



No. 11-165084- -00006-0000

Fecha: 2012-09-12 16:15:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 35

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

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

Número de expediente: 11 165.084

Solicitante: BOHERINGER INGELHEIM VETMEDICA, GMBH

Apoderado: CARLOS REINALDO OLARTE

Título de la Nueva Creación: SOLUCIÓN BEBIBLE FARMACÉUTICA DE TELMISARTAN

Gaceta: 647

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica
PROCAPS S.A.

Nombre o denominación /Razón social completa

WALTER TANAKA TATEKAWA

Nombre del representante legal

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

Número 890106527-5 _____

Dirección. CALLE 80 78B 201 _____ Ciudad BARRANQUILLA
Teléfono 055.3719900 Fax: _____ Correo electrónico _____

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

3. Datos del representante o apoderado:

MORENO BOHORQUEZ ELIANA ISAURA

51.975.664

83823

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

CRA 13 119-95 OFICINA 104

Dirección electrónica
negocios@optimum-co.com

No. Fax
(571)6121979

Número telefónico
(571)2131213

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

4. Fundamentos de la oposición

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

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

Prórroga:

SI

☐

NO

☐**5. Anexos**

- ☒ Comprobante de pago de la tasa.
- ☒ Poder, si fuera el caso.
- ☒ Fundamentos de la oposición. Se anexan 7 folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan 15 folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

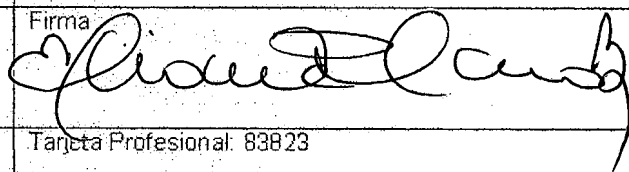
6. Firma

Nombre del Firmante

ELIANA ISaura MORENO BOHORQUEZ

CC. 51.975.664

Firma



Tarjeta Profesional: 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO NIT : 800.176.089-2 - / -					
 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA			No. 12 - 0093734	
				Bogotá D.C., Septiembre 12 de 2012 - 14:47:30	
RECIBIDO DE : PROCAPS S.A.				NI 890.106.527	
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	144688353	29/08/2012	3.780.000.00
*** Conceptos Pagados ***					
CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO	
1 50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	315.000.00	315.000.00	
				\$315.000.00	
			=====		
SON: **TRESCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***					
Responsable: _____					
Recibo de Caja Aplicado al Expediente No. _____					
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  No. 11-165084- -00006-0000 Fecha: 2012-09-12 16:15:32 Dep. 2020 DIR.NUEVASCR Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI Act. 400 OPOSIOBSERVTER Folios: 35					
Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia					
Web: www.slc.gov.co e-mal: Info@slc.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240					
, Septiembre 12 de 2012 - 14:47:31					

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

Referencia : Expediente N° 11 165084
Asunto : Oposición a la solicitud de patente de Invención titulada
"SOLUCIÓN BEBIBLE FARMACÉUTICA DE
TELMISARTAN"
Solicitante : BOHERINGER INGELHEIM VETMEDICA, GMBH.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 647 del 29 de junio de 2012

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**SOLUCIÓN BEBIBLE FARMACÉUTICA DE TELMISARTAN**", cuyo titular es **BOHERINGER INGELHEIM VETMEDICA, GMBH.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **TELMISARTAN**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 30 de noviembre de 2011, reivindicando prioridad bajo la solicitud EP20090160771 del 2009-05-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 647 del 29 de junio de 2012, cuya publicación internacional corresponde a la WO2010133638 del 2010-11-25.
- 2.2. La solicitud colombiana 11 165084 objeto de la presente oposición, se refiere a una solución farmacéutica, de preferencia una solución bebible farmacéutica del principio activo Telmisartan con un valor del pH mayor que 10 que contiene, adicionalmente, uno o más azúcar-alcoholes añadidos para mejorar el sabor y la

conservabilidad, en donde los azúcar-alcoholes o la solución farmacéutica presentan una proporción máxima de 1000 ppm en azúcares reductores.

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

- D1: US2007026026 publicada el 01 de febrero de 2007.

2.4. Ahora bien, el documento D1 está dirigido a la mejora de composiciones orales líquidas que incluyen losartan, o una sal farmacéuticamente aceptable o metabolito del mismo, y al menos un vehículo farmacéuticamente aceptable en una cantidad suficiente para proporcionar un pH de aproximadamente 6 o superior. Procesos para preparar tales composiciones y métodos de administración de tales composiciones se incluyen también. De forma particular el documento D1 da a conocer una solución que contiene losartán potásico (concentración: contiene 25mg/ml), un antagonista de receptor de angiotensina II, y xilitol a un pH de aproximadamente 7-10. Como una alternativa al manitol o sorbitol, xilitol puede ser utilizado.

2.5. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 165084 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con el mas importante de los tres requisitos necesarios para su protección, La Novedad.

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

2.7. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 20 de mayo de 2009 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, una solución farmacéutica, de preferencia una solución bebible farmacéutica del principio activo Telmisartan con un valor del pH mayor que 10 que contiene, adicionalmente, uno o más azúcar-alcoholes añadidos para mejorar el sabor y la conservabilidad, en donde los azúcar-alcoholes o la solución farmacéutica presentan una proporción máxima de 1000 ppm en azúcares reductores; sobre lo cual busca protección en el capítulo reivindicatorio.

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

industrial.”. La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

- 2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada “*SOLUCIÓN BEBIBLE FARMACÉUTICA DE TELMISARTAN*”, cuyo titular es **BOHERINGER INGELHEIM VETMEDICA, GMBH.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 647 del 29 de junio de 2012.

3. PRUEBAS

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

- D1: US2007026026 publicada el 01 de febrero de 2007.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

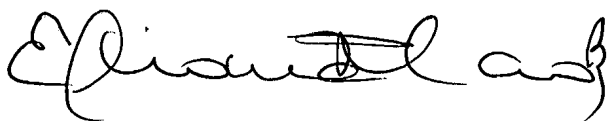
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US2007026026 publicada el 01 de febrero de 2007.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor director,



ELIANA ISAURA MORENO BOHORQUEZ.

C.C. 51'975.664 de Bogotá

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

ANEXO 1



US 20070026026A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0026026 A1**
Delmarre et al. (43) **Pub. Date: Feb. 1, 2007**(54) **ORAL LIQUID LOSARTAN COMPOSITIONS****Related U.S. Application Data**(76) **Inventors:** **David Delmarre**, Vernon Hills, IL (US); **Naga Mallika Surapaneni**, Mundelein, IL (US); **Carlos-Jullan Sison Centeno**, Chicago, IL (US); **Meagan Erica Weldele**, Overland Parks, KS (US); **Danchen Gao**, Chicago, IL (US)

(60) Provisional application No. 60/703,866, filed on Aug. 1, 2005.

Publication Classification(51) **Int. Cl.**
A61K 31/4184 (2007.01)
A61K 9/00 (2006.01)
(52) **U.S. Cl.** **424/400; 514/381****Correspondence Address:**
WINSTON & STRAWN LLP
PATENT DEPARTMENT
1700 K STREET, N.W.
WASHINGTON, DC 20006 (US)(57) **ABSTRACT**

The present invention is directed to improved oral liquid compositions that include losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher. Processes of preparing such compositions and methods of administering such compositions are also included.

(21) **Appl. No.:** **11/493,801**(22) **Filed:** **Jul. 27, 2006**

ORAL LIQUID LOSARTAN COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional application No. 60/703,866, filed Aug. 1, 2005, the entire contents of which is incorporated herein by express reference thereto.

TECHNICAL FIELD

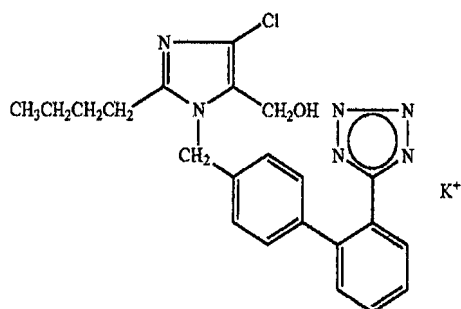
[0002] The present invention relates generally to oral liquid losartan compositions and processes for their preparation. The invention further relates to methods of treatment by administering the compositions.

BACKGROUND OF THE INVENTION

[0003] Losartan potassium, a pharmaceutically acceptable salt of losartan, is a white to off-white free flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, slightly soluble in common organic solvents, such as acetonitrile and methyl-ethyl ketone, and practically insoluble in chloroform. The melting point of losartan potassium is between 270° C. to 276° C. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

[0004] Losartan potassium, the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist. Angiotensin II, which is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase II), is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex.

[0005] Losartan potassium is also known as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C₂₂H₂₂ClKN₆O and it has the following structural formula:



[0006] Losartan is an active agent provided in solid oral dose forms that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6 to 9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not

[0007] Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues, but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

[0008] Following oral administration, the systemic bioavailability of losartan is approximately 33 percent. About 14 percent of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max}, but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10 percent decreased).

[0009] Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following solid oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1 percent of the dose compared to 14 percent of the dose in normal subjects) was seen in about 1 percent of individuals studied.

[0010] Losartan potassium is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. The usual starting dose of losartan potassium is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) and patients with a history of hepatic impairment. Losartan potassium can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

[0011] If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. If blood pressure is not controlled by losartan potassium alone, a low dose of a diuretic may be added.

[0012] U.S. Pat. No. 5,138,069 describes and claims a generic active compound that encompasses losartan. The '069 patent describes the active compound as a useful angiotensin II blocker, and its activity in treating hypertension and congestive heart failure. The '069 patent alleges that active ingredient formulations can be administered

dosage forms for oral administration, and that dosage forms can contain coloring and flavoring to increase patient acceptance.

[0013] The '069 patent, related U.S. Pat. Nos. 5,153,197 and 5,210,079, and unrelated U.S. Pat. No. 5,608,075, each specifically describe the formulation of the active ingredient into capsules, tablets, injectable solutions, and suspensions. An aqueous suspension of the active ingredient is prepared so that each 5 mL contains 100 mg of the active ingredient, 100 mg of sodium carboxymethylcellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

[0014] The '197 patent noted above claims methods of treating hypertension by administering losartan and pharmaceutical compositions comprising a pharmaceutically acceptable carrier, a diuretic and losartan. The '079 patent noted above discloses the use of losartan for treating chronic renal failure. The '075 patent noted above discloses distinct crystalline structures, or forms, of losartan potassium which were designated Form I and Form II based on their respective thermal stability. Form I is a low-temperature stable form, and Form II is a high temperature stable form. Form I has been shown to be the more thermodynamically stable polymorph at room temperature.

[0015] U.S. Pat. No. 5,266,583 discloses and claims a metabolite of losartan. The metabolite may be utilized in compositions such as tablets, capsules, or elixirs for oral administration. A syrup or elixir may contain the metabolite, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye, and a flavoring such as cherry or orange flavor.

[0016] In 1995, losartan became the first nonpeptide AT₁ antagonist approved by the U.S. Food and Drug Administration for clinical use. In particular, losartan is approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Losartan may be administered orally as its mono-potassium salt. Losartan potassium is available by prescription in tablet form as a sole active ingredient (CozaarTM, Merck) and as a co-active ingredient with hydrochlorothiazide (HyzaarTM, Merck). CozaarTM is available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

[0017] International Publication No. WO 03/035039 describes methods of treatment for hypertension and other disease states by delivering losartan in a gastric retained dosage form. The dosage form is preferably a tablet or capsule. The '039 publication, however, also describes liquid preparations of losartan. The liquid preparations may be prepared in the form of syrups or suspensions and contain about 0.2-20 weight percent of the active agent, with the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colorant agents, flavoring agents, saccharin and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable

[0018] International Publication No. WO 03/048135 relates to amorphous losartan potassium, losartan potassium in a crystalline form that is a hydrate, crystalline losartan potassium Form IV and solvates thereof, and crystalline losartan potassium Form V and solvates thereof. Liquid pharmaceutical compositions of losartan can include losartan dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin. The compositions can also contain emulsifying agents, viscosity-enhancing agents, sweetening agents, preservatives and chelating agents, and buffers. Capsules or tablets are the preferred oral dosage form.

[0019] Because of the ease of preparing solid dosage forms, tablets and capsules are often the preferred dosage form for many drugs including losartan. Indeed, the only FDA approved losartan products are in solid form, i.e., as tablets. Liquid dosage forms present more of a challenge because of the solubility and stability characteristics of the active compound, as well as the various excipients, in different solvents. In view of the foregoing, it would be desirable to have suitable oral liquid losartan compositions with improved dissolution and stability properties as an additional treatment option.

SUMMARY OF THE INVENTION

[0020] The present invention relates to an oral liquid composition that includes losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher. In one preferred embodiment, the pH is about 7 to 10. In a more preferred embodiment, the pH is about 7.4 to 8.6.

[0021] Typically, the at least one pharmaceutically acceptable carrier includes one or more of a wetting agent, surfactant component, stabilizing agent, solubilizing agent, thickening agent, sweetening agent, flavoring agent, perfuming agent, colorant agent, preservative agent, or buffering agent. Preferably, the carrier includes one or more of a solubilizing agent, a stabilizing agent, a sweetening agent, a flavoring agent, or a buffering agent.

[0022] The amounts of the components in the composition can vary. In one embodiment, the solubilizing agent is present in an amount of about 1 percent to 50 percent (v/v). Preferably, the sweetening agent is present in an amount of about 0.05 percent to 5 percent (w/v) or the buffering agent is present in an amount of about 30 percent to 70 percent (v/v).

[0023] More preferably, the carrier includes a glycol or glycerin, the sweetening agent includes a sucralose or saccharin-containing component, and the buffering agent includes a phosphate-containing buffer. In another preferred embodiment, the carrier further includes a flavoring agent, which preferably includes a fruit flavor. The fruit flavor may preferably include grapefruit, orange, lemon, lime, mango, strawberry, pineapple, cherry, or a combination thereof. Generally, the glycol is present in an amount of about 1 percent to 40 percent (v/v), and the glycerin is present in an amount of about 5 percent to 50 percent (v/v). In one embodiment, the phosphate-containing buffer includes sodium phosphate, potassium phosphate, or mixtures thereof. The concentration of phosphate salt in the buffering

embodiment, the phosphate salt concentration is about 80 mM to 120 mM. The losartan, or salt or metabolite thereof, is typically present in an amount of about 1 to 50 mg/mL of the composition.

[0024] In a preferred embodiment, the losartan, or salt or metabolite thereof, is present in an amount of about 8 mg/mL to 20 mg/mL of the composition, and the pharmaceutically acceptable carrier includes a glycol present in an amount of about 5 percent to 25 percent (v/v), glycerin present in an amount of about 20 percent to 40 percent (v/v), a sweetening agent present in an amount of about 0.5 percent to 2 percent (w/v), and a buffering agent present in an amount of about 40 percent to 60 percent (v/v).

[0025] Advantageously, the composition is at least substantially stable. In one embodiment, the degradation of losartan over a period of less than two months is no more than about 1 percent to 2 percent (w/w) at 50° C. In a preferred embodiment, the liquid compositions are substantially stable.

[0026] In an exemplary embodiment, the composition is in solution form.

[0027] The present invention further relates to an oral liquid composition that includes losartan, or a pharmaceutically acceptable salt or metabolite thereof, at least one of propylene glycol or glycerin, along with a sucralose or saccharin-containing component and a phosphate-containing buffer that includes sodium phosphate, potassium phosphate, or a mixture thereof, in an amount sufficient to provide a pH of about 6 or higher.

[0028] The present invention also encompasses stable oral liquid losartan compositions that include losartan or a pharmaceutically acceptable salt or metabolite thereof, a solubilizing agent, a sweetening agent, and a buffering agent, present in an amount sufficient to provide a pH of about 6 or higher over an extended period of time to minimize degradation of the losartan component.

[0029] The present invention additionally includes oral liquid compositions that include solutions of losartan, or a pharmaceutically acceptable salt or metabolite thereof, propylene glycol, glycerin, saccharin sodium, and potassium phosphate buffer, each in an amount sufficient to provide a pH of about 6 or higher.

[0030] The present invention also relates to a method of preparing an oral liquid losartan composition. The method includes dissolving an amount of losartan, or a pharmaceutically acceptable salt or metabolite thereof, into at least one liquid adjuvant to form a liquid losartan solution, and combining the liquid losartan solution with one or more additional pharmaceutically acceptable carriers sufficient to provide a pH of about 6 or higher to form the oral liquid losartan composition. Preferably, the at least one liquid adjuvant includes a buffering agent. The oral liquid losartan composition is typically a clear solution.

[0031] Furthermore, the present invention relates to a method of preventing, treating, or managing hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction in a mammal. The method includes administering to the mammal an effective amount of an oral liquid losartan composition that includes losartan, or a pharmaceutically

maceutically acceptable carrier, wherein the oral liquid losartan composition has a pH of about 6 or higher.

[0032] In one embodiment, the composition is administered once or twice a day. In another embodiment, the total daily dose of losartan is from about 25 mg to 100 mg.

[0033] The method preferably also includes administering at least one other therapeutic agent in association with the losartan. The other therapeutic agent(s) typically include another hypertensive agent. The at least one other hypertensive agent generally includes an angiotensin II antagonist, angiotensin converting enzyme inhibitor, or a neutral endopeptidase/angiotensin converting enzyme inhibitor, or a combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Further features and advantages of the invention can be ascertained from the detailed description that is provided below in connection with the following drawing(s):

[0035] FIG. 1 is a graph showing the solubility profile of losartan as a function of pH;

[0036] FIG. 2 is a graph showing the stability (measured by percent active) of losartan with different buffers at different times;

[0037] FIG. 3 is a graph showing the effect of different concentrations of propylene glycol on the stability of losartan;

[0038] FIG. 4 is a graph showing the stability of losartan (measured by percent active) with different excipient combinations as a function of time;

[0039] FIG. 5 is a graph showing the stability of losartan (measured by percent active) in solutions of propylene glycol, glycerin, and xylitol;

[0040] FIG. 6 is a graph showing the stability of losartan (measured by percent active) with different concentrations of glycerin and at different pHs; and

[0041] FIG. 7 is a graph showing the percent recovery of losartan at different temperatures in different containers.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0042] The present invention provides oral liquid compositions that include losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher. As used herein, "oral liquid composition(s)" include emulsions, solutions, suspensions, syrups and elixirs, but do not include solid dosage forms that include minor amounts of liquids therein, such as capsules or tablets. Preferably, "oral liquid composition(s)" mean losartan, or a pharmaceutically acceptable salt or metabolite thereof, in solution.

[0043] The present liquid dosage forms provide certain advantages over the solid forms conventionally available. For example, liquid dosage forms are much easier to swallow and typically do not require separate water to administer. Patient compliance is also easier to facilitate with the

liquid dosage forms. This is often an issue with very young patients and the elderly. Because the elderly are more likely to suffer from hypertension or high blood pressure than other members of the population, it would be particularly beneficial to have an antihypertensive drug in a palatable oral composition that can help increase patient compliance.

[0044] The active ingredient in the present invention is losartan. Losartan is preferably used in the form of a pharmaceutically acceptable salt or metabolite that retains the biological effectiveness and properties of losartan and is not biologically or otherwise undesirable. As used herein, "losartan" includes the agent itself, as well as its pharmaceutically acceptable salts or an active metabolite.

[0045] The term "pharmaceutically acceptable salt(s)" or "a pharmaceutically acceptable salt thereof" refers to salt(s) prepared from pharmaceutically acceptable non-toxic acid or bases including inorganic acids and bases and organic acids or bases. The pharmaceutically acceptable salts used in the present invention may be amphoteric, may be present in the form of internal salts, or both.

[0046] Losartan may form acid addition salts and salts with bases. Exemplary acids that can be used to form such salts include one or more mineral acids such as hydrochloric, hydrobromic, sulfuric or phosphoric acid or organic acids such as organic sulfonic acids and organic carboxylic acids. Salts formed with inorganic bases include, for example, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts, or any combination thereof. Salts derived from organic bases include, for example, one or more salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethyl aminoethanol, trimethylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, fumarate, maleate, succinate, acetate and oxalate.

[0047] A particularly suitable pharmaceutically acceptable salt is losartan potassium ($C_{22}H_{22}ClKN_6O$), which is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl)-phenyl]benzyl]imidazole-5-methanol monopotassium salt.

[0048] Losartan potassium can be prepared by any suitable method available to one of ordinary skill in the art. For instance, in Example 316, Part D of U.S. Pat. Nos. 5,128,355, 5,138,069 and 5,155,118, each of which are incorporated herein by express reference thereto, losartan is isolated as its potassium salt by crystallization from a mixture of isopropyl alcohol and heptane. The crystals were reported to have a melting point above 250° C.

[0049] Another suitable method of preparing a losartan salt is described in Example 5 of U.S. Pat. No. 5,962,500, and in Example 21 of U.S. Pat. Nos. 5,206,374 and 5,310,928, each of which are incorporated herein by express reference thereto. Losartan potassium salt was generated from a solution of losartan by extracting losartan from the solution with an adsorbent, treating the adsorbent with monobasic potassium phosphate and eluting losartan potassium from the adsorbent with 20 percent aqueous THF. The eluent was then concentrated and diluted with isopropyl alcohol, which yielded crystalline losartan potassium. The losartan potassium product was also obtained by spray

[0050] Yet another suitable method of preparing a losartan salt is described in Example 8 of U.S. Pat. Nos. 5,130,439, 5,206,374 and 5,310,928, each of which are incorporated herein by express reference thereto. Losartan potassium salt was crystallized from a mixture of isopropyl alcohol, water and heptane. The product was collected by filtration, rinsed with heptane and dried at 50° C. in a vacuum oven to yield a white solid that decomposed at 267° C. to 269° C.

[0051] It has now been discovered that the pH of an oral liquid losartan composition should be typically about 6 or higher to provide the surprisingly and unexpectedly improved solubility and stability of losartan in solution achieved by the present invention. In one embodiment, the pH is preferably at least about 7. Preferably, the pH is about 7 to 10 or 7.4 to 10, more preferably about 7.8 to 8.6. An exemplary pH is about 8.2. The pH of the oral liquid composition is preferably adjusted by at least one buffering agent.

[0052] The compositions are formed with a pharmaceutically acceptable carrier that preferably includes a pH modifier, such as a buffering agent, to facilitate obtaining a pH of about 6 or more. The compositions of the invention preferably further include one or more wetting agents or surfactants, stabilizing agents, thickening agents, sweetening agents, flavoring agents, perfuming agents, colorant agents, preservative agent, solubilizing agents, isotonicizing agents, antioxidant components, and chelating agents. In the case of each of these pharmaceutically acceptable carriers, any suitable type or amount of carrier available to those of ordinary skill in the art may be included according to the invention so long as it does not preclude the losartan from remaining in solution. Therefore, one or more of these carriers can also act as a solvent for losartan. Losartan may be dissolved or suspended in a solvent such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin. Suitable vegetable oils include, e.g., sesame oil, corn oil, olive oil, cottonseed oil, or a mixture thereof.

[0053] A wetting agent or surfactant component that can be included in the liquid compositions of the present invention, when used, include one or more quaternary ammonium compounds, such as benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride; TPGS, dioctyl sodium sulfosuccinate; polyoxyethylene alkylphenyl ethers, such as nonoxynol 9, nonoxynol 10, and octoxynol 9; poloxamers (polyoxyethylene and polyoxypropylene block copolymers); polyoxyethylene fatty acid glycerides and oils, such as polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™, Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, such as polyoxyethylene (20) cetostearyl ether; polyoxyethylene fatty acid esters, such as polyoxyethylene (40) stearate; polyoxyethylene sorbitan esters, such as polysorbate 20 and polysorbate 80 (e.g., Tween™ 80, ICI); propylene glycol fatty acid esters, such as propylene glycol laureate (e.g., Lauroglycol™, Gattefosse); sodium lauryl sulfate; fatty acids and salts thereof, such as oleic acid, sodium oleate and triethanolamine oleate; glyceryl fatty acid esters, for example glyceryl monostearate; sorbitan esters, such as sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; tyloxapol; lecithin; stearyl triethanolamine; laurylaminopropionic acid; and mixtures thereof. Such sur-

together form about 0.25 weight percent to about 15 weight percent, preferably about 0.4 weight percent to about 10 weight percent, and more preferably about 0.5 weight percent to about 5 weight percent, of the total weight of the composition.

[0054] A thickening agent or viscosity-enhancing agent can be included to generally improve the mouth-feel of the composition and/or to help coat the lining of the gastrointestinal tract. While any suitable thickening agent can be included in the compositions of the present invention, a preferred thickening agent, when used, includes one or more of acacia, alginic acid bentonite, carbomer, carboxymethyl-cellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, glycerin, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum. Such a thickening agent, if present, will typically form about 0.1 weight percent to 20 weight percent, preferably about 0.3 weight percent to about 15 weight percent, and more preferably about 0.5 weight percent to 4 weight percent, of the total weight of the composition.

[0055] A sweetening agent, such as one or more of sorbitol, saccharin, sucralose, sodium saccharin, xylitol, sucrose, aspartame, fructose, neotame, sodium saccharate, glycyrrhizin dipotassium, acesulfame K, mannitol, propylene glycol, invert sugar, and mixtures thereof, can be added to modify the taste of the composition. Alternatively or in addition, a viscous sweetener such as one or more of a sorbitol solution, syrup (sucrose solution) glycerin, or high-fructose corn syrup can be used and, in addition to sweetening effects, can also be useful to increase viscosity and to retard sedimentation. Preferably, the sweetening agent includes a saccharin, more preferably sodium saccharin. Such a sweetening agent, if present, will typically be present in an amount sufficient to mask the bitterness of the losartan, or salt or metabolite thereof, and preferably to also mask any other off-flavor components included in the formulation. Typical amounts of sweetening agent include about 0.05 weight percent to about 10 weight percent, preferably about 0.1 weight percent to about 5 weight percent, more preferably about 0.5 weight percent to 2 weight percent, of the total weight of the composition.

[0056] A flavoring agent can enhance patient compliance by making the composition more palatable, particularly in the case of the imbibable compositions of the present invention. The flavoring agent is typically selected in type and amount to decrease or eliminate any bitter taste, i.e., a taste mask, that would otherwise be detectable by the patient to whom the compositions are administered. Examples of a suitable flavoring agent, when used, includes one or more of aspartame, saccharin, menthol, peppermint, anise, and any fruit flavor, such as one or more of grapefruit, orange, lemon, lime, mango, strawberry, pineapple, or cherry; or a combination thereof. A flavoring agent including grapefruit has been found to work especially well according to the invention. The flavoring agent, if present, will typically form about 0.01 weight percent to about 15 weight percent, preferably about 0.5 weight percent to about 10 weight percent, and more preferably about 0.1 weight percent to about 5 weight percent, of the total weight of the composition.

[0057] A colorant agent, when included, can provide the compositions with a more aesthetic and/or distinctive appearance. Colorant agents suitable for inclusion in the present invention include one or more water-soluble synthetic organic food additives (e.g., food dyes such as food red dye Nos. 2 and 3, food yellow dye Nos. 4 and 5 and food blue dye Nos. 1 and 2), water-insoluble lake dyes (e.g., aluminum salts of the above water-soluble synthetic organic food additives, etc.), and natural pigments (e.g., beta-carotene, chlorophyll, iron oxide red, etc.). Suitable colorants include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6. Such a colorant agent, if present, will typically form about 0.001 weight percent to about 1 weight percent, preferably about 0.005 weight percent to about 0.5 weight percent, and more preferably about 0.0075 weight percent to about 0.25 weight percent, of the total weight of the composition.

[0058] Examples of a suitable preservative component, when used, includes sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, ethylenediamine tetraacetic acid, paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenylethylalcohol, dehydroacetic acid, sorbic acid, benzalkonium chloride, benzethonium chloride, phenol, phenylmercuric nitrate, thimerosal, and mixtures thereof. A preservative can be added to the compositions at levels safe for ingestion to improve storage stability. A preservative component, if present, will typically form about 0.01 weight percent to about 5 weight percent, preferably about 0.05 weight percent to about 3 weight percent, and more preferably about 0.1 weight percent to about 2 weight percent, of the total weight of the composition.

[0059] The buffering agent preferably included in the liquid compositions can include a buffer solution of one or more gluconate, lactate, citrate, acetate, phosphate, and/or carbonate salts. In addition to providing the about 6 pH or greater, the buffering agent can also modulate drug solubility. Preferably, the buffering agent includes a phosphate, more preferably a potassium phosphate or sodium phosphate buffering agent. Such a buffering agent, if present, will typically form about 10 weight percent to about 80 weight percent, preferably about 30 weight percent to about 70 weight percent, and more preferably about 40 weight percent to about 60 weight percent, of the total weight of the composition.

[0060] Solubilizing and emulsifying agents are used to facilitate more uniform dispersion of an active ingredient or other excipient that is not generally soluble in the liquid carrier. Examples of a suitable emulsifying agent, if used, includes, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, cetyl alcohol, and mixtures thereof. Examples of a suitable solubilizing agent include glycol, glycerin, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate, and mixtures thereof. Preferably, the solubilizing agent includes a glycol. Preferred glycols include polyethylene glycol or propylene glycol, or both. The glycol can also act as a stabilizing agent. The solubilizing or emulsifying agent is/are generally present in an amount sufficient to dissolve or disperse the losartan, or salt or metabolite thereof, in the carrier. Typical amounts are from about 1

20 weight percent to about 65 weight percent, and more preferably about 25 weight percent to about 55 weight percent, of the total weight of the composition.

[0061] A suitable isotonicizing agent, if used, includes sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose, and mixtures thereof. A suitable amount of the isotonicizing agent, when included, is typically about 0.01 weight percent to about 5 weight percent, more preferably about 0.3 weight percent to about 4 weight percent, and more preferably about 0.5 weight percent to about 3 weight percent, of the total weight of the composition.

[0062] Examples of a suitable antioxidant component, if used, include one or more sulfites, tocopherol, vitamin E, and mixtures thereof. The antioxidant component provides long term stability to the liquid compositions. Addition of an antioxidant component can help enhance and ensure the stability of the compositions at ambient conditions for at least 18 to 24 months. A suitable amount of the antioxidant component, if present, is about 0.01 weight percent to about 3 weight percent, preferably about 0.05 weight percent to about 2 weight percent, and more preferably about 0.25 weight percent to about 1 weight percent, of the total weight of the composition.

[0063] Chelating agents can be added to trap metals that find their way into the compositions during processing. Suitable chelating agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), ethylenediamine (EDA), diethylenetriamine (DETA), aminoethylethanolamine (AEEA), and mixtures thereof. The chelating agent can be present in an amount of about 0.01 weight percent to about 3 weight percent, preferably about 0.05 weight percent to about 2 weight percent, and more preferably about 0.25 weight percent to about 1 weight percent, of the total weight of the composition.

[0064] Through selection and combination of excipients according to the invention, liquid losartan compositions can be provided that exhibit improved or more desired performance with respect to drug concentration, dissolution, dispersion, stability, safety, emulsification, efficacy, flavor, patient compliance, and/or other pharmacokinetic, chemical and/or physical properties. It has now been further discovered that a carrier that includes one or more of a solubilizing agent, or a sweetening agent, along with a buffering agent, is particularly advantageous in an oral liquid losartan composition. Preferably, two or more of the solubilizing agent, sweetening agent, or buffering agent will be included. In one more preferred embodiment, the solubilizing agent, sweetening agent, and buffering agent are all included along with the losartan, or salt or metabolite thereof.

[0065] The glycol, when used, may be any pharmaceutically acceptable glycol such as ethylene glycol, propylene glycol, polyethylene glycol, polypropylene glycol, and mixtures thereof. In a preferred embodiment, the glycol includes propylene glycol. In one embodiment, the sweetening agent typically includes a saccharin-containing component, and the buffering agent typically includes a phosphate-containing buffer.

[0066] The phosphate-containing buffer typically includes sodium phosphate, potassium phosphate, or mixtures thereof. As used herein, "sodium phosphate" and "potassium

salt including sodium dihydrogen phosphate monohydrate or sodium biphosphate, sodium monohydrogen phosphate heptahydrate or dibasic sodium phosphate, sodium monohydrogen phosphate dodecahydrate, potassium dihydrogen phosphate or potassium phosphate, and potassium monohydrogen phosphate, and any combination thereof. The concentration of phosphate salt in the buffering agent is typically from about 5 mM to 150 mM, preferably from about 50 mM to 120 mM, and more preferably is about 75 mM to 110 mM. An exemplary concentration of phosphate salt is 100 mM.

[0067] To provide a therapeutically or prophylactically effective amount of the active ingredient, losartan is generally present in an amount of about 1 to 50 mg/mL of the composition. The phrase "therapeutically effective amount" means that amount of losartan that provides a therapeutic benefit in the treatment or management of hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction, and general malaise associated therewith. The term "prophylactically effective amount" means that amount of losartan that, alone or with another active ingredient, inhibits or prevents hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction, and general malaise associated therewith.

[0068] The amounts of the other components in the composition may vary. Generally, the glycol can be present in an amount of about 1 percent to 40 percent (v/v) when included, the glycerin can be present in an amount of about 5 percent to 50 percent (v/v) when included, and/or the sweetening agent can be present in an amount of about 0.05 percent to 5 percent (w/v). The buffering agent is typically present in an amount of about 30 percent to 70 percent (v/v). As used herein, the terms (v/v) and (w/v) refer to percentages based on volume and percentages based on weight per volume, respectively. In one preferred embodiment, all four of these components are included in the liquid losartan compositions. In one embodiment, the losartan compositions of the invention—other than that present in any other carriers or the active ingredient—are at least substantially free of added water, preferably are entirely free of added water.

[0069] In a preferred embodiment, the losartan is present in an amount of about 8 mg/mL to 20 mg/mL of the composition, the glycol includes propylene glycol present in an amount of about 5 percent to 25 percent (v/v), the glycerin is present in an amount of about 20 percent to 40 percent (v/v), the sweetening agent includes saccharin sodium present in an amount of about 0.5 percent to 2 percent (w/v), and the buffering agent includes a phosphate-containing buffer present in an amount of about 40 percent to 60 percent (v/v). In an exemplary embodiment, the losartan is present in an amount of about 12.5 mg/mL, the propylene glycol is present in an amount of about 15 percent (v/v), the glycerin is present in an amount of about 30 percent (v/v), the potassium phosphate buffer is present in an amount of about 55 percent (v/v), and the saccharin sodium is present in an amount of about 1 percent (w/v).

[0070] The compositions of the present invention are preferably at least substantially stable. By "substantially stable" is meant a degradation of losartan in the composition over a period of at least two months that is no more than

of losartan originally present in the composition, preferably no more than about 3 percent, and more preferably no more than about 2 percent, at 50° C. In an exemplary embodiment, the degradation of losartan over a period of at least two months is no more than about 1 percent to 2 percent of the amount of losartan originally present at 50° C. In each of these embodiments, it is preferred that the above-noted losartan degradation is over a period of at least three months.

[0071] The present invention also relates to methods of preparing oral liquid losartan compositions. Typically, this can include dissolving an amount of losartan, preferably in a therapeutically or prophylactically effective amount, into at least one liquid adjuvant to form a liquid losartan solution and combining the liquid losartan solution with one or more additional pharmaceutically acceptable carriers to form the oral liquid losartan composition having a pH of about 6 or greater.

[0072] The at least one liquid adjuvant may be selected from any of the agents already described above. In one embodiment, the at least one liquid adjuvant includes a buffering agent that can provide the desired pH to the compositions. In a preferred embodiment, the oral liquid losartan composition is a clear solution. By "clear" is meant that the light transmission through the composition is typically at least about 70 percent, preferably at least about 90 percent, and more preferably at least about 95 percent. In an exemplary embodiment, the composition is substantially transparent to the naked eye.

[0073] The present invention also provides methods of preventing, treating, or managing hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction, in a mammal. As used herein, the terms "preventing, treating, or managing" cover preventing, treating, or managing the specified disease in a mammal, particularly a human, and includes: (i) preventing the disease from occurring in a subject that may be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development before or after it afflicts a patient; or (iii) relieving the disease, i.e., causing regression of the disease. As used herein, "mammal" is meant the class of warm-blooded vertebrate animals that have, in the female, milk-secreting organs for feeding the young. Mammals include humans, apes, many four-legged animals, whales, dolphins, and bats. It should also be understood that symptoms of any disease are also encompassed within the term "managed," such that managing hypertension may address some or all of the symptoms thereof with or without actually affecting the underlying disease itself.

[0074] The methods of the invention include administering to a mammal a therapeutically or prophylactically effective amount of an oral liquid losartan composition that includes losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier. The oral liquid losartan composition has a pH of about 6 or higher. These methods find utility in preventing or treating numerous disease states that are currently being treated with losartan and include, for example, hypertension, congestive heart failure, diabetic nephropathy and myocardial infarction.

[0075] The prophylactically or therapeutically effective amount of losartan will vary depending on the subject being

administration, and may be determined routinely by one of ordinary skill in the art. The dose, and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual agent. In general, the total daily dose range is from about 25 mg to 100 mg administered in single or divided doses orally. The composition may typically be administered once or twice a day. It may be necessary to use dosages outside the above ranges in some cases, as will be apparent to those of ordinary skill in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

[0076] The methods of the invention also contemplate the addition of one or more therapeutic agents with the losartan to provide an additive, more complete, or synergistic effect in preventing, treating, or managing a disease as noted herein. The additional "therapeutic agents," which can be prophylactic or therapeutic, may be administered in any dosage form(s) suitable for the formulation as are well known in the art. Such dosage forms include solid dosage forms, such as tablets, capsules, powders, and cachets, or liquid dosage forms, such as suspensions, syrups, solutions, and elixirs. The agent may be incorporated in the losartan liquid composition or may be administered in a separate dosage form. The dosage form containing the additional agent to be administered will, in any event, contain a quantity of the additional therapeutic agent(s) in an amount effective to alleviate the symptoms of the subject being treated. The selection of these additional therapeutic agents will depend upon the specific disease state being treated, and are described in detail below. Preferably, all active ingredients will be in an oral liquid suspension form, more preferably in a combined form to facilitate patient compliance.

[0077] For those embodiments of the invention where the losartan liquid composition is administered to treat hypertension, such additional therapeutic agents can include one or more diuretics, beta-blockers, angiotensin converting ("ACE") inhibitors, calcium channel blockers, alpha-blockers, alpha-beta blockers, vasodilators, alpha antagonists (centrally acting), or adrenergic neuron blockers, or a combination thereof; and preferably include one or more diuretics, beta-blockers, or calcium channel blockers, and combinations thereof.

[0078] For those embodiments of the invention where the losartan is administered to treat congestive heart failure, such additional therapeutic agents can include one or more of diuretics, ACE inhibitors, digoxin, vasodilators (direct vasodilators, calcium channel blockers and nitrates), beta blockers, or statins, or a combination thereof, and preferably diuretics, digoxin, direct vasodilators, or nitrates.

[0079] For those embodiments of the invention where the losartan is administered to treat diabetic nephropathy, such additional therapeutic agents can include one or more diuretics.

[0080] For those embodiments of the invention where the losartan is administered to treat myocardial infarction, such additional therapeutic agents can include one or more ACE inhibitors, diuretics, vasodilators, beta blockers, anticoagulants, or thrombolytics, or a combination thereof. A few examples of compounds within each of these classes is set forth below from which one of ordinary skill in the art may select as being suitable for administration in association with

[0081] Examples of thiazide diuretics include bendroflumethiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone and trichlormethiazide; and are preferably selected from the group consisting of hydrochlorothiazide and chlorothiazide. Commercially available thiazide diuretics include, for example, Naturetin™ (bendroflumethiazide, Squibb); Diuril™ (chlorothiazide, Merck); Thalitone™ (chlorthalidone, Boehringer); Microzide™; HydroDIURIL™; and Oretic™ (hydrochlorothiazide, Watson, Merck and Abbott, respectively); Saluron™ and Diurcardin™ (hydroflumethiazide, Bristol-Myers and American Home Products, respectively); Enduron™ (methyclothiazide, Abbott); Mykrox™ and Zaroxolyn™ (metolazone, Fisons); Renese™ (polythiazide, Pfizer); Hydromox™ (quinethazone, American Cyanamid); and Naqua™ (trichlormethiazide, Schering); and combinations thereof.

[0082] Examples of loop diuretics include bumetanide, ethacrynic acid and furosemide. Commercially available loop diuretics include, for example, Bumex™ (bumetanide, Roche Pharmaceuticals), Edecrin™ (ethacrynic acid, Merck), Lasix™ (furosemide, Hoechst) and Myrosemide™ (furosemide); and combinations thereof.

[0083] Examples of potassium-sparing diuretics include amiloride, spironolactone and triamterene. Commercially available potassium-sparing diuretics include, for example, Midamor™ (amiloride, Merck); Aldactone™ (spironolactone, G. D. Searle) and Dyrenium™ (triamterene, Smith Kline); and combinations thereof.

[0084] Suitable beta-blockers may include propranolol, timolol, and metoprolol; and combinations thereof. Examples of suitable ACE inhibitors may include captopril, enalapril, lisinopril, quinapril, ramipril, benazepril and fosinopril; and combinations thereof. Suitable calcium channel blockers may include verapamil, diltiazem, nimodipine, nifedipine, nicardipine, felodipine, isradipine, and amlodipine; and combinations thereof. Exemplary alpha-blockers may include prazosin, terazosin, doxazosin, phenoxymethamine and phentolamine; and combinations thereof. Suitable alpha-beta blockers include labetalol.

[0085] Examples of suitable vasodilators may include, e.g., hydralazine, minoxidil, diazoxide and nitroprusside; and combinations thereof.

[0086] Suitable alpha antagonists (e.g., centrally acting) may include methyl dopa, clonidine, guanabenz, and guanfacine; and combinations thereof.

[0087] Examples of suitable adrenergic neuron blockers may include guanfacine, guanethidine, guanadrel, and reserpine; and combinations thereof.

[0088] In a preferred embodiment, the method includes administering at least one other antihypertensive agent with the composition. It is to be understood that the term "antihypertensive drug" refers to various classes of antihypertensive agents including angiotensin II antagonists, ACE inhibitors and NEP/ACE inhibitors which contribute, with the antiplatelet drug, to inhibit onset of primary or secondary cerebral infarction. The at least one other hypertensive agent preferably includes an angiotensin II antagonist, angiotensin converting enzyme inhibitor, or a neutral endopeptidase/

[0089] A suitable angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or All antagonist) suitable for association with a losartan composition according to the invention includes, but is not limited to, one or more of irbesartan, valsartan, telmisartan, candesartan, tasosartan or eprosartan, or a pharmaceutically acceptable salt thereof, with irbesartan being preferred.

[0090] The angiotensin-converting enzyme inhibitor, or ACE inhibitor, which may be employed herein includes those containing a mercapto (—S—) moiety such as substituted proline derivatives, for example, any of those disclosed in U.S. Pat. No. 4,046,889, with captopril, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906. Other examples of mercapto containing ACE inhibitors that may be included herein according to the invention include rentiapril (fentiapril, Santen) disclosed in *Clin. Exp. Pharmacol. Physiol.* 10: 131 (1983); as well as pivopril.

[0091] Other examples of suitable ACE inhibitors that may be associated with losartan include any of those disclosed in U.S. Pat. No. 4,374,829, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790, phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamides disclosed in U.S. Pat. No. 4,432,971.

[0092] Other examples of suitable ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Nos. 80822 and 60668; Chugai's MC-838 disclosed in CA. 102:72588v and *Jap. J. Pharmacol.*, 40:373 (1986); Ciba-Geigy's CGS 14824 (3-(1-ethoxycarbonyl-3-phenyl-(1 S)-propyl)amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in *Eur. Therap. Res.*, 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in European Patent No. 79-022 and *Curr. Ther. Res.*, 40:74 (1986); Ru 44570 (Hoechst) disclosed in *Arzneimittelforschung* 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in *J. Cardiovasc. Pharmacol.* 9:39 (1987); Ro 31-2201 (Hoffman-LaRoche) disclosed in *FEBS Lett.* 165:201 (1984); lisinopril (Merck), indalaprill (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in *J. Cardiovasc. Pharmacol.*, 5:643, 655 (1983), spirapril (Schering) disclosed in *Acta. Pharmacol. Toxicol.*, 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in *Eur. J. Clin. Pharmacol.*, 31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and CI 925 (Warner-Lambert) ([3S-[2[R(*)R(*)]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in *Pharmacologist* 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in *J. Med. Chem.*, 26:394 (1983).

[0093] Preferred ACE inhibitors include fosinopril, captopril, enalapril, lisinopril, quinapril, benazepril, trandolapril, fentiapril, ramipril, moexipril; and combinations

[0094] Suitable NEP/ACE inhibitors may also be included herein in that they possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein include those disclosed in U.S. Pat. Nos. 5,508,272, 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 5,552,397, 4,749,688, 5,504,080, 5,612,359, and 5,525,723 and European Patent Application Nos. 0481,522, 0534363A2, 534,396 and 534,492.

[0095] The term “about,” as used herein, should generally be understood to refer to both numbers in a range of numerals. Moreover, all numerical ranges herein should be understood to include each whole integer within the range.

[0096] Each of the patent applications, patents, publications, and other published documents mentioned or referred to in the Detailed Description is incorporated herein in its entirety by express reference thereto, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

EXAMPLES

[0097] The invention is further defined by reference to the following examples, describing in detail the methods used to prepare the compositions of the present invention. It will be apparent to those of ordinary skill in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of the invention. These examples are for illustrative purposes only, and are not to be construed as limiting the appended claims.

Example 1

Solubility Studies for Losartan Potassium

Example 1.1

Comparative Losartan Solubility with and without a Buffering Agent

[0098] The solubility of losartan potassium was evaluated in water, sodium phosphate buffer, and ethanol. The materials used were losartan potassium; sodium phosphate buffer (SPB) prepared in-house at pHs of 1.9, 6.2, 7.2, and 8.2, at a concentration of 10 mM; and ethanol.

[0099] Small quantities of losartan potassium were added to 1 mL of the aqueous or alcohol media until crystals were visible by the eye. The results are provided in Table 1 below.

TABLE 1

Solvent	pH	Solubility (mg/mL)
Water + HCl	2.1	0.28
Water	5.5	>243
Water + NaOH	11.8	>239
SPB	8.2	>253
SPB	7.2	300
SPB	6.2	>241
SPB	1.9	0.048
Ethanol		130

[0100] As can be seen from the results of Table 1, the

nificantly in acidic conditions (pHs of 1.9 and 2.1). In contrast, no major differences in solubility for losartan potassium were observed in alkaline conditions between phosphate buffer solutions and sodium hydroxide solution.

[0101] After solubility was determined, each sample was stored at 50° C. overnight. After 24 hours, the samples were examined. Losartan potassium crystals were observed in the SPB at a pH of 6.2. Thus, additional testing was performed on the compositions having a pH of at least 7.2 or higher to confirm that higher pH formulations can avoid significant amounts of losartan crystal precipitation. Without being bound by theory, it is believed that this surprising result is achieved when the pH is more than one pH unit greater than the pKa of losartan potassium, which is between 5 and 6. Formulations at these pHs of about 7 or greater should prevent precipitation of the drug. These results were obtained without the use of high performance liquid chromatography (HPLC) methods.

Example 1.2

Comparative Solubility of Different Buffering Agents

[0102] The solubility of losartan potassium in different phosphate-containing buffers was examined and the solubility of losartan was measured using HPLC. The materials used were sodium phosphate buffer (SPB) prepared in-house and losartan potassium. Forty (40) mg of losartan potassium was weighed in a glass tube, 10 mL of SPB was added, and the resulting mixture was vortexed for 2 minutes. A sample of each solution was then taken and analyzed by HPLC. If the losartan did not completely dissolve, the tubes were centrifuged and a sample of the supernatant was taken and analyzed by HPLC. Each sample was stored at room temperature and data was collected as a function of time. Table 2 below provides the results of the solubility of losartan potassium as a function at different pHs and different times. FIG. 1 illustrates the solubility profile of losartan potassium as a function of pH.

TABLE 2

	SPB pH = 1.7	SPB pH = 6.2	SPB pH = 7.4	SPB pH = 8.2
0 hours	1.07	1.62	>250	>250
48 hours	0.152	1.65	>250	>250
480 hours	0.03	0.06	>250	>250

[0103] The data collected by HPLC confirm the results of Example 1.1, which was performed visually. Based on the results of this and the previous example, it can be seen that losartan potassium is practically insoluble at a pH under 6.2. The solubility of losartan also decreased with time at a pH of 1.7 and 6.2. Moreover, some re-precipitation was observed at a pH of 6.2. At pHs of 7.4 and higher, no precipitation was observed.

[0104] Based on these studies, pHs of 7.4 or higher were determined to be the most advantageous to prepare losartan

Example 2

Stability Studies for Losartan Potassium

Example 2.1

[0105] The effect of three variables on the stability of losartan potassium was investigated. The three variables were the pH of the buffer, cation of the buffer, and concentration of the phosphate salt in the buffer. The pHs studied were 7.4 and 8.2; the cations studied were potassium and sodium; and the concentrations studied were 10 mM and 100 mM.

[0106] The materials used were sodium phosphate buffer (SPB) and potassium phosphate buffer (PPB) prepared in-house and losartan potassium. Two hundred fifty (250) mg of losartan potassium was weighed in a glass tube, 10 mL of the appropriate buffer was added, and the resulting mixture was vortexed for 2 minutes. A sample of each solution was taken and analyzed by HPLC. The different solutions were then stored at 50° C. Samples were taken over time to study the stability of losartan potassium. The stability (measured as percent active on a weight

[0107] basis at different times) for each sample is provided in Table 3 below. FIG. 2 illustrates the stability of losartan as a function of time.

TABLE 3

	0 hours	24 hours	264 hours	672 hours
SPB, 10 mM pH = 7.4	99.96	99.90	99.12	98.49
SPB, 100 mM pH = 7.4	99.93	99.90	99.34	98.90
SPB, 10 mM pH = 8.2	99.93	99.91	99.68	99.59
SPB, 100 mM pH = 8.2	99.93	99.91	99.77	99.66
PPB, 10 mM pH = 7.4	99.93	99.90	99.14	98.74
PPB, 100 mM pH = 7.4	99.93	99.90	99.32	98.84

[0108] As can be seen from the above results, losartan potassium in SPB at a concentration of 10 mM and a pH of 7.4 showed the highest degradation with around 1.5 percent

of the original losartan degraded after about 1 month at 50° C. When the concentration of the buffer was increased to 100 mM, the stability of losartan surprisingly increased so that the degradation was only around 1 percent after about 1 month at 50° C. Losartan potassium in PPB presented a similar degradation profile at a pH of 7.4 compared to SPB. The cations in this case, i.e., potassium and sodium, did not have a significant influence on the stability of losartan potassium. When losartan is used in the form of its potassium salt, it is preferred that PPB is used in the buffering agent according to the invention.

[0109] It can also be seen from the results in Table 3 that losartan potassium in SPB at a pH of 8.2 and a concentration of 100 mM provided a better stability than at a pH of 7.4. At a pH of 8.2, there was only about 0.4 percent degradation observed after about 1 month at 50° C. The higher concentration of 100 mM compared to 10 mM of SPB also increased the stability of losartan potassium in solution.

[0110] According to the results obtained, the stability of losartan improved at a pH of 8.2 and a concentration of the buffer salt of 100 mM.

Example 2.2

[0111] The effect of different excipients at different concentrations on the stability of losartan potassium was studied.

A) Propylene Glycol (PG)

[0112] The effect of propylene glycol (PG) on the stability of losartan potassium in sodium phosphate buffer (SPB) at a pH of 7.2 was examined and studied. The materials used were SPB at a pH of 7.2 prepared in-house; losartan potassium; and PG. One hundred (100) mg of losartan potassium was weighed in a glass tube, X mL of SPB was added, the resulting mixture was vortexed for 2 minutes, (10-X) mL of PG was then added, and this mixture was vortexed for 1 minute. X represents the amount in mL of SPB added to provide 10 mL.

[0113] Three different compositions (10 percent, 15 percent, and 30 percent by volume PG) were prepared according to the method described above. Each formulation was evaluated by HPLC. The samples were then stored at 50° C. for about 1 month and analyzed periodically. The stability of losartan (measured by percent active) is illustrated graphically in FIG. 3 and is provided below in Table 4.

TABLE 4

	0 hours	96 hours	168 hours	192 hours	336 hours	504 hours	624 hours	672 hours	816 hours	840 hours
Losartan in SPB	99.74	99.77	99.48	—	99.26	99.01	—	99.09	—	—
Losartan in 90% SPB + 10% PG	99.72	99.60	99.63	—	99.79	99.68	—	—	—	99.53
Losartan in 85% SPB + 15% PG	99.88	—	—	99.83	—	—	99.67	—	99.56	—
Losartan in SPB + 30% PG	99.72	99.69	99.69	—	99.87	99.82	—	—	—	99.80

[0114] The stability of losartan potassium in 30 percent PG was unexpectedly good. The stability was similarly surprisingly good at both 10 percent and 15 percent PG, with less than 0.4 percent degradation after more than 1 month (816 hours) at 50° C.

[0115] In all the samples shown above, introducing PG surprisingly and unexpectedly improved the stability of losartan potassium in solution. The maximum daily intake of PG recommended in 24 hours, however, is 25 mg/kg. For a 100 mg dose, the patient would have to take 4 mL of a solution at 12.5 mg/mL of losartan potassium. At 30 percent PG, the minimum weight of the patient would have to be approximately 50 kg. Therefore, a concentration of 15 percent PG is preferred to stay within the limits of the recommended maximum daily intake of PG.

B) Propylene Glycol (PG) and Glycerin, and Propylene Glycol (PG) and Polyethylene Glycol 400 (PEG 400)

[0116] The stability of losartan potassium in solution was studied in two combinations: (1) propylene glycol (PG) and glycerin; and (2) propylene glycol (PG) and polyethylene glycol 400 (PEG 400). The materials used were sodium phosphate buffer (SPB) at a pH of 7.2 prepared in-house; losartan potassium; PG; glycerin; and PEG 400. One hundred (100) mg of losartan potassium was weighed in a glass tube, X mL of SPB at a pH of 7.2 was added, the resulting mixture was vortexed for 2 minutes, 1.5 mL of PG was added, this mixture was vortexed for 1 minute, and finally (8.5-X) mL of either glycerin or PEG 400 was added. X represents the amount in mL of SPB added to provide 8.5 mL.

[0117] Two different concentrations of glycerin (10 percent and 30 percent by volume) and 2 different concentrations of PEG 400 (10 percent and 30 percent by volume) were studied. Five different formulations were prepared and analyzed. Each sample was evaluated by HPLC. The samples were then stored at 50° C. for about 1 month and analyzed periodically. The stability of losartan (measured by percent active) is illustrated graphically in FIG. 4 and is provided below in Table 5.

TABLE 5

	0 hours	48 hours	192 hours	384 hours	624 hours	816 hours
Losartan in SPB + 15% PG	99.88	99.89	99.82	99.80	99.7	99.58
Losartan in SPB + 15% PG + 10% Glycerin	99.88	99.89	99.83	99.81	99.67	99.56
Losartan in SPB + 15% PG + 30% Glycerin	99.88	99.90	99.88	99.82	99.70	99.57
Losartan in SPB + 15% PG + 10% PEG 400	99.85	99.87	99.85	99.83	99.79	99.67
Losartan in SPB + 15% PG + 30% PEG 400	99.82	99.83	99.83	99.83	99.63	99.33

[0118] In SPB, losartan potassium in solution with 15 percent PG and up to 30 percent glycerin demonstrated less than 0.5 percent degradation after 816 hours at 50° C. The addition of glycerin at the studied concentrations did not

The addition of about 30 percent glycerin will also add sweetness to the composition and minimize or avoid the need to add a separate preservative.

[0119] Similar results were observed when glycerin was replaced by 10 percent PEG 400 with a slightly lower degradation (0.33 percent after 816 hours). Increasing the amount of PEG 400 to 30 percent in the composition, however, decreased the stability of losartan potassium. Thus, glycerin surprisingly demonstrated greater stability compared to PEG 400.

[0120] In addition, in another study (not described here) it was determined that both PG and PEG 400 improve the stability of losartan potassium in SPB. PEG 400, however, did not improve the stability of losartan potassium in water. Therefore, in one embodiment PG is preferred over PEG 400.

C) Propylene Glycol (PG), Glycerin and Xylitol

[0121] Even with 30 percent glycerin present, in some embodiments it is desired to add additional sweetener as the composition may not be sweet enough for some patients. Accordingly, a stronger sweetener was considered for use in the composition. Xylitol was considered to be a good candidate to increase the sweetness of the composition and also help stabilize losartan potassium in solution. Thus, the stability of a composition of propylene glycol (PG), glycerin, and xylitol was studied and evaluated. The materials used were sodium phosphate buffer (SPB) at a pH of 7.2 prepared in house; losartan potassium; PG; glycerin; and xylitol. One hundred (100) mg or 500 mg of losartan potassium were weighed in a glass tube, 200 mg or 400 mg of xylitol were added, 5.5 mL of SPB was added, and the resulting mixture was vortexed for 2 minutes. PG (1.5 mL) was then added, this mixture was vortexed for 1 minute, 3 mL of glycerin was added, and this mixture was finally vortexed for 1 minute.

[0122] Two different concentrations of losartan (25 mg/mL and 5 mg/mL) and 2 different concentrations of xylitol (1 percent and 2 percent measured by weight per volume) were studied. Four different formulations were

prepared and analyzed. Each sample was evaluated by HPLC. The samples were then stored at 50° C. for about 1 month and analyzed periodically. The stability of losartan (measured by percent active) is illustrated graphically in

TABLE 6

	0 hours	24 hours	168 hours	456 hours	840 hours
25 mg/mL losartan + 2% xylitol	100.00	99.97	99.88	99.72	99.30
5 mg/mL losartan + 2% xylitol	99.97	100.00	99.97	99.85	99.48
25 mg/mL losartan + 1% xylitol	100.00	99.97	99.88	99.73	99.30
5 mg/mL losartan + 1% xylitol	100.00	100.00	99.97	99.86	99.56

[0123] Losartan potassium at a concentration of 25 mg/mL degraded approximately 0.7 percent after about 1 month at 50° C. in solution with either 1 percent xylitol or 2 percent xylitol. When the concentration of losartan was reduced to 5 mg/mL, the degradation decreased to about 0.5 percent in solutions containing 2 percent xylitol and about 0.45 percent for 1 percent xylitol.

[0124] According to these results, losartan potassium in combination with xylitol was more stable when a lower concentration of losartan was used. The concentration of xylitol, however, did not change the stability of losartan in the range of concentrations studied.

Example 2.3

Flavoring Agent According to the Invention

[0125] Based on the above solubility and stability experiments, phosphate buffers at a concentration of 100 mM of the salt and at a pH of 8.2 were found to have demonstrated surprisingly and unexpectedly improved solubility and stability compared to phosphate buffers at a pH of 7.4. It was also desired to minimize the bitterness of losartan potassium.

[0126] The composition containing 2 percent of xylitol was still not sweet enough. Saccharin sodium was considered to be a possible replacement for xylitol due to its extreme sweetness obtained during the excipient compatibility screening, which also surprisingly increased the stability of the formulation. The sweetness provided by glycerin could also be increased.

[0127] Two different concentrations of glycerin (30 percent and 40 percent by volume) and 2 different pHs of the phosphate buffer (7.4 and 8.2) were studied. Four different compositions that contained saccharin were prepared and analyzed. The materials used were losartan potassium; saccharin sodium; propylene glycol (PG); glycerin; and potassium phosphate buffer (PPB) prepared in-house. Two hundred fifty (250) mg of losartan potassium was weighed, 100 mg of saccharin sodium added, X mL of PPB was added, and the resulting mixture was vortexed for 2 minutes. Three mL of PG were then added to the vortexed mixture, (17-X) mL of glycerin added, and this mixture vortexed for 2 minutes. X represents the amount in mL of PPB added to provide 17 mL. Each sample was then stored at 50° C. and evaluated by HPLC periodically. The stability of losartan (measured by percent active) is illustrated graphically in FIG. 6 and is

TABLE 7

	0 hour	72 hours	288 hours	1152 hours
30% glycerin, pH = 7.4	99.88	99.91	99.88	99.65
40% glycerin, pH = 7.4	99.88	99.88	99.88	99.73
30% glycerin, pH = 8.2	99.88	99.88	99.89	99.86
40% glycerin, pH = 8.2	99.88	99.88	99.92	99.82

[0128] Based on the results above, it was found that increasing the concentration of glycerin and replacing xylitol with saccharin surprisingly did not change the stability of losartan potassium in solution, however, the sweetness was beneficially increased to a more desired level. Xylitol can therefore be replaced by saccharin sodium without changing the stability of the composition. Minimal degradation was observed after 12 days (288 hours) and even at 1152 hours at 50° C.

[0129] Losartan potassium was again found to be more stable at a pH of 8.2, which confirmed the results of the previous experiments regarding pH and stability. It is possible to increase the concentration of glycerin without increasing the degradation of losartan potassium when using a buffer at a pH of 8.2.

[0130] According to all the studies performed, a preferred composition might include: propylene glycol (PG), glycerin, saccharin sodium, and potassium phosphate buffer at a pH of 8.2, along with sufficient active ingredient of losartan, or a salt or metabolite thereof.

Example 3

Oral Liquid Losartan Composition

[0131] An oral liquid losartan composition was prepared from losartan potassium at a concentration of 12.5 mg/mL, 15 percent (v/v) propylene glycol (PG), 30 percent (v/v) of glycerin, 55 percent (v/v) of potassium phosphate buffer (PPB) at a pH of 8.2, and 1 percent (w/v) saccharin sodium.

[0132] The materials used to prepare the composition were losartan potassium; PPB at a pH of 8.2 prepared in-house; PG; glycerin; and saccharin sodium. Two hundred (200) mg of PPB was added to a stainless steel beaker. To this was added 6.25 mg of losartan potassium while stirring at 300 rpm. The mixture was mixed for 5 minutes or until a clear solution was obtained. Five (5) grams of saccharin sodium was subsequently added, and the solution was mixed for 2 minutes or until it was clear. PG (77.7 g) was then added and the solution was mixed for 5 minutes. Next, glycerin (275.7 g) was added and the solution mixed for another 5 minutes. The container holding the glycerin and PG was then rinsed with 75.7 g of PPB, and this was added to the contents of the beaker. Finally, this solution was mixed for 5 minutes or until the composition was clear. The final volume of the composition was 500 mL.

[0133] Three samples of 25 mL each, was filled in 4 oz. glass bottles, 2 oz. plastic HDPE containers, and brown glass

container. One sample of each container (except for the stainless steel container) was then stored at 50° C., another one at 40° C. and finally the last sample at room temperature (RT). The stainless steel container was left at room temperature. Samples from each container were then analyzed by HPLC at different times. Table 8 displays the percentage of losartan potassium as a function of time in different containers. The margin of error in the data of the table below is ±0.5%.

TABLE 8

	Temperature (° C.)	0 hours	72 hours	312 hours	1008 hours
Glass Bottle	RT	99.82	99.92	99.80	99.70
Glass Bottle	50	99.82	99.95	99.80	99.90
Glass Bottle	40	99.82	99.92	99.92	99.90
HDPE	RT	99.82	99.92	99.78	99.90
HDPE	50	99.82	99.92	99.80	99.90
HDPE	40	99.82	99.92	99.83	99.90
Brown Glass Bottle	RT	99.82	99.92	99.83	99.90
Brown Glass Bottle	50	99.82	99.92	99.83	99.90
Brown Glass Bottle	40	99.82	99.92	99.83	99.90
Stainless Steel	RT	99.82	99.92	99.83	99.90

[0134] As demonstrated by the data above, the oral liquid losartan composition is stable as a function of time in all the different containers with minimal degradation observed after 1008 hours at room temperature, 40° C. and 50° C. These results demonstrate the superior stability of the losartan potassium in solution and confirm the conclusions of the other studies according to the invention.

[0135] To further confirm these results, the percent recovery of losartan potassium was also measured as a function of time in the different containers. Table 9 and FIG. 7 summarize the results obtained. The margin of error in the data in this table is ±2%.

TABLE 9

	Temperature (° C.)	0 hour	72 hours	312 hours	1008 hours
Glass Bottle	RT	100.00	99.52	99.85	99.04
Glass Bottle	50	100.00	99.93	100.19	99.28
Glass Bottle	40	100.00	99.78	99.91	99.27
HDPE	RT	100.00	100.38	100.42	99.07
HDPE	50	100.00	100.05	100.16	100.22
HDPE	40	100.00	99.51	99.94	99.83
Brown Glass Bottle	RT	100.00	100.00	100.32	99.33
Brown Glass Bottle	50	100.00	100.07	100.38	101.04

TABLE 9-continued

	Temperature (° C.)	0 hour	72 hours	312 hours	1008 hours
Brown Glass Bottle	40	100.00	99.77	100.17	99.15
Stainless Steel	RT	100.00	100.07	100.31	99.49

[0136] Small variations in the percentage of recovery as a function of time were observed in the different containers. In each container at room temperature, there was a small decrease in the recovery percentage of losartan potassium. At less than 1 percent, the decrease, however, was very small. Accordingly, glass bottles, plastic HDPE containers, brown glass bottles, and stainless steel containers are all suitable containers for holding the oral liquid losartan compositions and do not significantly decrease their stability. The preferred form of packaging the liquid formulations of the invention is in PET, HDPE, clear or a brown glass bottle, preferably in a HDPE container.

[0137] Although preferred embodiments of the invention have been described in the foregoing description, it will be understood that the invention is not limited to the specific embodiments disclosed herein but is capable of numerous modifications by one of ordinary skill in the art. It will be understood that the materials used and the chemical or pharmaceutical details may be slightly different or modified from the descriptions herein without departing from the methods and compositions disclosed and taught by the present invention.

What is claimed is:

1. An oral liquid composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher.
2. The composition of claim 1, wherein the pH is about 7 to 10.
3. The composition of claim 2, wherein the pH is about 7.4 to 8.6.
4. The composition of claim 1, wherein the at least one pharmaceutically acceptable carrier comprises one or more of a wetting agent, surfactant component, stabilizing agent, solubilizing agent, thickening agent, sweetening agent, flavoring agent, perfuming agent, colorant agent, preservative agent, or buffering agent.
5. The composition of claim 4, wherein the carrier comprises one or more of a solubilizing agent, a stabilizing agent, a sweetening agent, a flavoring agent effective to mask a bitter taste, or a buffering agent.
6. The composition of claim 5, wherein the carrier comprises a glycol or glycerin, the sweetening agent comprises a sucralose or saccharin-containing component, and the buffering agent comprises a phosphate-containing buffer.
7. The composition of claim 5, wherein the flavoring agent is present and comprises grapefruit, orange, lemon, lime, mango, strawberry, pineapple, cherry, or a combination thereof.
8. The composition of claim 6, wherein the phosphate-containing buffer comprises sodium phosphate, potassium

9. The composition of claim 8, wherein the concentration of phosphate salt in the buffering agent is from about 5 mM to 150 mM.

10. The composition of claim 9, wherein the phosphate salt concentration is about 80 mM to 120 mM.

11. The composition of claim 5 wherein the solubilizing agent is present in an amount of about 1 percent to 50 percent (v/v).

12. The composition of claim 5, wherein the sweetening agent is present in an amount of about 0.05 percent to 5 percent (w/v).

13. The composition of claim 5, wherein the buffering agent is present in an amount of about 30 percent to 70 percent (v/v).

14. The composition of claim 6, wherein the glycol is present in amount of about 1 percent to 40 percent (v/v), and the glycerin is present in an amount of about 5 percent to 50 percent (v/v).

15. The composition of claim 1, wherein the losartan, or salt or metabolite thereof, is present in an amount of about 1 to 50 mg/mL of the composition.

16. The composition of claim 1, wherein the losartan, or salt or metabolite thereof, is present in an amount of about 8 mg/mL to 20 mg/mL of the composition, and the pharmaceutically acceptable carrier comprises a glycol present in an amount of about 5 percent to 25 percent (v/v), glycerin present in an amount of about 20 percent to 40 percent (v/v), a sweetening agent present in an amount of about 0.5 percent to 2 percent (w/v), and a buffering agent present in an amount of about 40 percent to 60 percent (v/v).

17. The composition of claim 1, wherein the composition is at least substantially stable.

18. The composition of claim 1, wherein degradation of losartan over a period of less than two months is no more than about 1 percent to 2 percent (w/w) at 50° C.

19. The composition of claim 1, which is in solution form.

20. An oral liquid composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one of propylene glycol or glycerin, along with a sucralose or saccharin-containing component and a phosphate-containing buffer comprising sodium phosphate, potassium phosphate, or a mixture thereof, in an amount sufficient to provide a pH of about 6 or higher.

21. A stable oral liquid losartan composition comprising:

losartan or a pharmaceutically acceptable salt or metabolite thereof;

a solubilizing agent;

a sweetening agent; and

a buffering agent, present in an amount sufficient to provide a pH of about 6 or higher over an extended period of time to minimize degradation of the losartan.

22. A oral liquid composition comprising a solution of losartan, or a pharmaceutically acceptable salt or metabolite thereof, propylene glycol, glycerin, saccharin sodium, and potassium phosphate buffer, each in an amount sufficient to provide a pH of about 6 or higher.

23. A method of preparing an oral liquid losartan composition which comprises:

dissolving an amount of losartan, or a pharmaceutically acceptable salt or metabolite thereof, into at least one liquid adjuvant to form a liquid losartan solution; and

combining the liquid losartan solution with one or more additional pharmaceutically acceptable carriers sufficient to provide a pH of about 6 or higher to form the oral liquid losartan composition.

24. The method of claim 23, wherein the at least one liquid adjuvant comprises a buffering agent.

25. The method of claim 23, wherein the oral liquid losartan composition is a clear solution.

26. A method of preventing, treating, or managing hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction in a mammal which comprises administering to the mammal an effective amount of an oral liquid losartan composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier, wherein the oral liquid losartan composition has a pH of about 6 or higher.

27. The method of claim 26, wherein the composition is administered once or twice a day.

28. The method of claim 26, wherein the total daily dose of losartan is between about 25 mg to 100 mg.

29. The method of claim 26, which further comprises administering at least one other therapeutic agent.

30. The method of claim 29, wherein the at least one other therapeutic agent is at least one other hypertensive agent.

31. The method of claim 30, wherein the at least one other hypertensive agent comprises an angiotensin II antagonist, angiotensin converting enzyme inhibitor, or a neutral endopeptidase/angiotensin converting enzyme inhibitor.

* * * * *



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 11 165.084, titulada "SOLUCIÓN BEBIBLE FARMACÉUTICA DE TELMISARTAN", cuyo titular es **BOHERINGER INGELHEIM VETMEDICA, GMBH.** publicada en la gaceta No. 647 del 29 de junio de 2012.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativamente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

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

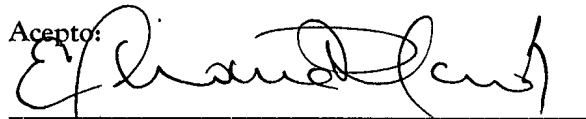
Dado y Firmado en Barranquilla (Colombia) a los 3 días del mes de Septiembre de 2012.


PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO
03 SET. 2012
PROCAPS S.A.

Acepto:



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



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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

03-12023990 024802 PROCAPS S.A. 02/08/2012 10:22:14

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libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) o el(los) documento(s) arriba citado(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

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C E R T I F I C A

Direccion Comercial:
CL 80 No 78 B - 201 en Barranquilla.
Dirección Electrónica: jcelis@procaps.com.co
Telefono: 3719278.
Direccion Judicial:
CL 80 No 78 B - 201 en Barranquilla.
Dirección Electrónica: jcelis@procaps.com.co
Telefono: 3719278.

C E R T I F I C A

DURACION: Que la sociedad no se halla disuelta y su término de duración se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los

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servicios de asesorias y consultoria en las areas administrativas; de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci3n
Autorizado		
\$*****2,000,000,000 *****	2,000,000 *****	1,000 *****
Suscrito		
\$*****1,298,000,000 *****	1,298,000 *****	1,000 *****
Pagado		
\$*****1,298,000,000 *****	1,298,000 *****	1,000 *****

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de

***** C O N T I N U A *****

03-12023990 024802 PROCAPS S.A.

No. 17912959

Barranquilla, 02 de Agosto de 2012 Hr: 10:22:14



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por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en

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cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982
CC.*****7,461,324
CC.*****8,671,834

Suplentes

***** C O N T I N U A *****



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PROCAPS S.A.-----
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1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente. Minski Gontovnik Ruben	CC.*****7463982

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente. Tanaka Tatekawa Walter	CC.*****16251923

C E R T I F I C A

Que según Acta No. 658 del 07 de Dic/bre de 2011 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Dic/bre de 2011 bajo el No. 176,066 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General. Otero Arteaga Javier Ernesto	CC.*****91263993
Vicepresidente Minski Gontovnik Jose	CC.*****8671834
Suplente del Presidente Minski Gontovnik Meyer	CC.*****7461324
Suplente del vicepresidente Carvajalino Pagano Marcela	CC.*****22579748

C E R T I F I C A

***** C O N T I N U A *****

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Que según Acta No. 159 del 16 de Enero de 2012 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 23 de Enero de 2012 bajo el No. 237,199 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Principal	
Rodriguez Rey Jose Luis	CC.*****72,001,912

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo, y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, 3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., el presidente debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuación: a.- Para que representen a la sociedad PROCAPS S.A. ante todo tipo de autoridades administrativas y jurisdiccionales, en asuntos de naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y presentar demandas, requerimientos, recursos, pedir y aportar pruebas, recibir, notificarse, ejercer la accion de tutela, tramitar incidente de desacato, comparecer en los procesos que cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de conciliar, por tanto pueden llegar a acuerdos conciliatorios, transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin representacion legal de la sociedad. PODERES ESPECIALES: a.- Se confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. Grupo A. WALTER NANAKA

***** C O N T I N U A *****



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

PROCAPS S.A.-----
NIT: 890.106.527-5.

TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, para que en nombre y representacion de PROCAPS ----
S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a
que este obligada la sociedad, en el giro normal de sus negocios y
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al señor MARLON -----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de -----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio ----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN -----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: EI representante legal de la -----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General -----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008,
otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente
se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008
bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento ----
publico Poder especial Amplio y Suficiente a la doctora MILENA ----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ----
facultada para firmar, como tambien los demas documentos -----

***** C O N T I N U A *****

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

PROCAPS S.A.

NIT: 890.106.527-5.

relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias.

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de 2010 bajo el Nro 4,201 del libro respectivo, Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, quien obra en el caracter de Presidente y/o Representante legal de la sociedad PROCAPS S.A., que por medio de este instrumento publico, otorga Poder Especial Amplio y Suficiente a la Doctora MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para que en nombre y representacion de la sociedad, Endose las Facturas Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa, queda facultada para realizar todo acto o tramite necesario para el cabal cumplimiento del presente mandato.

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de 2010 bajo el Nro 4,228 del libro respectivo, consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 en su condición de Presidente y representante legal de PROCAPS S.A., confiere poder especial, amplio y suficiente al señor RICARDO DORADO HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante el INVIMA, Fondo Nacional de Estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y peticiones de la empresa, según la competencia de estas entidades. Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado para presentar, gestionar, tramitar y firmar las diferentes solicitudes y peticiones de la empresa, según la competencia de estas entidades, como tambien presentar y firmar todo los documentos relacionados con estas solicitudes, notificarse de cualquier acto administrativo que expidan, aportar y solicitar las pruebas que sean necesarias, desistir, y en general a realizar todo tramite o acto necesario de tal forma que la sociedad en ningun momento quede sin representacion legal ante estas entidades, en cumplimiento fiel al mandato otorgado.

C E R T I F I C A

Que por Documento Privado del 03 de Agosto de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto de 2010 bajo el Nro 4,258 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las facultades otorgadas por los Estatutos Sociales, todo lo cual demuestro con el certificado de existencia y representación legal

***** C O N T I N U A *****



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.-----
NJT: 890.106.527-5.

expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de ---- edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes ---- actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS ----- (\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones ----- Cambiarias, Aduaneras y Tributarias a las que esta obligada la ---- sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda ----- facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el ---- cabal cumplimiento del presente mandato.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,813 del libro respectivo,----- consta que el señor RUBEN MINSKI GONTOVNIK, identificado con ----- C.C.7.463.982 de Barranquilla, en mi condición de Representante ---- Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las facultades otorgadas por los Estatutos Sociales, me permito ----- manifestarles que confiero poder especial, amplio y suficiente a MONICA DE HART DE OCHOA, identificada con C.C.32.676.025, para que en nombre y representación de la sociedad, realice operaciones de carácter Financiero con la firma conjunta de un(1)miembro del Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ---- perjuicios de las facultades otorgadas anteriormente a algunos de los funcionarios e inscritas en la Cámara de Comercio de esta ---- ciudad, como determino: -----

- GRUPO A -----
1. Monica De Hart De Ochoa -----
C.c. No. 32.676.025 -----
2. Javier Otero Arteaga -----
C.C. No. 91.263.993 -----
3. Gethel Moreno Romero -----
C.C. No.32.689.958 -----
GRUPO B -----
Marcela carvajalino Pagano -----
C.C. 22.579.748 -----

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

PROCAPS S.A.

NIT: 890.106.527-5.

Walter Tanaka Tatekawa

C.C. 16.251.923

Alain Cortesi Brunner

Cedula Extranjeria 215404

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,814 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a
JAVIER OTERO ARTEAGA, identificado con C.C.91.263.993, para que ----
en nombre y representación de la sociedad, realice operaciones de
carácter Financiero con la firma conjunta de un(1)miembro del Grupo
A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ----
perjuicios de las facultades otorgadas anteriormente a algunos de
los funcionarios e inscritas en la Cámara de Comercio de esta ----
ciudad, como determino.

GRUPO A

1. Monica De Hart De Ochoa

C.c. No. 32.676.025

2. Javier Otero Arteaga

C.C. No. 91.263.993

3. Gethel Moreno Romero

C.C. No.32.689.958

GRUPO B

Marcela carvajalino Pagano

C.C. 22.579.748

Walter Tanaka Tatekawa

C.C. 16.251.923

Alain Cortesi Brunner

Cedula Extranjeria 215404

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,815 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las

***** C O N T I N U A *****



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

PROCAPS S.A.-----
NIT: 890.106.527-5.

facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a
GETHEL MORENO ROMERO, identificada con C.C.32.689.958, para que ----
en nombre y representación de la sociedad, realice operaciones de
carácter Financiero con la firma conjunta de un(1)miembro del Grupo
A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ----
perjuicios de las facultades otorgadas anteriormente a algunos de
los funcionarios e inscritas en la Cámara de Comercio de esta -----
ciudad, como determino: -----

GRUPO A -----

- 1. Monica De Hart De Ochoa -----
C.c. No. 32.676.025 -----
- 2. Javier Otero Arteaga -----
C.C. No. 91.263.993 -----
- 3. Gethel Moreno Romero -----
C.C. No.32.689.958 -----

GRUPO B -----

- Marcela carvajalino Pagano -----
C.C. 22.579.748 -----
- Walter Tanaka Tatekawa -----
C.C. 16.251.923 -----
- Alain Cortesi Brunner -----
Cedula Extranjeria 215404 -----

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS
S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de
PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de
Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de
2012 bajo el Nro 4,816 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a
MARCELA CARVAJALINO PAGANO, identificada con C.C.22.579.748, para
que en nombre y representación de la sociedad, realice operaciones
de carácter Financiero con la firma conjunta de un(1)miembro del
Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin
perjuicios de las facultades otorgadas anteriormente a algunos de
los funcionarios e inscritas en la Cámara de Comercio de esta -----
ciudad, como determino: -----

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

PROCAPS S.A.

NIT: 890.106.527-5.

GRUPO A

1. Monica De Hart De Ochoa

C.c. No. 32.676.025

2. Javier Otero Arteaga

C.C. No. 91.263.993

3. Gethel Moreno Romero

C.C. No. 32.689.958

GRUPO B

Marcela carvajalino Pagano

C.C. 22.579.748

Walter Tanaka Tatekawa

C.C. 16.251.923

Alain Cortesi Brunner

Cedula Extranjeria 215404

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,817 del libro respectivo, consta que el señor RUBEN MINSKI GONTOVNIK, identificado con C.C. 7.463.982 de Barranquilla, en mi condición de Representante Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las facultades otorgadas por los Estatutos Sociales, me permito manifestarles que confiero poder Despecial, amplio y suficiente a WALTER TANAKA TATEKAWA, identificado con C.C. 16.251.923, para que en nombre y representación de la sociedad, realice operaciones de carácter Financiero con la firma conjunta de un(1)miembro del Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin perjuicios de las facultades otorgadas anteriormente a algunos de los funcionarios e inscritas en la Cámara de Comercio de esta ciudad, como determino:

GRUPO A

1. Monica De Hart De Ochoa

C.c. No. 32.676.025

2. Javier Otero Arteaga

C.C. No. 91.263.993

3. Gethel Moreno Romero

C.C. No. 32.689.958

GRUPO B

Marcela carvajalino Pagano

C.C. 22.579.748

Walter Tanaka Tatekawa

C.C. 16.251.923

Alain Cortesi Brunner

Cedula Extranjeria 215404

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de

***** C O N T I N U A *****

03-12023990 024802 PROCAPS S.A.

Barranquilla, 02 de Agosto de 2012 Hr:10:22:14



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 C A M A R A D E C O M E R C I O
 D E B A R R A N Q U I L L A
 04*****

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

PROCAPS S.A.-----
 NIT: 890.106.527-5.

Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,818 del libro respectivo,-----
 consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
 C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
 Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
 facultades otorgadas por los Estatutos Sociales, me permito -----
 manifestarles que confiero poder especial, amplio y suficiente a
 ALAIN CORTESI BRUNNER, identificado con C.C.215404, para que -----
 en nombre y representación de la sociedad, realice operaciones de
 carácter Financiero con la firma conjunta de un(1)miembro del Grupo
 A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ----
 perjuicio de las facultades otorgadas anteriormente a algunos de
 los funcionarios e inscritas en la Cámara de Comercio de esta -----
 ciudad, como determino: -----

GRUPO A -----

1. Monica De Hart De Ochoa -----

C.c. No. 32.676.025 -----

2. Javier Otero Arteaga -----

C.C. No. 91.263.993 -----

3. Gethel Moreno Romero -----

C.C. No.32.689.958 -----

GRUPO B -----

Marcela carvajalino Pagano -----

C.C. 22.579.748 -----

Walter Tanaka Tatekawa -----

C.C. 16.251.923 -----

Alain Cortesi Brunner -----

Cedula Extranjeria 215404 -----

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCIÓN DE DOCUMENTOS

PROCAPS S.A.

NIT: 890.106.527-5.

Que su última Renovación fue el: 22 de Marzo de 2012.

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

C E R T I F I C A

De conformidad con lo establecido en el Código de Procedimiento Administrativo y de lo Contencioso y de la Ley 962 de 2005, los Actos Administrativos de Registro aquí certificados quedan en firme Diez (10) días hábiles después de la fecha de inscripción, siempre que no sean objeto de recursos.

m. Rojas

