically acceptable surfactant, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

$$(\dots)$$

The solution composition of the invention can also comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability.

(...)

The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquids at about room temperature, approximately 20°C, for example, ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol (Transcutol®, Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like. A preferred pharmaceutically acceptable alcohol is ethanol or propylene glycol or a mixture thereof.

(...)

An even more preferred composition of the invention is a solution comprising

(a) ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 60%) by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 60%) by weight of the total solution and

(2) ethanol in the amount of from about 0% to about 12% (preferably, from about 10% to about 12%) by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% (preferably, from about 5% to about 10%) by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% (preferably, from about 10% to about 15%) by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 5% to about 10%) by weight of the total solution. In an even more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

(...)

Además reivindica:

4. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 70% by weight of the total solution and (2) ethanol or propylene glycol in the amount of from about 1% to about 15% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 1% to about 15% by weight of the total solution.

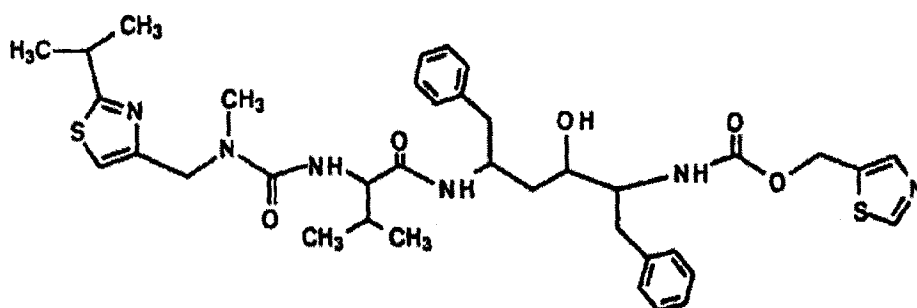
9. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

De nuevo vemos que el conjunto de características reveladas y descritas en la solicitud colombiana en trámite ya habían sido tenidas en cuenta en la solicitud internacional WO 98/22106, en consecuencia, los requisitos de patentabilidad, en especial el art 14 y 18, no se cumplen en virtud de lo revelado en dicho documento perteneciente al arte anterior.

- La solicitud internacional WO 00/74677 publicada el 14 de diciembre de 2000 y titulada "IMPROVED PHARMACEUTICAL FORMULATIONS" describe composiciones farmacéuticas mejoradas que comprenden uno o más compuestos inhibidores de proteasa HIV que tienen propiedades mejoradas de disolución en una mezcla de ácido graso, etanol y agua.

Luego en la parte descriptiva señala que:

A preferred composition of the invention is a solution comprising (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or, more preferably, a compound of formula III or V or



II

(Ritonavir)

(...)

In a more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

(...)

In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of about 0.025% by weight of the total solution.

In addition, the solution composition of the invention can comprise antioxidants (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability.

(...)

An even more preferred composition of the invention is a solution comprising (a) ritonavir in the amount of from about 1 % to about 30% (preferably, from about 5% to about 25%) by weight of the total solution,

(...)

The amount of water employed in the pharmaceutical composition of the instant invention comprises from about 0.4% to about 3.5% by weight of the total solution of water. Preferably, the weight of the total solution of water is from about 0.4% to about 2.0%; more preferably from about 0.4% to about 1.5%; and the most preferred being about 1%.

Además reivindica:

1. A pharmaceutical composition which is a solution comprising:
 - (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
 - (b) a pharmaceutically acceptable organic solvent which comprises a long chain fatty acid or a mixture of long chain fatty acids and ethanol;
 - (c) water; and
 - (d) optionally a pharmaceutically acceptable surfactant.
2. The composition according to Claim 1 wherein said HIV protease inhibiting compound is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).
7. The composition according to Claim 1 wherein the solution is encapsulated into a hard gelatin capsule or a soft gelatin capsule.

14. The composition of Claim 1 which comprises:
 - (a) ritonavir in the amount of from about 1% to about 30% by weight of the total solution;

Si bien es cierto que esta publicación internacional no revela el lleno de características contenidas en la solicitud colombiana en trámite, no lo es menos

que se trata de composiciones que comprenden Ritonavir en cápsulas de gelatina, solventes orgánicos adecuados, surfactantes, antioxidantes y agua dentro de la formulación; además, esta anterioridad junto con las otras hasta el momento expuestas, permiten evidenciar y reunir la información necesaria para poder llevar a cabo una formulación como la que se pretende ahora patentar.

- La publicación internacional WO 01/52821 publicada el 26 de Julio de 2000 y titulada "IMPROVES PHARMACEUTICAL FORMULATIONS" revela:

(57) Abstract: Improved pharmaceutical compositions are provided comprising one or more solubilized HIV protease inhibiting compounds having improved solubility properties in a medium and/or long chain fatty acid, or mixtures thereof, a pharmaceutically acceptable alcohol, and water.

(...)

The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquid at room temperature, for example ethanol, propylene glycol, 2-(ethoxyethoxy)ethanol (Transcutol[®], Gattefosse, Westwood, NJ), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, and the like, or mixtures thereof.

(...)

In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) solubilized ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) a

(...)

In a more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

(...)

In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of about 0.025% by weight of the total solution.

(...)

75% by weight of the total solution and (2) propylene glycol in the amount of from about 1% to about 15% by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5% and (d) a pharmaceutically

Además reivindica:

1. A pharmaceutical composition comprising:

- (a) a solubilized HIV protease inhibiting compound or a combination of solubilized HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
- (b) a pharmaceutically acceptable organic solvent which comprises a medium and/or long chain fatty acid or a mixture thereof, and propylene glycol;
- (c) water; and
- (d) optionally, a pharmaceutically acceptable surfactant.

2. The composition according to Claim 1 wherein said HIV protease inhibiting compound is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir).

7. The composition according to Claim 1 wherein the solution is encapsulated into a hard gelatin capsule or a soft gelatin capsule.

8. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) propylene glycol in the amount of from about 3% to about 12% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

9. The composition of Claim 1 wherein the solvent comprises (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution; (2) propylene glycol in the amount of from about 3% to about 12% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

Una vez más se observa que el conjunto de características reveladas y descritas en la solicitud colombiana en trámite ya habían sido tenidas en cuenta en la solicitud internacional en mención, en consecuencia, los requisitos de patentabilidad no se cumplen en virtud de lo revelado en dicho documento perteneciente al arte anterior.

- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2000 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" revela:

(57) Abstract: A soft elastic capsule is described containing a pharmaceutical agent or a mixture of pharmaceutical agents. The soft elastic capsule is prepared from a fill composition and a shell composition that impart acceptable physical characteristics to the soft elastic capsule when in an equilibrium state. The pharmaceutical agents of the fill composition are also soluble when the soft elastic capsule is in the equilibrium state.

(...)

Preferably, the initial fill composition is prepared at temperatures that avoid the degradation of a HIV protease inhibitor, for example, ritonavir.

(...)

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The alcohol of the fill composition can be propylene glycol, another suitable alcohol, or mixtures thereof. Suitable alcohols include, for example, ethanol, 2-(ethoxyethoxy)ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, and polyethylene glycol 400. Preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the initial fill composition, as measured by weight, in a range of 3-20%. More preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in a range of 9-14%. Most preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the range of 10-13% in the initial fill composition. Propylene

(...)

En el capítulo reivindicatorio se revela:

1. A soft elastic capsule having a fill and a shell, the fill comprising:

a pharmaceutical agent or combination of pharmaceutical agents,
an alcohol,
a fatty acid, and

the shell comprising:

gelatin, and
at least one plasticizing agent,

wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition, and wherein said equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.

The soft elastic capsule of claim 4 wherein said HIV inhibiting compound is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

7. The soft elastic capsule of claim 4 wherein said solubilized HIV inhibiting compound or said combination of solubilized HIV inhibiting compounds is present in said fill in a range of 10-35% by weight.

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8. The soft elastic capsule of claim 1 wherein said alcohol is propylene glycol or ethanol.
9. The soft elastic capsule of claim 8 wherein propylene glycol or ethanol are present in said fill in initial state in a range of 3–20% by weight.

Como se puede apreciar, estas anterioridades contienen y reivindican las características esenciales que sustentan la invención de la solicitud colombiana en trámite, específicamente lo que se refiere a el inhibidor de proteasa (ritonavir) en el tratamiento de VIH, las características del solvente y el porcentaje del mismo en la formulación, la presencia de antioxidantes, las proporciones del principio activo y demás componentes de la formulación, y finalmente la inclusión de dicha solución en cápsulas de gelatina.

Siendo evidente la anterioridad en la obtención de formulaciones con características idénticas a la de la solicitud colombiana en trámite, es importante resaltar que con la información necesaria para realizar este tipo de formulaciones (capsulas de gelatina blanda) contenida en el estado de la técnica, la producción de las formulaciones reivindicadas por dichas solicitud colombiana en trámite se reduce a la aplicación de todos los ensayos requeridos a nivel de preformulación y formulación reconocidos por cualquier persona versada en la materia¹.

Por lo expuesto respetuosamente llamo la atención sobre el hecho de que la solicitud de la referencia, en todas sus reivindicaciones, no cumple con los requisitos dispuestos en la Decisión 486 de 2000, por tal razón no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14 y 18 (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para

¹ Vila Jato J.L. TECNOLOGIA FARMACÉUTICA. Vol. II. Parte 1, Cáp. 2. Páginas 62 a 67.

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sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación internacional WO 95/07696 publicada el 23 de Marzo de 1995 y titulada "PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS" páginas 5, 6, 7, 11 y capítulo reivindicatorio.
- La publicación internacional WO 98/22106 publicada el 28 de Mayo de 1998 y titulada "PHARMACEUTICAL COMPOSITION" páginas 8, 9, 19, 11, 12 y capítulo reivindicatorio.
- La publicación internacional WO 00/74677 publicada el 14 de diciembre de 2000 y titulada "IMPROVED PHARMACEUTICALS FORMULATIONS" páginas 11, 18, 22, 23 y capítulo reivindicatorio.
- La publicación internacional WO 01/52821 publicada el 26 de Julio de 2000 y titulada "IMPROVES PHARMACEUTICAL FORMULATIONS" páginas 17, 18, 20 y capítulo reivindicatorio.
- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2000 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" página 13 y capítulo reivindicatorio.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



#141
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/425, 38/55, 9/48, 47/02, 47/12, 47/10		A1	(11) International Publication Number: WO 95/07696 (43) International Publication Date: 23 March 1995 (23.03.95)
(21) International Application Number: PCT/US94/09788 (22) International Filing Date: 30 August 1994 (30.08.94) (30) Priority Data: 08/120,886 13 September 1993 (13.09.93) US 08/188,511 28 January 1994 (28.01.94) US 08/267,331 28 June 1994 (28.06.94) US 08/288,873 15 August 1994 (15.08.94) US (71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors: AL-RAZZAK, Laman, A.; 233 W. Golf Road, Libertyville, IL 60048 (US). MARSH, Kennan, C.; 1499 McKinley, Lake Forest, IL 60045 (US). MANNING, Lourdes, P.; 1052 Talbot Lane, Grayslake, IL 60030 (US). KAUL, Dilip; 2024 Washington Street #110, Waukegan, IL 60085 (US). (74) Agents: CROWLEY, Steven, R. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).			(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS			
(57) Abstract A pharmaceutical composition is disclosed which comprises a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent comprising a pharmaceutically acceptable alcohol. The composition can optionally comprise a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids. The solution can optionally be encapsulated in hard gelating capsule or soft elastic gelating capsules. The solution can optionally be granulated with a pharmaceutically acceptable granulating agent.			

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solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

In order to have a suitable oral dosage form of compound III, the oral bioavailability of compound III should be at least 20%. Preferably, the oral bioavailability of compound III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug. It has been found that compound III has good solubility in pharmaceutically acceptable organic solvents and that the solubility in such solvents is enhanced by at least four times in the presence of a pharmaceutically acceptable acid. Unexpectedly, these solutions of compound III in organic solvents provide an oral bioavailability of from about 20% to about 40% in dogs. Quite unexpectedly, administration of the solution as an encapsulated dosage form (soft elastic capsules or hard gelatin capsules) provides an oral bioavailability of as high as about 90% or more. In addition, quite unexpectedly, when certain solution compositions of compound III are granulated by mixing with a pharmaceutically acceptable granulating agent and the resulting solid composition is administered to dogs, an acceptable oral bioavailability is observed.

Disclosure of the Invention

In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

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The solution composition of the invention can also comprise from about 0 to about 3 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition) of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids. Preferably, the pharmaceutically acceptable acid or mixture of pharmaceutically acceptable acids is present in a total amount of from about 0.2 to about 2.0 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition).

The solution composition of the invention can also comprise from about 0% to about 10% (by weight of the total solution) of water. In addition, the solution composition of the invention can comprise a pharmaceutically acceptable surfactant or a mixture of pharmaceutically acceptable surfactants. In addition, the solution composition of the invention can comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability. Solutions encapsulated in a SEC may also comprise glycerin for physical stability.

The compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for compound II when compared to non-formulated compound II (base) or non-formulated compound II (acid addition salt), or even when compared to a mixed aqueous/organic solution (50% water, 20% ethanol, 30% propylene glycol) of compound II (methanesulfonate acid addition salt).

The term "pharmaceutically acceptable organic solvent" as used herein refers to polypropylene glycol; polyethylene glycol (for example, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 540, polyethylene glycol 1450, polyethylene glycol 6000, polyethylene glycol 8000 (all available from Union Carbide) and the like); pharmaceutically acceptable alcohols which are liquids at about room temperature, approximately 20°C, (for example, propylene glycol, ethanol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like); polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil) or

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Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp.) and the like); saturated polyglycolized glycerides (for example, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like, available from Gattefosse, Westwood, NJ 07675); polyoxyethylene alkyl ethers (for example, cetomacrogol 1000 and the like); polyoxyethylene stearates (for example, PEG-6 stearate, PEG-8 stearate, polyoxyl 40 stearate NF, polyoxyethyl 50 stearate NF, PEG-12 stearate, PEG-20 stearate, PEG-100 stearate, PEG-12 distearate, PEG-32 distearate, PEG-150 distearate and the like); ethyl oleate, isopropyl palmitate, isopropyl myristate and the like; N-methylpyrrolidinone; parafin; cholesterol; lecithin; suppository bases; pharmaceutically acceptable waxes (for example, carnauba wax, yellow wax, white wax, microcrystalline wax, emulsifying wax and the like); pharmaceutically acceptable silicon fluids; sorbitan fatty acid esters (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like); pharmaceutically acceptable saturated fats or pharmaceutically acceptable saturated oils (for example, hydrogenated castor oil (glyceryl-tris-12-hydroxystearate), cetyl esters wax (a mixture of primarily C14-C18 saturated esters of C14-C18 saturated fatty acids having a melting range of about 43-47°C), glyceryl monostearate and the like); and the like.

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated polyglycolized glyceride is characterized by its nominal drop point, its nominal hydroxyl and saponification values and its nominal composition in fatty acids. The free glycerol content is less than 1%.

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room temperature; or it refers to semi-solid solutions wherein the pharmaceutically active agent is dissolved in a pharmaceutically acceptable solvent or mixture of solvents which is a liquid at temperatures above about room temperature (particularly, at about the temperature of the human body) but is a solid or semi-solid at about room temperature.

A preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and (2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Yet another preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and (2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

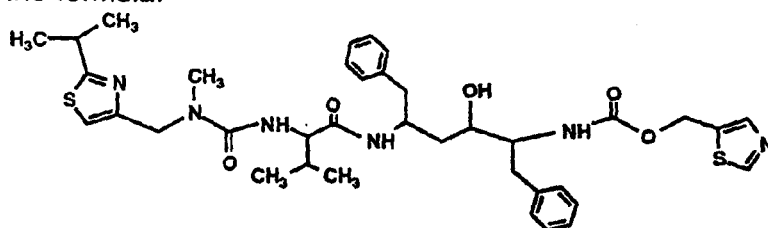
Yet another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.
2. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
3. The composition of Claim 1 further comprising a pharmaceutically acceptable acid.
4. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

5. A pharmaceutical composition comprising a solution of a compound of the formula:



in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

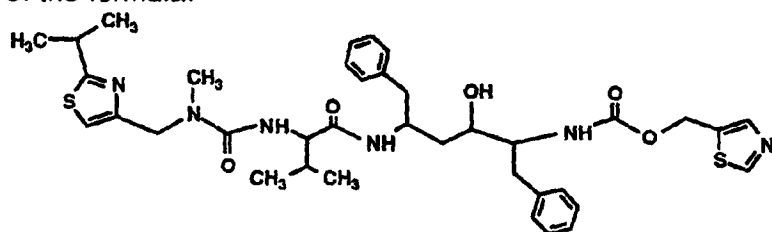
6. The composition of Claim 5 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
7. The composition of Claim 5 further comprising a pharmaceutically acceptable acid.

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8. The composition of Claim 5 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

9. A pharmaceutical composition comprising a solution of (a) a compound of the formula:



; and

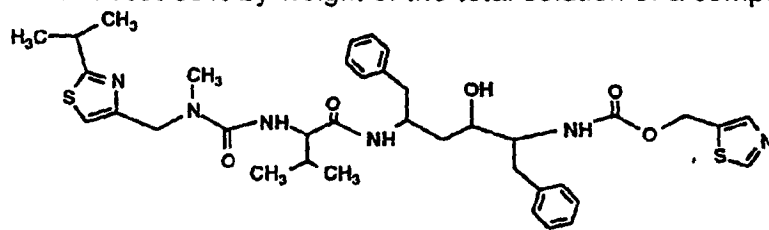
(b) a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

10. The composition of Claim 9 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

11. The composition of Claim 9 further comprising water.

12. The composition of Claim 9 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

13. The composition of Claim 9 comprising a solution of (a) from about 2% to about 30% by weight of the total solution of a compound of the formula:



; and

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(b) from about 0.2 molar equivalent to about 3 molar equivalents, based upon the amount of the compound of part (a), of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol and the solvent comprising from about 50 % to about 95 % by weight of the total solution.

14. The composition of Claim 13 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

15. The composition of Claim 13 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at room temperature and (b) a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C, said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogeneous mixture with the alcohol or mixture of alcohols, said homogeneous mixture being a solid or semi-solid at about 20°C, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

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16. The composition of Claim 15 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% by weight of the total solution or a total amount of from about 20% to about 60% by weight of the total solution of (i) a saturated polyglycolized glyceride or (ii) a mixture of saturated polyglycolized glycerides, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

17. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 20% to about 25% by weight of the total solution and (2) a total of from about 1.5 to about 2 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 20 % to about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

18. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by

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weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

19. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of about 2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

20. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 10% to about 15% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

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21. The composition of Claim 13 comprising a solution of (a) about 8.8 % by weight of the total solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane ; and (b) about 2 molar equivalents, based upon the amount of the compound of part (a), of hydrochloric acid in a mixture comprising about 82 % by weight of the total solution of propylene glycol, about 3.5 % by weight of the total weight of the solution of ethanol and about 4.4 % by weight of the total solution of water.

22. The composition of Claim 21 wherein the solution is encapsulated in a hard gelatin capsule.

23. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 4% to about 30% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 10% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 8% , and (c) polyethylene glycol 540 in the amount of from about 25% to about 60% by weight of the total solution or saturated polyglycolized glyceride in the amount of from about 25% to about 60% by weight of the total solution.

24. The composition of Claim 23 wherein the solution is encapsulated in a hard gelatin capsule.

25. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 20% to about 25% by weight of the

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total solution and (2) a total of about two molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

26. The composition of Claim 25 wherein the solution is encapsulated in a hard gelatin capsule.

27. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of a mixture of citric acid and hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

28. The composition of Claim 27 wherein the solution is encapsulated in a hard gelatin capsule.

29. The composition of Claim 16 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)-amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of p-toluene- sulfonic acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of from about

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2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution.

30. The composition of Claim 29 wherein the solution is encapsulated in a hard gelatin capsule.

31. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)-amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 22% by weight of the total solution and (2) a total of about 1.6 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

32. The composition of Claim 31 wherein the solution is encapsulated in a hard gelatin capsule.

33. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)-amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 18% by weight of the total solution and (2) a total of about 0.5 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

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34. The composition of Claim 33 wherein the solution is encapsulated in a hard gelatin capsule.

35. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)-amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 22% by weight of the total solution and (2) a total of about 1.8 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

36. The composition of Claim 35 wherein the solution is encapsulated in a hard gelatin capsule.

37. The composition of Claim 16 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)-amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 17% by weight of the total solution and (2) a total of about 0.4 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 14% by weight of the total solution, (b) ethanol in the amount of about 12% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

38. The composition of Claim 37 wherein the solution is encapsulated in a hard gelatin capsule.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/20794 (22) International Filing Date: 12 November 1997 (12.11.97) (30) Priority Data: 08/754,390 21 November 1996 (21.11.96) US (71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors: LIPARI, John; 6600 Apollo Drive, Racine, WI 53406 (US). AL-RAZZAK, Laman, A.; 2325 Hybernia Drive, Highland Park, IL 60035 (US). GHOSH, Soumojeet; Apartment 2A, 219 Dittmer Lane, Lindenhurst, IL 60046 (US). GAO, Rong; Apartment 201, 4255 Greenleaf Court, Park City, IL 60085 (US). KAUL, Dilip; 4334 Buckingham Drive, Gurnee, IL 60031 (US). (74) Agents: CROWLEY, Steven, R. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: PHARMACEUTICAL COMPOSITION (57) Abstract A liquid pharmaceutical composition providing improved oral bioavailability is disclosed for compounds which are inhibitors of HIV protease. In particular, the composition comprises a solution in a pharmaceutically acceptable organic solvent of (a) the HIV protease inhibitor and optionally, (b) a surfactant. The composition can optionally be encapsulated in either hard gelating capsules or soft elastic capsules (SEC).		

Compound III has an aqueous solubility of approximately 6 micrograms per milliliter at pH >2. This is considered to be extremely poor aqueous solubility and, therefore, compound III in the free base form would be expected to provide very low oral bioavailability. In fact, the free base form of compound III, administered as an unformulated solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

Acid addition salts of compound III (for example, bis-hydrochloride, bis-tosylate, bis-methane sulfonate and the like) have aqueous solubilities of <0.1 milligrams/milliliter. This is only a slight improvement over the solubility of the free base. This low aqueous solubility would not make practical the administration of therapeutic amounts of an acid addition salt of compound III as an aqueous solution. Furthermore, in view of this low aqueous solubility, it is not surprising that the bis-tosylate of compound III, administered as an unformulated solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

In order to have a suitable oral dosage form of compound III, the oral bioavailability of compound III should be at least 20%. Preferably, the oral bioavailability of compound III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug. It has been found that compound III has good solubility in pharmaceutically acceptable organic solvents and that the solubility in such solvents is enhanced in the presence of a pharmaceutically acceptable long chain fatty acid. Administration of the solution as an encapsulated dosage form (soft elastic capsules or hard gelatin capsules) provides an oral bioavailability of as high as about 60% or more.

Disclosure of the Invention

In accordance with the present invention, there is a pharmaceutical composition which is a solution comprising

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- (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478, or a combination of a compound of the formula II or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula IV or saquinavir or indinavir or nelfinavir or VX-478), or, more preferably, a combination of a compound of the formula III or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula V or saquinavir or indinavir or nelfinavir or VX-478)),
- (b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol,
- and, optionally,
- (c) a pharmaceutically acceptable surfactant.

In the above solution composition, preferred HIV protease inhibitors as individual compounds are the compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478. In the above composition, preferred combinations of HIV protease inhibitors are the compound of formula III and the compound of formula V, the compound of formula III and saquinavir, the compound of formula III and indinavir, the compound of formula III and nelfinavir, the compound of formula III and VX-478, nelfinavir and the compound of formula V, nelfinavir and saquinavir, nelfinavir and indinavir, nelfinavir and VX-478.

Also in accordance with the present invention, there is a pharmaceutical composition which is a solution comprising

- (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478, or a combination of a compound of the formula II or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula IV or saquinavir or indinavir or nelfinavir or VX-478), or, more preferably, a

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combination of a compound of the formula III or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula V or saquinavir or indinavir or nelfinavir or VX-478)),

(b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol,

and, optionally,

(c) a pharmaceutically acceptable surfactant, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

In the above encapsulated solution composition, preferred HIV protease inhibitors as individual compounds are the compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478. In the above composition, preferred combinations of HIV protease inhibitors are the compound of formula III and the compound of formula V, the compound of formula III and saquinavir, the compound of formula III and indinavir, the compound of formula III and nelfinavir, the compound of formula III and VX-478, nelfinavir and the compound of formula V, nelfinavir and saquinavir, nelfinavir and indinavir, nelfinavir and VX-478.

The solution composition of the invention can also comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability.

The compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for HIV protease inhibitors. In particular, the compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for compound III when compared to non-formulated compound III (base) or non-formulated compound III (acid addition salt).

The term "pharmaceutically acceptable long chain fatty acid" as used herein refers to saturated, mono-unsaturated or di-unsaturated C₁₂ to C₁₈ carboxylic acids which are liquids at room temperature. Preferred long chain fatty acids are mono-unsaturated C₁₆-C₂₀ carboxylic acids which are liquids at room temperature. A most preferred long chain fatty acid is oleic acid.

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The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquids at about room temperature, approximately 20°C, for example, ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like. A preferred pharmaceutically acceptable alcohol is ethanol or propylene glycol or a mixture thereof.

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant for example, polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.) or polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil)) or Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp. and the like) or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylenepolypropylene glycol, such as Poloxamer®124, Poloxamer®188, Poloxamer®237, Poloxamer®388, Poloxamer®407 and the like, (BASF Wyandotte Corp.) or a mono fatty acid ester of polyoxyethylene (20) sorbitan (for example, polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20) and the like) and the like or a sorbitan fatty acid ester (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like). A preferred pharmaceutically acceptable surfactant is polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethylene (20) sorbitan monolaurate (Tween® 20), polyoxyethylene (20) sorbitan monooleate (Tween® 80) or a sorbitan fatty acid ester, for example sorbitan oleate. A most preferred pharmaceutically acceptable surfactant is polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.).

A preferred composition of the invention is a solution comprising (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or

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saquinavir or nelfinavir or indinavir or, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir, or, most preferably, a compound of the formula III or V); or a combination of a compound of the formula II or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula IV or saquinavir or indinavir or nelfinavir, or, more preferably, a combination of a compound of the formula III or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula V or saquinavir or indinavir or nelfinavir), or, most preferably, a combination of a compound of formula III and a compound of formula V) in the amount of from about 1% to about 50% (preferably, from about 1% to about 40%; more preferably, from about 10 % to about 40%; most preferably, from about 15% to about 40%) by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 60%) by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% (preferably, from about 30% to about 70%; more preferably, from about 40% to about 60%) by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% (preferably, from about 6% to about 12%) by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% (preferably, from about 2% to about 20% and most preferably, from about 5% to about 15%) by weight of the total solution. In a preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

Preferably, the pharmaceutically acceptable organic solvent comprises from about 50% to about 99% by weight of the total solution. More preferably, the pharmaceutically acceptable organic solvent or mixture of pharmaceutically acceptable organic solvents comprises from about 50% to about 75% by weight of the total solution.

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CLAIMS

What is claimed is:

1. A pharmaceutical composition which is a solution comprising
(a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds,
(b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol,
and, optionally,
(c) a pharmaceutically acceptable surfactant.

2. The composition of Claim 1 comprising
(a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds in the amount of from about 1% to about 50% by weight of the total solution,
(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% by weight of the total solution and
(2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
(c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% by weight of the total solution.

3. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

4. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 70% by weight of the total solution and (2) ethanol or propylene

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glycol in the amount of from about 1% to about 15% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 1% to about 15% by weight of the total solution.

5. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 5% to about 15% by weight of the total solution.

6. The composition of Claim 1 wherein the solvent comprises (1) oleic acid in the amount of from about 40% to about 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 10% to about 15% by weight of the total solution.

7. The composition of Claim 1 wherein the HIV protease inhibiting compound is selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane;

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-(2(R)-hydroxy-4-phenyl-3(S)-))N-(2-quinolylcarbonyl)-L-asparaginy]amino)butyl)-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

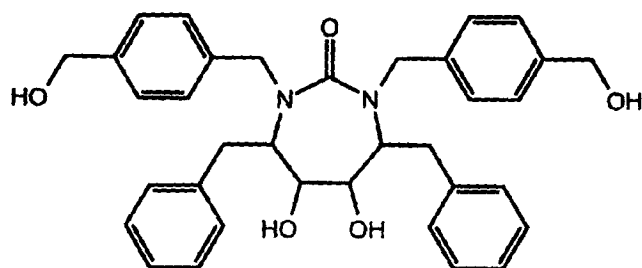
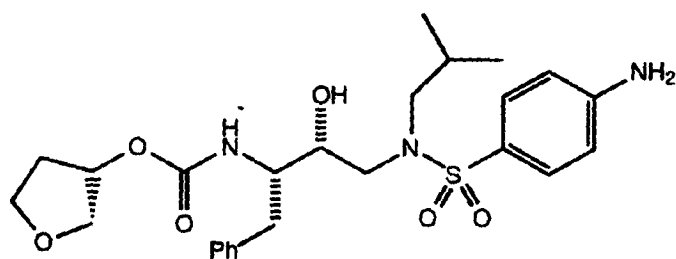
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5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

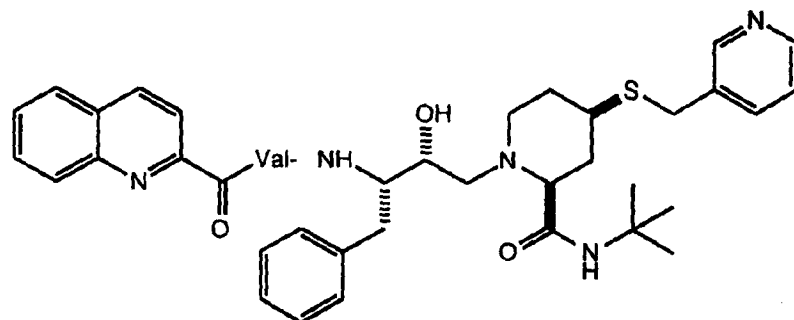
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

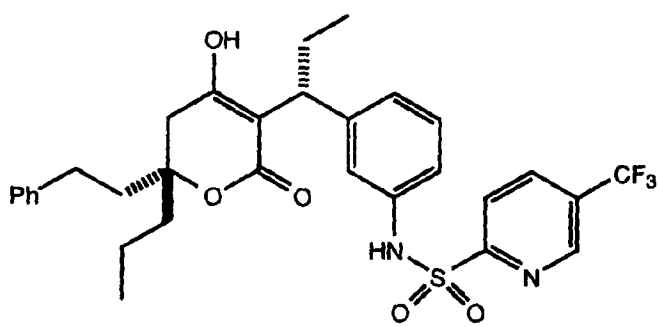
(1S-(1R*(R*),2S*)) -N¹(3-(((1,1-dimethylethyl)amino]carbonyl)(2-methylpropyl)amino)-2-hydroxy-1-(phenylmethyl)propyl)-2-((2-quinolinylcarbonyl)amino)-butanediamide;



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; and



or a pharmaceutically acceptable salt of any of the above.

8. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir, (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane, indinavir, saquinavir, nelfinavir or VX-478.

9. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

10. The composition of Claim 1 wherein the combination of HIV protease inhibiting compounds is:
 ritonavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane;
 ritonavir and indinavir;

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ritonavir and saquinavir;
ritonavir and nelfinavir;
ritonavir and VX-478;
saquinavir and nelfinavir;
indinavir and nelfinavir;
nelfinavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane; or
nelfinavir and VX-478.

11. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane.

12. The composition of Claim 1 comprising
(a) ritonavir in the amount of from about 1% to about 30% by weight of the total solution,
(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
(c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% by weight of the total solution.

13. The composition of Claim 12 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

14. The composition of Claim 12 comprising
(a) ritonavir in the amount of from about 5% to about 25% by weight of the total solution,

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(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 12% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 5% to about 10% by weight of the total solution.

15. The composition of Claim 14 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

16. The composition of Claim 1 comprising

(a) ritonavir in the amount of from about 1% to about 30% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 15% to about 99% by weight of the total solution and

(2) ethanol in the amount of from about 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution.

17. The composition of Claim 16 comprising

(a) ritonavir in the amount of from about 5% to about 25% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and

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- (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 10% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

18. The composition of Claim 16 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

19. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 62% to about 64% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

20. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 65% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 5% by weight of the total solution.

21. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 60% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

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(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

22. The composition of Claim 1 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
- (c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% by weight of the total solution.

23. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 35% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 12% by weight of the total solution and
- (c) a pharmaceutically acceptable surfactant in the amount of from about 2% to about 20% by weight of the total solution.

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24. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 20% to about 99% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 20% to about 99% by weight of the total solution and (2) ethanol in the amount of from about 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution

25. The composition of Claim 24 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 35% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

26. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 30% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises

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a mixture of (1) oleic acid in the amount of about 50% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

27. The composition of Claim 1 comprising

(a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibitor in the amount of from about 1% to about 50% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 10% to about 98% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 98% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% by weight of the total solution.

28. The composition of Claim 27 comprising

(a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and another HIV protease inhibitor in the amount of from about 5% to about 40% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 120% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 5% to about 10% by weight of the total solution.

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29. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibitor in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 10% to about 98% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 10% to about 98% by weight of the total solution and (2) ethanol in the amount of from about 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution.

30. The composition of Claim 29 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and another HIV protease inhibitor in the amount of from about 5% to about 40% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and
- (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 10% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

31. The composition of Claim 29 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-

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diphenylhexane in the amount of from about 1% to about 50% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 10% to about 88% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

32. The composition of Claim 31 comprising

(a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 40% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 40% to about 65% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in .

33. The composition of Claim 27 comprising

(a) a mixture of ritonavir in the amount of about 5% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 30% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 45% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

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34. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 15% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 50% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

35. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 5% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 60% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

36. The composition of Claim 27 comprising a mixture of ritonavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:16 to about 5:1.

37. The composition of Claim 36 comprising a mixture of ritonavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane, the

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ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:8 to about 3:1.

38. The composition of Claim 1 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibiting compound in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 10% to about 88% by weight of the total solution and (2) propylene glycol in the amount of from about 5% to about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

39. The composition of Claim 38 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 40% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 40% to about 65% by weight of the total solution and (2) propylene glycol in the amount of from about 6% to about 8% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

40. The composition of Claim 38 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 1% to about 50% by weight of the total solution,

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- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
(1) oleic acid in the amount of from about 10% to about 88% by weight of the total solution and (2) propylene glycol in the amount of from about 5% to about 10% by weight of the total solution and
(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

41. The composition of Claim 40 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 40% by weight of the total solution,
(b) a pharmaceutically acceptable organic solvent which comprises a mixture of
(1) oleic acid in the amount of from about 40% to about 65% by weight of the total solution and (2) propylene glycol in the amount of from about 6% to about 8% by weight of the total solution and
(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

42. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 6.0% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 24% by weight of the total solution,
(b) a pharmaceutically acceptable organic solvent which comprises a mixture of
(1) oleic acid in the amount of about 52.5% by weight of the total solution and
(2) propylene glycol in the amount of about 7.5% by weight of the total solution and
(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

43. The composition of Claim 41 comprising a solution of (a) a mixture of ritonavir in the amount of about 5% by weight of the total solution and (2S, 3S,

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5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 25% by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 52.5% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution.

44. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 8% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 24% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 50.5% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

45. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 8.25% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 22% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 52.25% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

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46. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 5% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 30% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 47.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

47. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 15% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 52.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

48. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 13% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 17% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 52.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and

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(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

49. The composition of Claim 41 comprising a mixture of ritonavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:16 to about 5:1.

50. The composition of Claim 47 comprising a mixture of ritonavir and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:8 to about 3:1.

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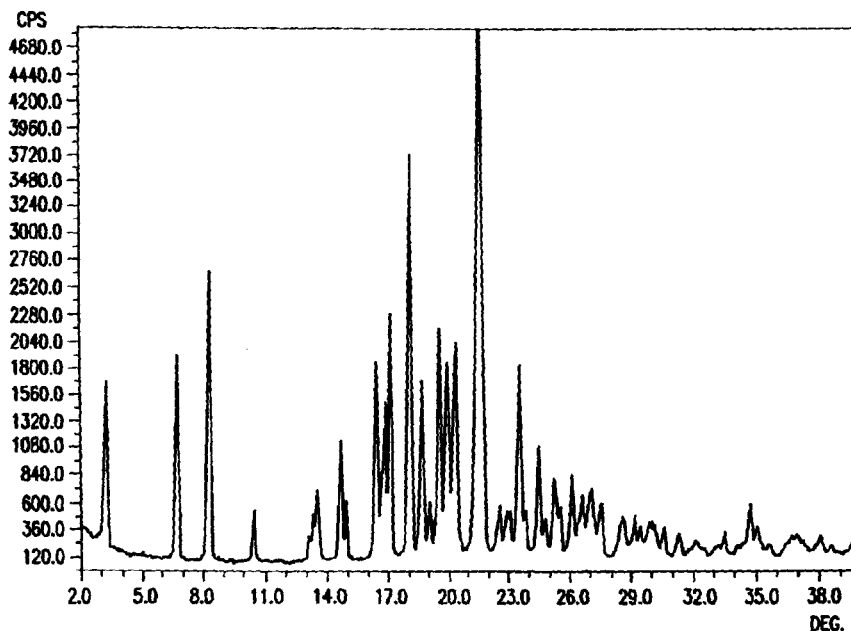
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(54) Title: **IMPROVED PHARMACEUTICAL FORMULATIONS**



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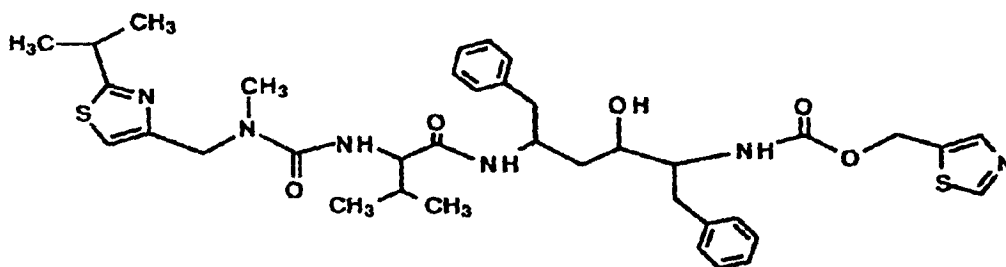
(57) Abstract: Improved pharmaceutical compositions are provided comprising one or more HIV protease inhibiting compounds having improved dissolution properties in a mixture of a fatty acid, ethanol, and water.

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wherein R1 is lower alkyl and R2 and R3 are phenyl and related compounds or a pharmaceutically acceptable salt thereof, disclosed in PCT Patent Application No. W0 94/14436, published July 7, 1994 and U.S. Patent No. 5,541,206, issued July 30, 1996, both of which are incorporated herein by reference. The compounds of formula I are useful to inhibit HIV infections and, thus, are useful for the treatment of AIDS.

In particular, the compound of formula II, has been found to be especially effective as an inhibitor of HIV protease.



II

The most preferred compound of formula II is (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir; a compound of formula III) or a pharmaceutically acceptable salt thereof.

Other examples of HIV protease inhibiting compounds also include compounds of formula IV:

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Summary of the Invention

The instant invention provides a pharmaceutical composition comprising at least one HIV protease inhibiting compound in a pharmaceutically acceptable solution of a long chain fatty acid, ethanol, and water, wherein said HIV protease inhibiting compound contained therein has improved solubility properties.

Detailed Description of the Invention

The instant invention comprises a solution of an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds or pharmaceutically acceptable salts thereof in a pharmaceutically acceptable organic solvent comprising a mixture of at least one pharmaceutically acceptable long chain fatty acid, ethanol, and water.

The compositions of the instant invention provide greatly improved solubility for HIV protease inhibiting compounds contained therein when compared to analogous compositions without added water.

A preferred composition of the invention is a solution comprising (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or, more preferably, a compound of formula III or V or

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from about 1 % to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 1% to about 15% (preferably, from about 3% to about 12%) by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5%, and (d) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 2.5% to about 10%) by weight of the total solution.

In an even more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

A most preferred composition of the invention is a solution comprising (a) ritonavir in the amount of about 10% by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 70% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 3% to about 12%, preferably, about 12%, by weight of the total solution, (c) water in the amount of from about

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0.4% to about 1.5% and (d) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of about 0.025% by weight of the total solution.

The term "pharmaceutically acceptable long chain fatty acid" as used herein refers to saturated, mono- or di-unsaturated C₁₂ to C₁₈ carboxylic acids which are liquids at room temperature. Preferred long chain fatty acids are mono-unsaturated C₁₆-C₂₀ carboxylic acids which are liquids at room temperature. A most preferred long chain fatty acid is oleic acid.

The amount of water employed in the pharmaceutical composition of the instant invention comprises from about 0.4% to about 3.5% by weight of the total solution of water. Preferably, the weight of the total solution of water is from about 0.4% to about 2.0%; more preferably from about 0.4% to about 1.5%; and the most preferred being about 1%.

In addition, the solution composition of the invention can comprise antioxidants (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability.

The term "pharmaceutically acceptable acid" as used herein refers to (i) an inorganic acid such as hydrochloric acid,

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91CLAIMS

We Claim:

1. A pharmaceutical composition which is a solution comprising:
 - (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
 - (b) a pharmaceutically acceptable organic solvent which comprises a long chain fatty acid or a mixture of long chain fatty acids and ethanol;
 - (c) water; and
 - (d) optionally a pharmaceutically acceptable surfactant.
2. The composition according to Claim 1 wherein said HIV protease inhibiting compound is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).
3. The composition according to Claim 1 wherein said combination of HIV protease inhibiting compounds is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane.

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4. The composition according to Claim 1 wherein said HIV protease inhibiting compound or combination of HIV protease inhibiting compounds is selected from the group consisting of:

2S, 3S, 5S) - 5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl)methyl) amino) carbonyl) amino-1, 6-diphenyl-3-hydroxyhexane (ritonavir);

2S, 3S, 5S) - 5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl)methyl) amino) carbonyl) amino-1, 6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S) - 2- (2, 6-

Dimethylphenoxyacetyl)

amino-3-hydroxy-5- [2S- (1-tetrahydro-pyrimid-2-onyl) -3-methyl butanoyl] amino-1, 6-diphenylhexane;

N- (2 (R) -hydroxy-1

(S) -indanyl) -2 (R) -phenylmethyl-4 (S) -hydroxy-5- (1- (4- (3-pyridylmethyl) -2 (S) -N' - (t-butylcarboxamido) -piperazinyl)) -penta neamide (indinavir);

N-tert-butyl-decahydro-2- [2 (R) -hydroxy-4-phenyl-3 (S) - [[N- (2-quinolylcarbonyl) -L-asparaginy] amino] butyl] - (4aS, 8aS) -isoquinolin e-3 (S) -carboxamide (saquinavir);

5 (S) -Boc-amino-4 (S) -hydroxy-6-phenyl-2 (R) -

phenylmethylhexanoyl- (L) -Val- (L) -Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala- (2S, 3S) -

3-amino-2-hydroxy-4-butanoyl 1, 3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala- (2S, 3S) -3-amino-2-hydroxy-4-butanoyl-1, 3-thiazolidine-4-t-butylamide;

[1S- [1R- (R-), 2S*]) -N¹ [3- [[(1, 1 -

dimethylethyl) amino] carbonyl] (2-methylpropyl) amino] -2-

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hydroxy-1 - (phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;
VX-478;
DMP-323;
DMP-450;
AG1343 (nelfinavir);
BMS 186,318;
SC-55389a;
BILA 1096 BS; and
U-140690,
or a pharmaceutically acceptable salt thereof.

5. The composition according to Claim 1 wherein said long chain fatty acid is oleic acid.

6. The composition according to Claim 1 wherein said surfactant is Polyoxyl 35 castor oil (Cremophor EL®).

7. The composition according to Claim 1 wherein the solution is encapsulated into a hard gelatin capsule or a soft gelatin capsule.

8. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 3% to about 12% by weight of the

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total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

9. The composition of Claim 1 wherein the solvent comprises (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 3% to about 12% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

10. The composition of Claim 9 wherein the HIV protease inhibiting compound is selected from the group consisting of:

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-

Dimethylphenoxyacetyl)

amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;

N-(2(R)-hydroxy-1

(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-penta neamide (indinavir);

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N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-

phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-

3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*]]-N¹[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-

hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinoliny]carbonyl)amino]-butanediamide;

VX-478;

DMP-323;

DMP-450;

AG1343 (nelfinavir);

BMS 186,318;

SC-55389a;

BILA 1096 BS; and

U-140690,

or a pharmaceutically acceptable salt thereof.

11. The composition of Claim 9 wherein the HIV protease inhibiting compound is ritonavir, (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl

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butanoyl) amino-1,6diphenylhexane, indinavir, saquinavir, nelfinavir, or VX-478.

12. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

13. The composition of Claim 12 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

14. The composition of Claim 1 which comprises:

(a) ritonavir in the amount of from about 1% to about 30% by weight of the total solution;

(b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% by weight of the total solution and (2) ethanol in the amount of from about 3% to about 12% by weight of the total solution; and

(c) water in the amount of from about 0.4% to about 1.5% by weight of the total solution; and

(d) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution.

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15. The composition of Claim 14 which comprises:

(a) ritonavir in the amount of from about 5% to about 10% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in the amount of from about 70% to about 75% by weight of the total solution; and (2) ethanol in the amount of from about 3% about 12% by weight of the total solution;

(c) water in the amount of from about 0.4% to about 1.5% by weight of the total solution; and

(d) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

16. The composition of Claim 15 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1

PCT

(57) Abstract: Improved pharmaceutical compositions are provided comprising one or more solubilized HIV protease inhibiting compounds having improved solubility properties in a medium and/or long chain fatty acid, or mixtures thereof, a pharmaceutically acceptable alcohol, and water.

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are mono-unsaturated C₁₆-C₂₀ fatty acids which are liquids at room temperature. A most preferred fatty acid is oleic acid, with or without additional medium and/or long chain fatty acids in the mixture. One suitable source of said
5 oleic acid is Henkel Corporation.

The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquid at room temperature, for example ethanol, propylene glycol, 2-2(ethoxyethoxy)ethanol (Transcutol[®], Gattefosse, Westwood,
10 NJ), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, and the like, or mixtures thereof.

Preferred pharmaceutically acceptable solvents comprise (1) pharmaceutically acceptable medium and/or long
15 chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol or propylene glycol in the amount of from about 1% to about 15% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 3.5% by weight of the
20 total solution. More preferred pharmaceutically acceptable solvents comprise (1) a pharmaceutically acceptable medium and/or long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution and (2) ethanol or propylene glycol in the amount of from about 3%
25 to about 12% by weight of the total solution. Even more preferred pharmaceutically acceptable solvents comprise (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution and (2) ethanol or propylene glycol in the amount of from about 3% to about 12% by
30 weight of the total solution.

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In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) solubilized ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable medium and/or long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 1% to about 15% (preferably, from about 3% to about 12%) by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5% and (d) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% (preferably, from about 2.5% to about 10%) by weight of the total solution.

In a more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

An even more preferred composition of the invention is a solution comprising (a) solubilized ritonavir in the amount of from about 1 % to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) oleic

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In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) a combination of solubilized HIV protease inhibiting compounds which are ritonavir and ABT-378 in the amount of from about 1% to about 45% (preferably, from about 5% to about 45%) by weight of the total solution, and (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable medium and/or long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution and (2) propylene glycol in the amount of from about 1% to about 15% by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5% and (d) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% (preferably, from about 2.5% to about 10%) by weight of the total solution.

In a more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

An even more preferred composition of the invention is a solution comprising (a) a combination of solubilized HIV protease inhibiting compounds which are ritonavir and ABT-378 in the amount of from about 1% to about 45% (preferably, from about 5% to about 45%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of

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102CLAIMS

What is claimed is:

- 5 1. A pharmaceutical composition comprising:
- (a) a solubilized HIV protease inhibiting compound or
a combination of solubilized HIV protease
inhibiting compounds, or pharmaceutically
acceptable salts thereof;
- 10 (b) a pharmaceutically acceptable organic solvent
which comprises a medium and/or long chain fatty
acid or a mixture thereof, and propylene glycol;
- (c) water; and
- (d) optionally, a pharmaceutically acceptable
15 surfactant.
2. The composition according to Claim 1 wherein said
HIV protease inhibiting compound is (2S,3S,5S)-5-(N-(N-((N-
methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-
20 L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-
amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir).
3. The composition according to Claim 1 wherein said
combination of HIV protease inhibiting compounds is
25 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-
methyl)amino)carbonyl)-L-valinyl)amino-2-(N-
((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-
hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-
dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-
30 tetrahydropyrimid-2-onyl)-3-methyl-

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butanoyl) amino-1,6-diphenylhexane (ABT-378).

4. The composition according to Claim 1 wherein said HIV protease inhibiting compound or combination of HIV protease inhibiting compounds is selected from the group consisting of:
- (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl) amino) carbonyl)-L-valinyl) amino-2-(N-((5-thiazolyl) methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir);
- 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl) amino-1,6-diphenylhexane;
- N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
- N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginy] amino] butyl]- (4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
- 5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
- 1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl
- 1,3-thiazolidine-4-t-butylamide;
- 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

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[1S-[1R-(R-),2S*]]-N¹ [3-[[[(1,1 -
dimethylethyl) amino] carbonyl] (2-methylpropyl) amino]-2-
hydroxy-1 - (phenylmethyl) propyl]-2-[(2-
quinolinylcarbonyl) amino]-butanediamide;

5 VX-478;

DMP-323;

DMP-450;

AG1343 (nelfinavir);

BMS 186,318;

10 SC-55389a;

BILA 1096 BS; and

U-140690 (tipranavir),

or a pharmaceutically acceptable salt thereof.

15 5. The composition according to Claim 1 wherein said
medium and/or long chain fatty acid is oleic acid.

6. The composition according to Claim 1 wherein said
surfactant is Polyoxyl 35 castor oil (Cremophor EL®).

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7. The composition according to Claim 1 wherein the
solution is encapsulated into a hard gelatin capsule or a
soft gelatin capsule.

25 8. The composition of Claim 1 wherein the solvent
comprises (1) a pharmaceutically acceptable long chain
fatty acid in the amount of from about 40% to about 75% by
weight of the total solution; (2) propylene glycol in the
amount of from about 3% to about 12% by weight of the total

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solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

9. The composition of Claim 1 wherein the solvent
5 comprises (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution; (2) propylene glycol in the amount of from about 3% to about 12% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total
10 solution.

10. The composition of Claim 9 wherein the HIV protease inhibiting compound is selected from the group consisting of:

15 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-

20 hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)

amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;

N-(2(R)-hydroxy-1

25 (S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-iso

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- quinoline-3(S)-carboxamide (saquinavir);
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-
phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-
5 3-amino-2-hydroxy-4-butanoyl
1,3-thiazolidine-4-t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-
2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
[1S-[1R-(R-), 2S*]]-N¹ [3-[[[(1,1'-
10 dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-
hydroxy-1-(phenylmethyl)propyl]-2-[(2-
quinolinylcarbonyl)amino]-butanediamide;
VX-478;
DMP-323;
15 DMP-450;
AG1343 (nelfinavir);
BMS 186,318;
SC-55389a;
BILA 1096 BS; and
20 U-140690 (tipranavir),
or a pharmaceutically acceptable salt thereof.

11. The composition of Claim 9 wherein the HIV
protease inhibiting compound is ritonavir, (2S, 3S,
25 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-
hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl
butanoyl) amino-1,6diphenylhexane, indinavir, saquinavir,
nelfinavir, or VX-478.

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12. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

5 13. The composition of Claim 12 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

14. The composition of Claim 1 which comprises:

10 (a) ritonavir and ABT-378 in the amount of from about 1% to about 45% by weight of the total solution;

15 (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% by weight of the total solution and (2) propylene glycol in the amount of from about 1% to about 15% by weight of the total solution; and

20 (c) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

15. The composition of Claim 14 which comprises:

25 (a) ritonavir and ABT-378 in the amount of from about 1% to about 45% by weight of the total solution,

30 (b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in the amount of from about 70% to about 75% by weight of the total solution; and (2) propylene glycol in the amount of from about 1% about 8% by weight of the total solution; and

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(54) Title: SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR

(57) Abstract: A soft elastic capsule is described containing a pharmaceutical agent or a mixture of pharmaceutical agents. The soft elastic capsule is prepared from a fill composition and a shell composition that impart acceptable physical characteristics to the soft elastic capsule when in an equilibrium state. The pharmaceutical agents of the fill composition are also soluble when the soft elastic capsule is in the equilibrium state.

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In the current invention, a portion of the amount of alcohol present in the initial fill composition will migrate into the shell of the soft elastic capsule upon equilibrium of the fill components with the shell components. A substantially smaller portion, if any, of the amounts of the other components of the fill composition, for example, the pharmaceutical agents, the fatty acid, and the surfactant, will migrate into the shell upon equilibrium. Therefore, the ranges by percentage weight in the fill composition of the pharmaceutical agents, the fatty acid, and the surfactant, as described herein, sufficiently reflect the concentration of these components of the fill composition in both the initial state and the equilibrium state.

Included in this embodiment, the increased amount of alcohol in the initial fill composition is also sufficient to retain the solubility of the pharmaceutical agent or combination of pharmaceutical agents upon equilibration of the fill composition with the shell composition. The initial fill composition is also formulated to include an amount of alcohol, for example, propylene glycol, sufficient to solubilize the pharmaceutical agent or pharmaceutical agents, for example, HIV protease inhibitors, without the addition of heat. Preferably, the initial fill composition is prepared at temperatures that avoid the degradation of a HIV protease inhibitor, for example, ritonavir.

Included in this embodiment, the increased amount of alcohol in the fill composition is also sufficient to properly plasticize the shell of the soft elastic capsule upon equilibrium of the fill composition and the shell composition. The amount of plasticizing agent in the initial shell composition is not sufficient to provide proper plasticity to the shell if no additional plasticizing agent(s), for example, alcohol, migrates into the shell during equilibrium or is otherwise added. For example, a initial shell composition formulated to be underplasticized will produce a soft elastic capsule having a shell that is too brittle if no additional alcohol, for example, polypropylene glycol, migrates into the shell. In the current invention, the excess alcohol contained in the initial fill composition can contribute to the plasticity of the shell and can become a plasticizing agent in the shell upon equilibrium.

The alcohol of the fill composition can be propylene glycol, another suitable alcohol, or mixtures thereof. Suitable alcohols include, for example, ethanol, 2-2(ethoxyethoxy)ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, and polyethylene glycol 400. Preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the initial fill composition, as measured by weight, in a range

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WE CLAIM:

1. A soft elastic capsule having a fill and a shell, the fill comprising:
 - a pharmaceutical agent or combination of pharmaceutical agents,
 - an alcohol,
 - a fatty acid, andthe shell comprising:
 - gelatin, and
 - at least one plasticizing agent,wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition, and wherein said equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
2. The soft elastic capsule of claim 1 wherein the amount of alcohol present in said fill in initial state is in the range of 100-200% greater than the amount necessary to solubilize said pharmaceutical agent.
3. The soft elastic capsule of claim 1 wherein a portion in the range of 40-50% of the amount of alcohol present in said fill in initial state migrates into the shell upon equilibrium state.
4. The soft elastic capsule of claim 1 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
5. The soft elastic capsule of claim 4 wherein said HIV inhibiting compound is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-

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valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The soft elastic capsule of claim 4 wherein said combination of solubilized HIV inhibiting compounds is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir).
7. The soft elastic capsule of claim 4 wherein said solubilized HIV inhibiting compound or said combination of solubilized HIV inhibiting compounds is present in said fill in a range of 10–35% by weight.
8. The soft elastic capsule of claim 1 wherein said alcohol is propylene glycol or ethanol.
9. The soft elastic capsule of claim 8 wherein propylene glycol or ethanol are present in said fill in initial state in a range of 3–20% by weight.
10. The soft elastic capsule of claim 1 wherein said alcohol concentration in the fill decreases by not more than 20% after reaching said equilibrium state.
11. The soft elastic capsule of claim 10 wherein after reaching said equilibrium state said shell has acceptable physical characteristics.
12. The soft elastic capsule of claim 11 wherein the acceptable physical characteristics of said shell comprise
 - a hardness in the range of about 4.5 to about 9 Newtons,
 - a total weight of said capsule within 95% of initial weight of capsule and total weight of said fill within 85% of initial weight of said fill,
 - a moisture content of not more than 2% of said fill weight of said capsule,

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a disintegration time of not more than 30 minutes, and
an alcohol concentration of at least 40 mg per gram of said fill.

13. The soft elastic capsule of claim 1 wherein said fatty acid is oleic acid.
14. The soft elastic capsule of claim 13 wherein said oleic acid is present in said fill composition in initial state in the range of 50-80% by weight.
15. The soft elastic capsule of claim 1 wherein said fill further comprises a surfactant.
16. The soft elastic capsule of claim 15 wherein said surfactant is Polyoxyl 35 castor oil (Cremophor EL[®]).
17. The soft elastic capsule of claim 15 wherein said surfactant is present in the range of 0-10% by weight of the fill.
18. The soft elastic capsule of claim 1 wherein the gelatin in said capsule is present in the range of 30-60 % by weight of the shell.
19. The soft elastic capsule of claim 1 wherein the plasticizing agent is sorbitol, glycerin, macrogols, or AndrisorbTM.
20. The soft elastic capsule of claim 19 wherein the plasticizing agent is present in initial state in the range of 4-18% by weight of the shell.
21. The soft elastic capsule of claim 1 wherein the ratio of the weight percentage of gelatin to plasticizing agent at said equilibrium state is in the range of 2:1 to 4:1.
22. The soft elastic capsule of claim 1 wherein the fill in an initial state comprises:
is (2S, 3S, 5S)-5-(N-(N-(N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-

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2-(2,6 dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir) in the range of 10–35% by weight of the fill composition; polyethylene glycol in the range of 3–20% by weight of the fill composition; oleic acid in the range of 50–80% by weight of the fill; and wherein the shell in an initial state comprises: gelatin in the range of 30–60% by weight of the shell, and Andrisorb in the range of 4–18% by weight of the shell.

23. A method for making soft elastic capsules containing a pharmaceutical agent or a combination of pharmaceutical agents, the method comprising the steps of:
- preparing a fill composition wherein the fill composition comprises
 - a pharmaceutical agent or combination of pharmaceutical agents,
 - a fill alcohol, and
 - a fatty acid;
 - preparing a shell composition wherein the shell composition comprises
 - gelatin, and
 - at least one plasticizing compound;
 - forming an soft elastic capsule wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition; and
 - equilibrating said soft elastic capsule wherein equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
24. The method of claim 23 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
25. The method of claim 23 wherein said alcohol is propylene glycol or ethanol.

AA 3286877
ESTAMPADO
20 1H



ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----
En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
Identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 c/Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

13 AGO 2007
WILLY VALENZUELA
NOTARIO VENTINERO
Bogotá D.C.

4534
OCT 23

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3ª de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

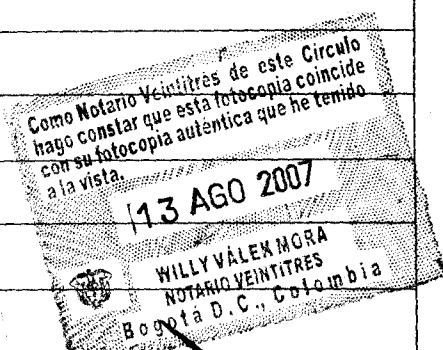
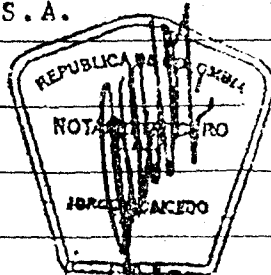
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

Se agregan comprobantes. Derechos \$30,000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m. Barberi

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 1

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CERTIFICA:

NOMBRE:TECNOQUIMICAS S A

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL :---C 23 7 39

DIRECCION NOTIFICACION JUDICIAL:---C 23 7 39

CIUDAD:CALI

MATRICULA MERCANTIL NRO. 7049-4 FECHA MATRICULA : 01 DE JULIO DE 1957

FILIADO

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS LIMITADA

CERTIFICA:

QUE POR ESCRITURA NRO. 8438 DEL 30 DE DICIEMBRE DE 1970 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE ENERO DE 1971 BAJO EL NRO. 42260 DEL LIBRO IX , LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) .

CERTIFICA:

QUE POR ESCRITURA NRO. 2139 DEL 21 DE ABRIL DE 1972 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE ABRIL DE 1972 BAJO EL NRO. 794 DEL LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) . POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C. A. .

*** CONTINUA ***

IMPRESO POR DANABANCO S.A. N° 462-1377-0-163-34809

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 2

CERTIFICA:

QUE POR ESCRITURA NRO. 3255 DEL 30 DE AGOSTO DE 1983 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE AGOSTO DE 1983 BAJO EL NRO. 62343 DEL LIBRO IX ,LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES EN SOCIEDAD AN?NIMA BAJO EL NOMBRE DE TECNOQUIMICAS S A .

CERTIFICA:

QUE POR ESCRITURA NRO. 5664 DEL 12 DE DICIEMBRE DE 2005 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 19 DE DICIEMBRE DE 2005 BAJO EL NRO. 14102 DEL LIBRO IX ,SE APROBO LA FUSION POR ABSORCION ENTRE (ABSORBENTE) TECNOQUIMICAS S.A. Y (ABSORBIDA (S)) DISTRIBUIDORA FARMACEUTICA CALOX COLOMBIANA S.A. - EN LIQUIDACION-, ORGANIZACION FARMACEUTICA AMERICANA S.A. OFA - EN LIQUIDACION- .

CERTIFICA:

REFORMAS DOCUMENTO INS LIBRO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
E.P. 4075 16922	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	
E.P. 5718 17242	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	
E.P. 5507 17529	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	
E.P. 3124 18365	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 3325 18366	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 5726 19258	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	
E.P. 2374 19368	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	
E.P. 2793 22616	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	
E.P. 2794 22617	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	
E.P. 6365 23489	30/12/1961	NOTARIA PRIMERA DE CALI	23/01/1962	
E.P. 1383 23850	21/03/1962	NOTARIA PRIMERA DE CALI	28/03/1962	
E.P. 3396 26016	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963	

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PAGINA No. 3

E.P. 8853	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964
27107			
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964
27181			
E.P. 2743	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27681			
E.P. 2744	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964
27682			
E.P. 7057	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964
28591			
E.P. 1693	26/04/1965	NOTARIA PRIMERA DE CALI	28/04/1965
29569			
E.P. 1799	10/05/1966	NOTARIA PRIMERA DE CALI	11/05/1966
31623			
E.P. 2498	18/11/1966	NOTARIA CUARTA DE CALI	25/11/1966
2757			
E.P. 2792	27/12/1966	NOTARIA CUARTA DE CALI	05/01/1967
33009			
E.P. 2209	25/09/1967	NOTARIA CUARTA DE CALI	04/10/1967
34591			
E.P. 6933	20/12/1967	NOTARIA SEGUNDA DE CALI	28/12/1967
35082			
E.P. 6363	14/11/1968	NOTARIA SEGUNDA DE CALI	26/11/1968
37141			
E.P. 7711	31/12/1968	NOTARIA SEGUNDA DE CALI	04/02/1969
37615			
E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI	18/10/1969
39341			
E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970
41379			
E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI	14/10/1971
44154			
E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI	10/11/1971
44367			
E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971
44716			
E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI	15/10/1973
5505 IX			
E.P. 8741	31/12/1973	NOTARIA SEGUNDA DE CALI	08/03/1974
7636 IX			
E.P. 9270	31/12/1974	NOTARIA SEGUNDA DE CALI	31/01/1975
11772 IX			
E.P. 9504	31/12/1974	NOTARIA SEGUNDA DE CALI	04/04/1975
12441 IX			
E.P. 7566	05/12/1975	NOTARIA SEGUNDA DE CALI	09/01/1976
15581 IX			
E.P. 2671	09/05/1980	NOTARIA SEGUNDA DE CALI	22/10/1980
41529 IX			

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PAGINA No. 4

E.P. 779	10/03/1982	NOTARIA DECIMA DE CALI	03/08/1982
54655 IX			
E.P. 4324	10/11/1982	NOTARIA DECIMA DE CALI	30/06/1983
61172 IX			
E.P. 1269	18/03/1986	NOTARIA DECIMA DE CALI	01/04/1986
83730 IX			
E.P. 5089	24/09/1986	NOTARIA DECIMA DE CALI	29/09/1986
87933 IX			
E.P. 7064	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987
2552 IX			
E.P. 7065	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987
2553 IX			
E.P. 5929	14/07/1989	NOTARIA DECIMA DE CALI	26/07/1989
20225 IX			
E.P. 8569	29/09/1989	NOTARIA DECIMA DE CALI	02/10/1989
22250 IX			
E.P. 10571	04/12/1992	NOTARIA DECIMA DE CALI	15/12/1992
60929 IX			
E.P. 10249	18/12/1995	NOTARIA DECIMA DE CALI	20/12/1995
10214 IX			
E.P. 2359	22/05/1997	NOTARIA TERCERA DE CALI	27/05/1997
3813 IX			
E.P. 2624	30/06/2000	NOTARIA TERCERA DE CALI	07/07/2000
4740 IX			
E.P. 3814	15/09/2000	NOTARIA TERCERA DE CALI	18/09/2000
6381 IX			
E.P. 3588	30/07/2004	NOTARIA TERCERA DE CALI	04/08/2004
8542 IX			
E.P. 2224	24/05/2006	NOTARIA TERCERA DE CALI	30/05/2006
6565 IX			

CERTIFICA:

VIGENCIA: 01 DE ENERO DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y

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PAGINA No. 5

COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS.D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO, INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION. PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSION DE LA SOCIEDAD, SU TRANSFORMACION, LA ENAJENACION O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCION O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACION MODIFICACION DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICION DE ACCIONES PROPIAS, CON SUJECION A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERES DE LA SOCIEDAD.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA

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ASESORIA CAMARA DE COMERCIO DE CALI

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02Z050814037

PAGINA No. 6

ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDR? ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDR? LAS SIGUIENTES FUNCIONES ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POL?TICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECON?MICA Y LABORAL; APROBAR PLANES DE INVERSI?N Y DE PRODUCCI?N; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCI?N Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEM?S ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACI?N Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACI?N QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CAR?CTER DE RESERVAS DE INVERSI?N, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RA?CES CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANT?A O SUPERIOR A CIEN MIL D?LARES AMERICANOS (\$US100.000.00). 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD LOS REPRESENTANTES LEGALES CUANDO SU CUANT?A SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A US\$300.000.00. L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPA??A A LA CELEBRACI?N DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M) SERVIR DE ?RGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPA??A.

LA ADMINISTRACI?N INMEDIATA DE LA COMPA??A, SU REPRESENTACI?N LEGAL Y LA GESTI?N DE LOS NEGOCIOS SOCIALES ESTAR?N A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN A?O, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODR?N ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPA??A CON EXCEPCI?N DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTAR?N SOMETIDOS EN EL DESEMPE?O DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACI?N INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACI?N LEGAL DE LA COMPA??A, LA GESTI?N COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCI?N ADMINISTRATIVA, LA COORDINACI?N Y LA SUPERVISI?N GENERAL DE LA EMPRESA, LAS CUALES CUMPLIR?N CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECI?N A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 7

COMO REPRESENTANTES LEGALES DE LA COMPA??A EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CAR?CTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACI?N DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSO ADMINISTRATIVAS EN QUE LA COMPA??A TENGA INTER?S E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CR?DITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PARAGRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACION Y SIN REQUERIR AUTORIZACION PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACION, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACION DE CUANTIA ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

DOCUMENTO: ACTA No. 393 DEL 20 DE ENERO DE 1993

ORIGEN: JUNTA DIRECTIVA

INSCRIPCION: 26 DE ENERO DE 1993 No. 62203 DEL LIBRO IX

FUE (RON) NOMBRADO (S) :

PRESIDENTE EJECUTIVO
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

VICEPRESIDENTE EJECUTIVO
JUAN MANUEL BARBERI OSPINA
C.C.14949561

VICEPRESIDENTE EJECUTIVO
JUAN BAUTISTA DE LOS RIOS GUTIERREZ

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 8

C.C.17108621

VICEPRESIDENTE EJECUTIVO
EMILIO SARDI APARICIO
C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 38 DEL 03 DE FEBRERO DE 1992
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 05 DE JUNIO DE 1992 No. 54016 DEL LIBRO IX

DOCUMENTO: ACTA No. 54 DEL 31 DE MARZO DE 2000
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 24 DE MAYO DE 2000 No. 3622 DEL LIBRO IX

DOCUMENTO: ACTA No. 65 DEL 27 DE JULIO DE 2006
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 04 DE AGOSTO DE 2006 No. 9191 DEL LIBRO IX

FUE(RO) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

SEGUNDO RENGLON
JUAN MANUEL BARBERI OSPINA
C.C.14949561

TERCER RENGLON
JUAN BAUTISTA DE LOS RIOS GUTIERREZ
C.C.17108621

CUARTO RENGLON
EMILIO SARDI APARICIO
C.C.14434582

QUINTO RENGLON
DIEGO HUMBERTO QUIJANO REISSNER

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02Z050814037

PAGINA No. 9

C.C.16615708

SUPLENTES

PRIMER RENGLON

GUSTAVO ADOLFO SANCHEZ LESMES

C.C.16625960

SEGUNDO RENGLON

VICTOR RICARDO ROSA GARCIA

C.C.6811102

TERCER RENGLON

ANTONIO JAIRO RAMIREZ ECHAVE

C.C.16741040

CUARTO RENGLON

ERNESTO TRUJILLO PEREZ

C.C.14984104

QUINTO RENGLON

ANA MARIA ALVAREZ

C.C.31170896

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARZO DE 2003

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL

DELOITTE & TOUCHE LTDA D & T LTDA

NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004

ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA

INSCRIPCION: 30 DE AGOSTO DE 2004 No. 9417 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 10

REVISOR FISCAL PRINCIPAL
LUIS FERNANDO QUICENO BENAVIDES
C.C.6106227

REVISOR FISCAL SUPLENTE
JESUS DARIO LOPEZ CASELLA
C.C.16789097

CERTIFICA:

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULIO DE 1996 NOTARIA DECIMA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULIO DE 1996 BAJO EL NRO. 144 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A CARLOS ALBERTO QUINTERO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO.

14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR.

B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 11

QUE POR ESCRITURA NRO. 2719 DEL 15 DE JULIO DE 1999 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE AGOSTO DE 1999 BAJO EL NRO. 323 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A SAMUEL GOMEZ UPEGUI, MAYOR DE EDAD, VECINO DE CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 16.633.490, GERENTE DEL DISTRITO DE VENTAS DEL OCCIDENTE COLOMBIANO DE LA SOCIEDAD, CON SEDE EN CALI, UBICADO EN LA CALLE 23 NRO. 4-66, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESA FACULTAD PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRAPROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

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Operacion : 022050814037

PAGINA No. 12

QUE POR ESCRITURA NRO. 2873 DEL 10 DE JULIO DE 2001 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 06 DE SEPTIEMBRE DE 2001 BAJO EL NRO. 213 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A MARIA TERESA CANON DE GUZMAN, IDENTIFICADA CON LA CEDULA DE CIUDADANIA NRO. 31.238.104 DE CALI, CARLOS ARTURO PENA NIETO IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.483.439 DE BOGOTA Y ANGELA MARIA CORREA CARDONA IDENTIFICADA CON LA CEDULA DE CIUDADANIA No.66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL Y EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A LA SOCIEDAD EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CREDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LAS CUENTAS CORRIENTES DE COMPENSACION, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRESTAMO EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICION DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS O DECLARACIONES QUE DEBAN HACERSE ANTE EL BANCO DE LA REPUBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO. LOS APODERADOS SUSCRIBIRAN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A TECNOQUIMICAS S. A. ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARACTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. LOS APODERADOS SE CENIRAN RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER NOTIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: 1o.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operation : 02Z050814037

PAGINA No. 13

LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORQUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTA A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS FORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTA A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 309 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 300
DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y
SUFICIENTE A DANIEL AMEZQUITA, MAYOR DE EDAD, VECINO DE BARRANQUILLA,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 14

IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 8.681.962 DE BARRANQUILLA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL DE LA ZONA ATLANTICA DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VENTILE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02Z050814037

PAGINA No. 15

PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 310 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 301 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A CARLOS ORLANDO MUTIS, MAYOR DE EDAD, VECINO DE BUCARAMANGA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 91.200.418 DE BUCARAMANGA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO, Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD

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BOGOTA, D.C. - BUCARAMANGA S.A. - 11/08/2007

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 16

SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 308 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE MARZO DE 2002 BAJO EL NRO. 318 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A HERNANDO ANGULO MOYANO, MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.322.139 DE BOGOTA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

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Operacion : 02Z050814037

PAGINA No. 17

RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAYO DE 1995 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTA A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS, PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL

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Fecha : 20070814

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Operacion : 02Z050814037

PAGINA No. 18

PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DICIEMBRE DE 2004 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE ENERO DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. EL APODERADO SE CE?IRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTIEMBRE DE 2005 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTUBRE DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SE?OR JUAN BAUTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

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Operacion : 02Z050814037

PAGINA No. 19

DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

EL PRESENTE PODER SE CONFIERE PARA QUE LOS APODERADOS ACTUEN ANTE CUALQUIER PERSONA O AUTORIDAD ADMINISTRATIVA DEL ORDEN NACIONAL, DEPARTAMENTAL, DISTRITAL Y LOCAL; ANTE LAS AUTORIDADES CONTENCIOSO ADMINISTRATIVAS Y JUDICIALES, PARA OBTENER LA PROTECCION DE NUESTRA PROPIEDAD INTELECTUAL Y CONTRA LAS PRACTICAS RESTRICTIVAS DE LA COMPETENCIA Y LOS ASUNTOS DE COMPETENCIA DESLEAL, A CUYO EFECTO LA AUTORIZO, EN TODO LO CONCERNIENTE A LOS SIGUIENTES ASUNTOS: A) OBTENCION DE PATENTES DE INVENCION, DE MODELO DE UTILIDAD, ESQUEMAS DE TRAZADOS DE CIRCUITOS INTEGRADOS, DISEÑOS INDUSTRIALES, EL REGISTRO DE MARCAS DE PRODUCTOS O SERVICIOS; LEMAS COMERCIALES; DEPOSITO DE NOMBRES Y ENSEÑAS COMERCIALES, INDICACIONES GEOGRAFICAS; RENOVACION DE SIGNOS DISTINTIVOS, RENOVACIONES, AFECTACIONES AL REGISTRO, INSCRIPCION DE CONTRATOS, SOLICITUD Y RENOVACION DE NOMBRES DE DOMINIO; B) PRESENTACION DE OPOSICIONES AL REGISTRO DE MARCAS DE TERCERO, PRESENTACION DE ALEGATOS EN DEFENSA DE OPOSICIONES AL REGISTRO, ACCION DE CANCELACION, ACCION POR INFRACCION DE DERECHOS, REVOCATORIA DIRECTA, ACCION DE NULIDAD, ACCION DE NULIDAD Y RESTABLECIMIENTO DEL DERECHO, ACCION REIVINDICATORIA, ACCIONES DE TUTELA, POPULARES, DE GRUPO, DE CLASE; ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; C) AGOTAMIENTO DE LA VIA GUBERNATIVA, EJERCICIO DEL DERECHO DE PETICION ANTE CUALQUIER PERSONA O AUTORIDAD; D) SOLICITUD DE MEDIDAS CAUTELARES, PRESENTACION DE ACCIONES MEDIANTE PROCESOS CIVILES, PENALES, ADMINISTRATIVOS O CONTENCIOSO ADMINISTRATIVOS RELACIONADOS CON ESTOS DERECHOS U OTROS DE DIFERENTE NATURALEZA, MEDIDAS EN FRONTERA, ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; E) OBTENER Y TRAMITAR TODO LO RELACIONADO CON EL RECONOCIMIENTO DE DERECHOS DE AUTOR, DERECHOS CONEXOS Y NUEVAS TECNOLOGIAS Y SU PROTECCION LEGAL; F) SOLICITUD DE REGISTRO Y RENOVACION DE CONTRATOS DE TRANSFERENCIA DE TECNOLOGIA; G) OBTENER Y TRAMITAR TODO LO RELACIONADO CON LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES. RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I)

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 20

SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR ESCRITURA NRO. 2065 DEL 15 DE MAYO DE 2006 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 30 DE MAYO DE 2006 BAJO EL NRO. 76 DEL LIBRO V , SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A PAULINA MARIA AGUDELO, MAYOR DE EDAD, VECINA DE MEDELLIN, IDENTIFICADA CON LA CEDULA CIUDADANIA NRO.43723508 DE ENVIGADO, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO, CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02Z050814037

PAGINA No. 21

DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

CAPITAL AUTORIZADO: \$27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: \$500
CAPITAL SUSCRITO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500
CAPITAL PAGADO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.158 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

CONTROLADA: INDUGRAFICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INDUGRAFICAS S.A. CORRESPONDEN AL DESARROLLO DE NEGOCIOS RELACIONADOS CON LAS ARTES GRAFICAS, LA DISTRIBUCION DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO

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COPIA PARA CAMARA DE COMERCIO DE CALI

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 22

EN EL INTERNACIONAL.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS E INDUGRAFICAS S.A. EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.159 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

CONTROLADA: TECNOFAR TQ S.A.
DOMICILIO: VILLA, RICA DEPARTAMENTO DEL CAUCA
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOFAR TQ S.A. CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PRODUCTOS VETERINARIOS Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR, PRODUCTOS DE ASEO PARA EL HOGAR Y LA FABRICACION Y DISTRIBUCION DE ENVASES PLASTICOS PARA TODO TIPO DE USO.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS Y TECNOFAR, EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE EL 27 DE MARZO DE 2001 BAJO EL NRO.1979 DEL LIBRO IX, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA MARZO 21 DE 2001, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR LA SOCIEDAD TECNOQUIMICAS S.A.

MATRIZ: TECNOQUIMICAS S.A.
DOMICILIO: SANTIAGO DE CALI.
NACIONALIDAD: COLOMBIANA

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

Hora Certificado 09:59:16

Operacion : 02Z050814037

PAGINA No. 24

RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI
UBICADO EN: --CARRETERA JAMUNDI KM. 23 DE JAMUNDI
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO
UBICADO EN: --CL. 15 NRO. 30 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO
FECHA MATRICULA : 14 DE ABRIL DE 2003
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE
MARZO DE 2007 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.
DADO EN CALI A LOS 14 DIAS DEL MES DE AGOSTO DEL A?O 2007 HORA: 09:41:53



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070814

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Operation : 02Z050814037

PAGINA No. 25

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO FISCAL DE CAJA : 07 - 65,183
FECHA : AGOSTO 13 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69811233	13/08/2007	512,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

103
225
131

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 64,378
FECHA : AGOSTO 10 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	62975047	10/08/2007	22,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69810796	09/08/2007	768,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69810797	09/08/2007	99,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69810798	09/08/2007	2,456,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69810801	09/08/2007	144,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	72,000.00
		31 PRORROGA DE TERMINOS	72,000.00
		TOTAL :	\$ 72,000.00

SON: SETENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.