

FORMULARIO ÚNICO DE OPOSICIÓN



OPOSICIÓN A:

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

②

Número del expediente: 11-002.094

Solicitante: **FORESIGHT BIOTHERAPEUTICS INC**

**SOLICITUD
PUBLICADA**

Apoderado: JESÚS MARIA MÉNDEZ BERMÚDEZ

Título de la nueva creación o denominación del signo:

POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS

Gaceta: _____ **634**

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Teléfono: 371 99 00 Fax: 373 08 18 E-mail:	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>51'975.664</u> TP <u>83823</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

⑤ Comprobante de pago No.

12-00 145180

Fecha

02 / 19 / 2012

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISaura MORENO BOHORQUEZ

FIRMA:



C.C. 51975.664

TP. 83823

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

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 12 - 0014518
		Bogotá D.C., Febrero 14 de 2012 - 11:08:21

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	380130170	10/02/2012	2.520.000.00

*** 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. 11-002094- -00005-0000

Fecha: 2012-02-14 11:32:18 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 44



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. 11 002.094, titulada **"POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLÓGICAS"**, cuyo titular es **FORESIGHT BIOTHERAPEUTICS INC**, publicada en la gaceta No. 634 del 21 de NOVIEMBRE de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar 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 08 días del mes de Febrero de 2012.

PROCAPS S.A.

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

APROBADO
08 FEB. 2012
PROCAPS S.A.

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Ante el Notario Tercero de Barranquilla se presento:
WALTER TANAKA TATEKAWA
identificado con: C 16 251 923 PALMIRA
Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo representa.
Barranquilla: 09 FEB. 2012

[Handwritten signature]

NOTARIA TERCERA DEL CIRCULO
DE BARRANQUILLA
ALFONSO LUIS JAVIERA
NOTARIO



***** Pag. 1
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
09*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

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

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

PROCAPS S.A.-----

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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) arriba citada(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.

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

03-12001740 024802 PROCAPS S.A.
Barranquilla, 16 de Enero de 2012

Hr:11:10:47

No. 16673729



***** Pag. 2
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
09*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Dirección para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

Correo electrónico:

mlozada@procaps.com.co

Pagina Web:

Teléfono:

3719272

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 M O S

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 servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion,

***** 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.

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 Acción
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 corresponde 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 por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente , quien ejercera la representa-

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



***** Pag. 3
C A M A R A D E C O M E R C I O
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

cion 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 cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos

***** 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.

o de la Junta Directiva. El Vicepresidente tendra (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	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	.*****

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



***** Pag. 4
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
09*****

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

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

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.******7,463,982

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.******16,251,923

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.******91,263,993
Vicepresidente Minski Gontovnik Jose	CC.******8,671,834
Suplente del Presidente Minski Gontovnik Meyer	CC.******7,461,324
Suplente del vicepresidente Carvajalino Pagano Marcela	CC.******22,579,748

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

***** 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.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 158 del 17 de Junio de 2011 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 Junio de 2011 bajo el No. 170,929 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Suplente	
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 Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organó 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 continuacion: 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

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



***** Pag. 5
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
09*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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 transacción. Grupo A. WALTER NANAKA
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 representación 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 también los demás documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.- Otorgar poder especial amplio y suficiente al señor MARLÓN ----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representación de ----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los trámites 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 títulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: El 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,-----

***** 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.

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 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 MISNKI GONTOVNIK, cc. No. 7.463.982 en su condicion 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 Nnacional de estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y peticiones de la empresa, segun 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, segun 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

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



***** Pag. 6
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
09*****

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

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

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 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 está 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 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

Que su última Renovación fue el: 31 de Marzo de 2011.

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

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre

***** 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.

que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. Rojas

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

Referencia : Expediente N° 11 002094
Asunto : Oposición a la solicitud de patente de Invención titulada
"POVIDONA YODADA, UN PRESERVATIVO
ALTERNATIVO NOVEDOSO PARA COMPOSICIONES
OFTALMOLOGICAS"
Solicitante : FORESIGHT BIOTHERAPEUTICS INC
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 634 del 21 de noviembre de 2011

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **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 "**POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS**", cuyo titular es **FORESIGHT BIOTHERAPEUTICS INC**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **POVIDONA YODADA**. 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 11 de enero de 2011, reivindicando prioridad bajo la solicitud US20080129222 del 2008-06-12; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 634 del 21 de **noviembre** de 2011, cuya publicación internacional corresponde a la WO2009151619 del 2009-12-17.
- 2.2. La solicitud colombiana 11 002094 objeto de la presente oposición, se refiere a una preparación oftálmica preservada que comprende Povidona yodada (PVP-I) en una concentración suficiente para preservar la preparación oftálmica, y por lo menos un miembro seleccionado del grupo que consiste de un compuesto esteroideal anti-

inflamatorio, un compuesto no esteroidal anti-inflamatorio, un compuesto antibacteriano, un compuesto antialérgico, y un compuesto anti-glaucoma. La solicitud también incluye agregar a una preparación oftálmica PVP-I en una cantidad suficiente para preservar la preparación oftálmica.

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: US2007219170 publicada el 20 de septiembre de 2007.
- D2: US6328991 publicada el 11 de diciembre de 2001.

2.4. Así entonces, el documento D1, se refiere a una composición oftálmica tópica compuesta de 0,01% a 10,0% de povidona yodada combinada con un fármaco anti-inflamatorio esteroide o no esteroide. Esta solución según la invención es útil en el tratamiento de infecciones activas de al menos un tejido del ojo (por ejemplo, la conjuntiva y la córnea) de causas bacterianas, micobacterianas, virus, hongos, o amebiana, así como tratamiento para prevenir tales infecciones en entornos clínicos apropiados (abrasión corneal por ejemplo, la profilaxis post-operatorio, post-LASIK/LASEK profilaxis y, el documento uno menciona que la solución es eficaz en la prevención de la infección e inflamación oftálmica es pacientes post-operatorios. Adicionalmente, de forma particular en la descripción, Dicho documento D1 enseña de forma particular en los párrafos 0007, 0013, 0025, 0032,

0043 y 0075 una preparación oftálmica conservada que comprende: a) una povidona-yodada (PVP-I) a una concentración suficiente para tratar infecciones de la conjuntiva y de la córnea y b) al menos un miembro seleccionado del grupo que consiste en compuestos anti-inflamatorios esteroides y compuestos anti-inflamatorios no esteroides.

2.5. Consecuentemente, el documento D2 que se refiere a una composición química, el método y los productos para la administración en el canal vaginal, revela de forma particular en las columnas 1 y 19 una composición farmacéutica que comprende PVP-I (Povidona yodada), que actúa como un excelente conservante, y en la que la PVP-I proporciona una acción anti-infectiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 en combinación con el documento D2, carece de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 002094 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado*

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 620 50 21 - Fax. (571) 6 12 19 79

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

Bogotá Colombia

de manera evidente del estado de la técnica.”. A la fecha de prioridad, 12 de junio de 2008, a partir del documento D1 en combinación con D2, un experto en la materia puede llegar de manera evidente a combinar la preparación oftálmica conservada enseñada en el Documento D1, con la propiedad conservante de PVP-I revelada en el documento D2 para desarrollar una mejora de la preparación oftálmica conservada donde la povidona-yodo (PVP-I) proporciona una propiedad conservante un y una característica antimicrobiana, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada ***“POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS”***, cuyo titular es FORESIGHT BIOTHERAPEUTICS INC, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 634 del 21 de noviembre de 2011.

3. PRUEBAS

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

- D1: US2007219170 publicada el 20 de septiembre de 2007.
- D2: US6328991 publicada el 11 de diciembre de 2001.

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: US2007219170 publicada el 20 de septiembre de 2007.
 - D2: US6328991 publicada el 11 de diciembre de 2001.

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Bogotá Colombia



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

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

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 620 50 21 - Fax. (571) 6 12 19 79

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

Bogotá Colombia

ANEXO 1



US 20070219170A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0219170 A1**
Samson et al. (43) **Pub. Date: Sep. 20, 2007**

(54) **OPHTHALMIC COMPOSITIONS
COMPRISING POVIDONE-IODINE**

Publication Classification

(76) Inventors: **C. Michael Samson**, New York,
NY (US); **Bo Liang**,
Lawrenceville, NJ (US); **Joseph A.**
Capriotti, New York, NY (US)

(51) **Int. Cl.**
A61K 31/56 (2006.01)

(52) **U.S. Cl.** **514/171**

Correspondence Address:

**MINTZ LEVIN COHN FERRIS GLOVSKY &
POPEO**
666 THIRD AVENUE
NEW YORK, NY 10017

(21) Appl. No.: **11/636,293**

(22) Filed: **Dec. 7, 2006**

Related U.S. Application Data

(60) Provisional application No. 60/782,629, filed on Mar.
14, 2006, provisional application No. 60/848,315,
filed on Sep. 29, 2006.

(57) **ABSTRACT**

A topical ophthalmic composition comprised of povidone-iodine 0.01% to 10.0% combined with a steroid or non-steroidal anti-inflammatory drug. This solution is useful in the treatment of active infections of at least one tissue of the eye (e.g., conjunctiva and cornea) from bacterial, mycobacterial, viral, fungal, or amoebic causes, as well as treatment to prevent such infections in appropriate clinical settings (e.g. corneal abrasion, postoperative prophylaxis, post-LASIK/LASEK prophylaxis). Additionally the solution is effective in the prevention of infection and inflammation in the post-operative ophthalmic patient.

OPHTHALMIC COMPOSITIONS COMPRISING POVIDONE-IODINE

RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Application Ser. No. 60/782,629 filed Mar. 14, 2006 and U.S. Provisional Application Ser. No. 60/848,315 filed Sep. 29, 2006. All patents, patent applications, and references cited anywhere in this specification are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Infectious conjunctivitis is an ophthalmic disorder characterized by inflammation of the conjunctiva secondary to invasion of a microbe. Microbes capable of causing conjunctivitis in humans include bacteria (including *Mycobacteria* sp), viruses, fungi, or amoebae. Current treatment for bacterial conjunctivitis consists of antibiotic drops. Because antibiotic drops are ineffective against viral conjunctivitis, treatment of such infections consists only of relieving symptoms. Treatments for fungi and amoeba conjunctivitis consist of a small selection of medications which lacks anti-bacterial or anti-viral activity and which, in addition, is toxic to the ocular surface.

[0003] Diagnosis of the various causative agents such as bacteria, virus, or fungus, in infectious conjunctivitis is not economically feasible because accurate diagnosis requires sophisticated laboratory culture not easily integrated into the average healthcare practice. Because accurate diagnosis is impractical, most conjunctivitis is presumed to be bacterial without culturing and is treated with antibiotics. Antibiotic treatment is suboptimal because it is ineffective against viral or fungal conjunctivitis.

[0004] The use of steroids is approached cautiously in the setting of ocular infection. While steroids can have the benefit of reducing the severity of the inflammation in an acute infection, they are also known to increase susceptibility to certain infections.

[0005] Topical corticosteroids are routinely used to control ocular inflammation. Their mechanism of action involves the inhibition of the immune response and the subsequent tissue destruction that exuberant inflammation may cause. Corticosteroid has the undesirable side effect of limiting the body's intrinsic ability to fight infection. In fact, inopportune steroids usage can worsen the course of an infection secondary to mycobacteria, virus, or fungus. Thus, the use of a combined antimicrobial-steroid medication in ocular infections is recommended only under careful observation of a trained ophthalmologist because of these significant risks. In fact, Tobradex® (Alcon), the most commonly prescribed combination ophthalmic antimicrobial-steroid drug, specifically lists 'viral disease of the cornea and conjunctiva, mycobacteria infection, and fungal infection' as absolute contraindications to its use. Clearly, these combination drugs were not intended to be used in the face of infectious conjunctivitis in which bacterial infection cannot be confirmed.

[0006] In summary, there is currently no ophthalmic antimicrobial drug with broad activity against all the causes of conjunctivitis or keratitis, and there is currently no approved antimicrobial/steroid, or antimicrobial/non steroidal anti-

inflammatory combination drug that can be safely used in infectious conjunctivitis or keratitis that can potentially be viral or fungal in origin.

SUMMARY OF THE INVENTION

[0007] The invention is an ophthalmic composition comprised of povidone-iodine 0.01%-10% (weight/weight or weight/volume) combined with an anti-inflammatory medication, a steroid, or a combination of both anti-inflammatory and a steroid. In a preferred embodiment, the povidone-iodine (PVP-I) is between 0.1% and 2.5%, between 0.5 and 2%, between 0.75 and 2%, between 0.8 and 2%, between 0.9 and 2%, between 1% and 2% or between 1% and 1.5%. In another embodiment, the total weight of the PVP-I, anti-inflammatory and steroid is between 0.1% and 4.5%. This solution is useful in the treatment of infections of the conjunctiva and cornea. The broad spectrum of povidone-iodine would allow this combination to be used in cases of ocular conjunctival or corneal infection caused by mycobacteria, viruses, fungi, and amoeba; this is in distinction to currently available combination antimicrobial-steroid ophthalmic compositions, which are contraindicated in the aforementioned infections. Additionally the solution will be useful in the infectious prophylaxis and inflammatory control of patients recovering from recent ophthalmic surgery. There are no currently available antimicrobial/anti-inflammatory or antimicrobial/steroid combinations useful for viral, fungal, mycobacterial and amoebic infections in the post-operative period.

[0008] One embodiment of the invention is directed to an ophthalmic composition suitable for topical administration to an eye, effective for treatment and/or prophylaxis of a microorganism infection or a disorder of at least one tissue of the eye. Prophylaxis may be, for example, prophylaxis from infection following surgery, prophylaxis from infection after birth for the newborn, or prophylaxis from accidental contact with contaminating material. Accidental contact with contaminating material may occur, for example, during surgery or during food processing. The composition comprises povidone-iodine in a concentration between 0.01% to 10%, and an anti-inflammatory, a steroid, or a combination thereof.

[0009] The mammalian eye can be divided into two main segments: the anterior segment and the posterior segment. The anterior segment is the front third of the eye that includes the tissues in front of the vitreous humor: the cornea, iris, ciliary body, and lens. Within the anterior segment are two fluid-filled spaces: the anterior chamber and the posterior chamber. The anterior chamber is located between the posterior surface of the cornea (i.e. the corneal endothelium) and the iris. The posterior chamber is located between the iris and the front face of the vitreous. The posterior segment is the back two-thirds of the eye that includes the anterior hyaloid membrane and all tissues behind it: the vitreous humor, retina, choroid, and optic nerve. In some animals, the retina contains a reflective layer (the tapetum lucidum) which increases the amount of light each photosensitive cell perceives, allowing the animal to see better under low light conditions.

[0010] It was surprising to discover that the formulations of povidone-iodine combined with steroids, when present in a suitable pH range, eliminated the undesired irritating effect of PVP-I to the eye. The invention provides pH stable

aqueous suspensions of water-insoluble drugs that remain in such a state even after extended periods of storage.

[0011] In a preferred embodiment, the ophthalmic composition contains povidone-iodine at a concentration between 0.1% and 2.5% by weight, or more preferably, between 0.5% and 2% by weight. In another preferred embodiment, the ophthalmic composition has a total weight of povidone-iodine, an anti-inflammatory, a steroid of between 0.1% to 2.5% (weight to volume, or weight to weight) or between 0.1% to 4.5%.

[0012] The steroid of the ophthalmic composition may be at a concentration of between 0.01 and 10%. In a preferred embodiment, the steroid is at a concentration of between 0.05 and 2%.

[0013] The ophthalmic composition may further comprise (1) a topical anesthetic which relieves pain (2) a penetration enhancer which enhances the penetration of povidone-iodine into the tissues of the eye (this may be a topical anesthetic) (3) an antimicrobial preservative, which, for example, may be at a concentration of about 0.001% to 1.0% by weight; (4) a co-solvent or a nonionic surface agent—surfactant, which, for example, may be about 0.01% to 2% by weight; (5) viscosity increasing agent, which, for example, may be about 0.01% to 2% by weight; and (6) a suitable ophthalmic vehicle.

[0014] The ophthalmic composition may be in the form of a solution, a suspension, an emulsion, an ointment, a cream, a gel, or a controlled-release/sustain-release vehicle. For example, the composition may be in the form of a contact lens solution, eyewash, eyedrop, and the like.

[0015] The ophthalmic composition may be used for treatment and/or prophylaxis of a microorganism infection. The microorganism may be a bacterium, a virus, a fungus, or an amoeba, a parasite, or a combination thereof. The bacteria may be a mycobacterium. Further, the solution may be used to treat or for prophylaxis of disorders such as conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

[0016] For example, the ophthalmic composition may comprise the following: 0.5 to 2% (w/w) polyvinylpyrrolidone-iodine complex; 0.05 to 2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA (ethylenediaminetetraacetic acid); 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; at pH range from 5 to 7. More specifically, the ophthalmic composition may comprise the following: 1.0% (w/w) polyvinylpyrrolidone-iodine complex; 0.1% (w/w) steroid; 0.01% (w/w) EDTA dehydrate; 0.3% (w/w) sodium chloride salt; 0.05% (w/w) tyloxapol; 1.2% (w/w) sodium sulfate; and 0.25% (w/w) hydroxyethylcellulose; at pH range from 5.5 to 6.5. In one embodiment, the composition consists essentially of 0.5 to 2% (w/w) polyvinylpyrrolidone-iodine complex; 0.05 to 2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA (ethylenediaminetetraacetic acid); 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; at pH range from 5 to 7. In another embodiment, the composition consists essentially of 1.0% (w/w) polyvinylpyrrolidone-iodine complex; 0.1% (w/w) steroid; 0.01% (w/w) EDTA disodium salt; 0.3% (w/w) sodium chloride salt; 0.05% (w/w) tyloxapol; 1.2% (w/w) sodium sulfate; and 0.25% (w/w) hydroxyethylcellulose; at pH range from 5.5 to 6.5.

[0017] It is known, of course, that EDTA can be in many forms such as a free acid, disodium, or tetrasodium salts. The steroid may be dexamethasone, prednisolone or prednisone. These steroids may be in their sodium phosphate form (e.g., dexamethasone sodium phosphate, prednisolone sodium phosphate, or prednisone sodium phosphate) or acetate form (e.g., dexamethasone acetate, prednisolone acetate, or prednisone acetate). Prednisolone is an active metabolite of prednisone and it is understood that prednisone may be used instead of prednisolone.

[0018] In a preferred embodiment, the ophthalmic composition retains at least 90% of its PVP-I and at least 90% of its steroid after 1 month, 2 months, 3 months, 6 months or 1 year after it is manufactured. This can be accomplished, at least, by producing the ophthalmic composition according to the formula listed above (e.g. previous two paragraphs). This stability is maintained even when the composition is stored at room temperature in a lighted indoor environment of 100 lux to 1000 lux. In one preferred embodiment, the composition is an aqueous solution.

[0019] In another embodiment, the invention is directed to a method for treating and/or prophylaxis of an eye disorder or a microorganism infection of at least one tissue of the eye comprising the step of administering one of more doses of an ophthalmic composition, discussed above, to the eye. The eye disorder may be, for example, a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis. The microorganism may be a bacteria (e.g., mycobacteria), virus, fungi, or amoebae.

[0020] In the method, the treatment may comprise administering a solution of the invention where the sum of the povidone-iodine, the anti-inflammatory, and the steroid is between 0.001 mg to 5 mg per dose. Further, the dose volume may be between 10 microliters to 200 microliters or between 50 microliters to 80 microliters; about one drop per eye. Administration may be between 1 to 24 times a day, between 2 to 4 times a day or between 2 to 24 times a day.

[0021] In one embodiment, the method further comprises a step of storing the solution for at least one month, at least two months, at least three months, at least six months, or at least one year before it is administered. The storage may be in a clear bottle (a container that does not substantially block light) in a lighted environment. A lighted environment may be, for example, an indoor lighted environment with about 100 lux to 1000 lux of light.

DETAILED DESCRIPTION OF THE INVENTION

[0022] In a preferred embodiment, the compositions of the present invention are administered topically. The dosage range is 0.001 to 5.0 mg/per eye; wherein the cited mass figures represent the sum of the three components: anti-inflammatory, povidone-iodine and topical anesthetic. Dosage for one eye is understood to be about one drop of solution. One drop of solution may be between 10 μ l to 200 μ l, between 20 μ l and 120 μ l, or between about 50 μ l (microliters) to about 80 μ l of solution or any values in between. For example, dispensers such as pipettors can dispense fluid drops from at least 1 μ l to 300 μ l and any value in between.

[0023] In a preferred embodiment, the solution may be administered as an eye drop using any of the many types of

TABLE 2

Samples	concentration (mg/mL)/3 wks	concentration (mg/mL)/7 wks	Concentration change %
CLS-A05B01	0.94	0.92	-2.13
CLS-A10B01	0.86	0.90	4.65
CLS-A15B01	0.93	0.86	-7.53

[0069] HPLC spectra have shown that there were no new peaks appearing compared with standard controls. The spectra suggested that there was no reaction between PVP-Iodine and dexamethasone at all.

[0070] Stability Test of Dexamethasone Sodium Phosphate in the Sample Using HPLC

[0071] The USP method was performed. The concentration data of dexamethasone sodium phosphate is tabulated in chart form below in Table 3. A05C01 (1 day), A10C01, A15C01 (3 days) in 40° C. oven.

TABLE 3

Sample name	Initial Concentration (mg/mL)	Concentration (mg/mL)	Concentration Change %
A05C01	1.273	1.244	-2.28
A10C01	0.948	1.075	13.40
A15C01	1.355	1.148	-15.28

[0072] HPLC spectra have shown that there was a new peak appearing in the samples of A10C01 and A15C01 compared with standard controls and A05C01. The concentrations of dexamethasone sodium phosphate were altered more than 10% in the samples of A10C01 and A15C01.

[0073] In another experiment, we have found, surprisingly, that eye drops of the following formulation: 0.5 to 2% (w/w) polyvinylpyrrolidinone-iodine complex; 0.05 to 0.2% (w/w) steroid; 0.005% to 0.02% (w/w) EDTA; 0.01 to 0.5% (w/w) sodium chloride; 0.02 to 0.1% (w/w) tyloxapol; 0.5% to 2% (w/w) sodium sulfate; and 0.1 to 0.5% (w/w) hydroxyethylcellulose; wherein said steroid is dexamethasone, prednisolone, prednisone, or acetate forms thereof, or sodium phosphate forms thereof were stable for 1 month, 3 months and up to 6 months. Based on data gathered so far, such a solution appears to be capable of storage of up to at least 1 year from the date for manufacturer. Stability is defined as a deviation in concentration of the major components (PVP-I and steroid) by less than 10% over a period of time. Thus, the PVP-I was not reduced to less than 90% over the period of 1 month, 3 months, and 6 months while the solution is in storage and based on our data at 6 months, it appears that the solution would be stable for at least one year. Storage conditions was at room temperature, in clear bottles, in indoor lighting of 100 to 1000 lux of incandescent and/or fluorescent lighting. The stability may be attributed to the unique combination of PVP-I and dexamethasone, prednisolone, prednisone (including acetate forms and sodium phosphate forms of these steroids). We have additionally found that the other reagents (EDTA, sodium chloride, tyloxapol, sodium sulfate; and hydroxyethylcellulose) when present, further contributed to stability.

[0074] We have found, when comparing various formulations during development, that PVP-I confers a number of advantages in the formulation. Briefly, PVP-I formulations have the following improved properties compared to an

iodine solution: (1) less irritating to the skin and eye, (2) washable, (3) increased stability, (4) increased stability in light, (5) low systemic toxicity, (6) less side effects. Also, based on current knowledge, PVP-I is neutral with respect to scar tissue formation.

Example 4

Antimicrobial Assays

[0075] Solutions of PVP-iodine combinations with various anti-inflammatory steroids were tested for antimicrobial activity against common pathogenic bacteria, yeast, fungi and viruses. The broth inoculation method of Antimicrobial Assays (USP) was used to conduct the efficacy test of the treatment of various concentrations of the solutions of PVP-iodine combinations against pure ocular isolates. It was found that the concentrations of PVP-iodine from 0.03% can dose-dependently produce the suppressing effects on microbial growth. The antimicrobial effects can be further supported by completely eliminating all species tested within 72 hours of inoculating treatment with 0.03% solution. The optimal efficacy of antimicrobial effects can be achieved at concentrations above 0.5%. Above the concentrations, the solution can effectively kill and eliminate all species tested even under a condition of immediate contact without further inoculation. For example, a solution of 1% PVP-iodine and 0.1% dexamethasone (wt %) was found to kill on contact *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, Methicillin Resistant *Staphylococcus Aureus*, *Klebsiella pneumoniae*, *Candida parapsilosis*, *Candida albicans* and *Apergillus niger*. The results clearly demonstrated the efficacy of the solutions on eliminating microbial growth.

Example 5

Adenovirus Testing

[0076] Solutions of PVP-iodine combinations with dexamethasone were tested for antiviral activity against human adenovirus. A 0.5 mL aliquot of each test and control article was combined with 0.5 mL of virus stock in a sterile tube. The tubes were then incubated at 37° C. for 30 minutes. AOOB01 was used as the positive control. Hank's Balanced Salt Solution (HBSS) was used as the negative control. Immediately following incubation the test and control articles were titrated for infectious HAdV-4.

TABLE 4

Antiviral Activity	
Customer Sample Number	HAdV-4 Titer (Log ₁₀ TCID ₅₀ /mL)
A00B01	4.4
A10B01	≤1.6
A15B01	≤1.6
A20B01	≤1.6
HBSS	4.0

[0077] Following a 30 minute incubation of the test articles with virus, A00B01 had no effect on virus infectivity,

[0056] The LC-MS spectra of A05C01, A10C01, and A15C01 confirmed the dexamethasone phosphoric acid (MH⁺=472.9) peak. The LC-MS spectra of A05D01, A10D01, and A15D01 confirmed the prednisolone phosphoric acid (MH⁺=440.9) peak.

[0057] However, the LC-MS experiments of A05K01 and A10K01 confirmed the finding of reaction between PVP-I and ketorolac tromethamine. For A05K01, there was a small amount of ketorolac left in the sample (MH⁺=256.1), the major peak is: MH⁺=381.9. For A10K01 and A15K01, there was no ketorolac left and has converted to a new compound (MH⁺=381.9) completely.

[0058] LC-MS experiments of A00B01P008 (control), A05B01P008 and A10B01P008 confirmed the finding of reaction between PVP-I and proparacaine. For the control, two peaks: MH⁺=295.1 (proparacaine) and MH⁺=392.9 (dexamethasone) were observed in the LC-MS spectrum. Comparing A05B01P008 with A10B01P008, the proparacaine peak (MH⁺=295.1) relative to the dexamethasone peak (MH⁺=392.9) became much smaller, which suggests povidone iodine reacted with proparacaine.

Example 3

Production of Povidone-Iodine/Dexamethasone/
Proparacaine Suspensions

[0059]

Amount (wt. %)	
PVP-I	0.0 to 1.5
Dexamethasone, Micronized, USP	0.1
Proparacaine hydrochloride, USP	0.08%
EDTA, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or Sodium hydroxide	q.s. for pH adjustment to 5.7-5.9
Sterile water, USP	q.s. to 100

[0060] In a 400 mL beaker was added 100 g sterile water, hydroxyethylcellulose (0.75 g, 0.25% w/w) was added under vigorous stirring with an ARROW overhead stirrer. Sodium chloride (0.9 g, 0.3% w/w) was slowly added while dissolving, followed by addition of EDTA (0.03 g, 0.01% w/w), sodium sulfate (3.6 g, 1.2% w/w) and proparacaine hydrochloride salt (0.24 g, 0.08% w/w) sequentially. After stirring for 10 minutes, tyloxapol (0.15 g, 0.05% w/w) dissolved in water was transferred into the above solution. The reaction mixture was stirred for 1 hour and dexamethasone (0.3 g, 0.1% w/w) was added and homogenized for 10 minutes and then q.s. to 180 g with sterile water to give the bulk solution 5. 60 g each of the bulk solution 5 was transferred into four 125 mL beakers, and povidone-iodine complex (0.0 g, 0.5 g, 1.0 g) was added into the respective solutions while stirring. The pH value was adjusted to around 5.8 by addition of sodium hydroxide or sulfuric acid and q.s. the solution to 100 g to afford samples A00B01P008, A05B01P008, and A10B01P008.

[0061] During the production of these samples, strong smell of iodine was observed. It was speculated that PVP-I reacted with proparacaine very rapidly. The speculation was confirmed by LC-MS spectra. The dexamethasone and pro-

paracaine peaks in the combination samples with PVP-I became very small or even disappeared.

Stability of the Solutions

[0062] The amount of titratable iodine in the solutions was determined by titration method after various week of sample storage at room temperature.

[0063] Titration Method: 5 mL of each sample was transferred into a 125 mL beaker by pipette, and 1 mL of 1% (w/v) starch indicator solution was added. The solution was titrated with 0.0025N sodium thiosulfate solution until the blue color disappeared completely. The volume of sodium thiosulfate solution used was determined.

$$\text{Titratable Iodine (mg)} = V \text{ (mL, volume used for titration)} \times 12.69 \text{ (mg/mL)/2}$$

[0064] The calculated titratable iodine (mg) is listed in Table 1.

TABLE 1

Stability Data Summary (Available Iodine)					
sample	Iodine (mg) 0 wk	Iodine (mg) After 1 wk	Iodine (mg) change %	Iodine (mg) after 8 wks	Iodine (mg) change %
CLSA05B00	2.32	2.25	-3.02		
CLSA15B00	7.31	7.17	-1.92		
CLSA03B01	1.36	1.27	-6.62	1.08	-20.59
CLSA05B01	2.27	2.32	2.2	2.25	-0.88
CLSA10B01	4.28	4.28	0	4.25	-0.7
CLSA15B01	7.28	7.36	1.1	7.52	3.3
CLSA20B01	9.87	9.9	0.3	9.71	-1.62

	Iodine (mg) (After 4 wks)	Iodine (mg) (After 12 wks)	Iodine (mg) change %
CLSA10C01	4.25	4	-5.9
CLSA15C01	6.79	6.54	-3.7
CLSA10D01	4.6	4.38	-4.8
CLSA15D01	6.44	6.41	-0.5

	0 wk	After 5 wks	
CLSA05K01	1.81	0	-100
CLSA10K01	4.54	1.87	-58.8
CLSA15K01	7.17	4.57	-36.3

[0065] The data of concentration of PVP-Iodine after weeks of storage at room temperature, either at dark or light, have suggested that stable combination formulations have been achieved for PVP-iodine combinations with dexamethasone, or dexamethasone sodium phosphate or prednisolone sodium phosphate. The 0.3% (wt. %) PVP-I combination with dexamethasone is less stable than those of above 0.5% PVP-Iodine combinations with dexamethasone, which have less than 5% alteration of the available iodine concentration after 8 weeks.

[0066] Data has also suggested PVP-I reacted with ketorolac tromethamine. At 0.5% PVP-I in the sample after five weeks, there was no titratable iodine left. At 1.5% and 1.5% of PVP-I in the samples, the titratable iodine was depleted significantly at 58.8% and 36.3%, respectively.

[0067] Stability Test of Dexamethasone in the Sample Using HPLC

[0068] The USP method was performed. The concentration of dexamethasone data is tabulated in chart form below in Table 2:

[0044] Although a topical steroid is of tremendous benefit in the treatment of ocular inflammation, its use is fraught with risks. Topical steroids applied to the eye act by a variety of well described genomic and non-genomic mechanisms to reduce the production of constituent proteins of the inflammatory cascade, decrease vascular permeability, decrease the production of pro-inflammatory cytokines, decrease the potency of soluble inflammatory factors, inhibit the production of acute phase proteins, decrease leukocyte migration and increase the stability of cell membranes. Through all of these mechanisms, topically applied steroids can reduce the local concentrations of activated products toxic to the eye including the gelatinase, collagenase and matrixmetalloproteinase families of proteins. With this reduction in potentially toxic substances comes the increased risk of prolonged infection and potential infection. If the topical steroid is given in combination with an appropriate antimicrobial (i.e. and antibacterial for bacterial infection, an antiviral for viral infection, an antifungal for fungal infection) its risk can be reduced and/or eliminated. The usual practicing ophthalmologist cannot reliably distinguish the causative agent in most cases of acute external eye infection in a time frame relevant to the prescription of treatment. Thus the beneficial effects one may gain from the prompt use of topical steroids are delayed or eliminated entirely as the clinician either waits for culture results or more likely delays treatment indefinitely. The novel combination of a polymicrobicidal effective against bacteria, viruses and fungi and a topical steroid eliminates this risk and allows the immediate control of inflammation and eradication of pathogen. In our view, this is the most preferred embodiment of the present invention.

[0045] We also noted that the other components in our preferred composition appear to further stabilize the formulation. That is, the EDTA, sodium chloride, tyloxapol, sodium sulfate and hydroxyethylcellulose appear to have additional beneficial effects of further stabilizing the composition.

[0046] The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto. All patents, patent applications, and references cited anywhere is hereby incorporated by reference in their entirety.

EXAMPLES

[0047] Throughout this section the letter "A" in a sample name refers to Povidone-Iodine complex ("PVP-I"), A00 refers to PVP-I at 0.0%, A03 refers to PVP-I at 0.3%, A05 refers to PVP-I at 0.5%, A10 refers to PVP-I at 1.0%, A15 refers to PVP-I at 1.5%, A20 refers to PVP-I at 2.0%, A40 refers to PVP-I at 4.0% and so on.

[0048] Similarly, the letter "B, C, D, K, P" in a sample name refers to dexamethasone, dexamethasone sodium phosphate, prednisolone sodium phosphate, ketorolac (also called ketorolac) and proparacaine, respectively. B00 refers to dexamethasone at 0.0%, B01 refers to dexamethasone at 0.1%, C01 refers to dexamethasone sodium phosphate at

0.1%, D01 refers to prednisolone sodium phosphate at 0.1%, K01 refers to ketorolac at 0.1%, and P008 refers to proparacaine at 0.08%, and so on.

Example 1

Production of Povidone-Iodine/Dexamethasone Suspensions

[0049]

Amount (wt. %)	
Povidone-Iodine (PVP-I)	0.0 to 4.0
Dexamethasone, Micronized, USP	0.1
EDTA, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or Sodium hydroxide	q.s. for pH adjustment to 5.7-6.0
Sterile water, USP	q.s. to 100

[0050] Experimental Procedures:

[0051] In a 1000 mL beaker was added 400 g sterile water, hydroxyethylcellulose (2.25 g, 0.25% w/w) was added under vigorous stirring with an overhead stirrer. Sodium chloride (2.70 g, 0.3% w/w) was slowly added while dissolving, followed by addition of EDTA (0.09 g, 0.01% w/w) and sodium sulfate (10.8 g, 1.2% w/w). After stirring for 10 minutes, tyloxapol (0.45 g, 0.05% w/w) dissolved in water was transferred into the above solution. The reaction mixture was stirred for 1 hour and q.s. to 540 g with sterile water and was stirred for another 10 minutes to give "bulk solution 1."

[0052] 60 g each of the bulk solution 1 was transferred into two 125 mL beakers, and povidone-iodine complex (0.5 g, 1.5 g) was added into the respective solution while stirring. The pH value was adjusted to the range of 5.7 to 6.0 by addition of sodium hydroxide or sulfuric acid and q.s. the suspensions to 100 g with sterile water to give control samples A05B00 and A15B00, respectively.

[0053] The remaining 417 g of the bulk solution 1 was added dexamethasone (0.7 g, 0.1% w/w) and homogenized for 5 minutes and then q.s. to 420 g to give bulk solution 2.

[0054] 60 g each of the bulk solution 2 was transferred into seven 125 mL beakers, and povidone-iodine complex (0.0 g, 0.3 g, 0.5 g, 1.0 g, 1.5 g, 2.0 g, and 4.0 g) was added into the respective solution while stirring. The pH value was adjusted to the range from 5.7 to 6.0 by addition of sodium hydroxide or sulfuric acid and q.s. the suspensions to 100 g with sterile water to give samples A00B01, A03B01, A05B01, A10B01, A15B01, A20B01 and A40B01, respectively. The LC-MS spectra of all samples confirmed the finding that there was no reaction between PVP-I and dexamethasone at all. The dexamethasone (MH⁺=392.9) peak has not been altered to other mass peaks.

Example 2

Production of Solutions of Povidone-Iodine/Dexamethasone Sodium Phosphate; Povidone-Iodine/Prednisolone Sodium Phosphate; and Povidone-Iodine/Ketorolac

[0055] In a similar manner, solutions of A00C01, A03C01, A05C01, A10C01, A15C01, A00D01, A03D01, A05D01, A10D01, A15D01, A00K01, A05K01, A10K01, and A15K01 were produced.

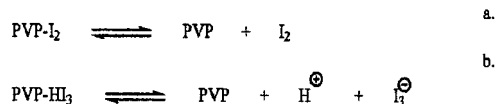
thereof. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

Viscosity Agents

[0034] The compositions of the invention may contain an optional viscosity agent—that is, an agent that can increase viscosity. Viscosity increased above that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulation, to decrease physical separation of components of a suspension or emulsion of the formulation and/or to otherwise improve the ophthalmic formulation. Such viscosity builder agents include as examples polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, other agents known to those skilled in the art, or a combination thereof. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The Formulation

[0035] The following two reactions must be considered for the chemistry of PVP-I in aqueous solutions:



[0036] The affinity of free iodine (I₂) for reaction with —OH, —SH and —NH functional groups is well described in the literature and forms the basis for the anti-microbial activity of iodine-containing solutions (Rackur H. *J. Hosp. Infect.*, 1985; 6: 13-23, and references therein). Dexamethasone (9-Fluoro-11 β , 17, 21-trihydroxy-16 α -methylpregna-1, 4-diene-3, 20-dione) contains three such moieties (—OH) at the 11, 17 and 21 positions. A person in the field would conclude that these hydroxyl groups would be prone to covalent substitution reactions by the free iodine generated in the solution equilibrium reaction described above for PVP-I₂.

[0037] In deriving the present formulations, experiments of combinations of various anti-inflammatories and PVP-I, or steroids and PVP-I, were performed. It was observed that most formulations were unsuccessful because of the rapid reaction between PVP-I and the added reagent (anti-inflammatory or steroid). Some of these unsuccessful formulations are described elsewhere in this disclosure. Particularly, the limiting factor for lower concentrations of PVP-I solutions is stability and efficacy as a microbicidal.

[0038] It is thus the object of the present invention to discover novel formulation of combinations of PVP-I and an anti-inflammatory to solve three problems of stability, efficacy and non-irritating to the eye. We have found, unexpectedly, that a 1% PVP-I solution is effective for treatment of infection or prophylaxis of infections when combined with dexamethasone. The literature has previously indicated that while 1% PVP-I is desirable, the side effects of ocular administration precluded its use. The undesirable side effects include pain and irritation.

[0039] It was surprising to discover that the solution of PVP-I and dexamethasone remains stable for many months.

Based on the stability data disclosed, we conjecture that the compositions of the invention may be stable for years—although experiments are still ongoing at this point. It is a further unexpected result that the reaction of dexamethasone and PVP-I does not proceed to any appreciable extent at room temperature, in light or dark, over time. Unexpectedly the reaction between the free iodine in solution and the hydroxyl groups present on the dexamethasone molecule as compounded in our formulation does not proceed.

[0040] Due to the high propensity of oxidative potential of PVP-I, the resulted stable combination of PVP-I and dexamethasone is unexpected for the average worker/scientist/physician in this field. It was observed when the concentration of PVP-I is larger than 0.5%, a stable combination formulation can be achieved. Surprisingly, it was found that 0.3% PVP-I combination with dexamethasone was much less stable. This is once again unexpected because the lower concentrations of iodine are expected to be less reactive and hence, less destructive to either parts. After 8 weeks, the available iodine in the combination (0.3% PVP-I initially) decreased by 20%. Though 0.1% diluted PVP-I has the strongest antimicrobial activity (Gottardi W. *J. Hosp. Infect.*, 1985; 6(Suppl): 1-11) our data showed we need at least 0.5% PVP-I in combination with dexamethasone to show the best antimicrobial activity. We have observed PVP-I reacted with Ketorolac (a non-steroidal anti-inflammatory) rapidly and the Ketorolac was completely consumed and the available iodine in the PVP-I complex was reduced significantly depending on the ratio between Ketorolac and PVP-I. The combination of PVP-I and dexamethasone sodium phosphate also proved to be less successful but also useful. We observed some dissociation of PVP-I complex to an unknown polymeric complex in the UV spectra and the iodine reduction is around 5% after 12 weeks. It was further observed that PVP-I reacts immediately with proparacaine and releases free iodine rapidly.

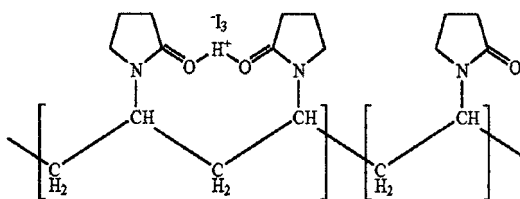
[0041] Surprisingly, the combination formulation has contributed to the stability of diluted PVP-I solution. The available iodine of a 0.625% povidone-iodine solution was 91% at 25° C. and 98% at 4° C. after 5 weeks storage, respectively. (*Iryo Yakugaku* 2003, 29(1), 62-65). Our data showed that our formulation stabilized the diluted PVP-I solution. After 8 weeks at room temperature, the available iodine in solutions with 0.5% and 1% PVP-I were over 99%.

[0042] The use of topical steroids alone is contraindicated in suspected viral and fungal infections of the human eye. Furthermore the use of combination anti-bacterial/steroid solutions is contraindicated in the setting of suspected viral infection. There are no steroid-containing solutions described that are safe for use in the human eye in the setting of presumed viral or fungal infection. It is therefore unexpected to the authors and others in the field that a steroid-containing solution would be of use in the treatment of an acute viral or fungal ocular infection.

[0043] A potent anti-inflammatory steroid allows the temperance of the potentially devastating ocular immune response in the setting of an active infection. However, due to the antiseptic (antibacterial, antiviral, and antifungal, antiprotozoal) power of PVP-I, the compound is useable in the setting of active infection without the risk of worsening the infection. This unique property (poly-antimicrobicide and potent anti-inflammatory) is a significant improvement over all other ocular antibiotics and anti-inflammatory.

eye drop dispensers on the market. Although not required, the container for the compositions of the invention may be clear, translucent, and opaque and may contain other properties or combination of properties such as being glass lined, tamper proof, packaged in single or few dose aliquots, and a combination thereof.

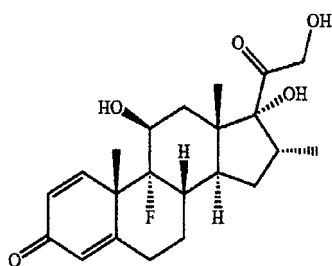
[0024] Povidone-iodine has the following chemical structure:



[0025] Suitable anti-inflammatories for the compositions and methods of the invention include, at least, the following: ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorlac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, or a derivative or combination thereof. Ketorolac (also called ketorlac, or ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAID) in the family of propionic acids.

[0026] Suitable steroids for the compositions and methods of the invention include, at least: dexamethasone, dexamethasone alcohol, dexamethasone sodium phosphate, fluomethalone acetate, fluomethalone alcohol, lotoprendol etabonate, medrysone, prednisolone, prednisone, prednisolone acetate, prednisolone sodium phosphate, rimexolone, hydrocortisone, hydrocortisone acetate, lodoxamide tromethamine, or a derivative or combination thereof. It is understood, for any of the chemicals of this disclosure, that the chemicals may be in various modified forms such as acetate forms, and sodium phosphate forms, sodium salts, and the like.

[0027] Dexamethasone has the following chemical structure:



[0028] It is known that any of the reagents mentioned anywhere in this disclosure may be in chemically equivalent forms such as salts, hydrides, esters and other modifications of the basic chemical. For example, dexamethasone in any of the compositions and methods of the invention may be replaced with any of its derivatives, including esters and salts thereof. Examples of such derivatives include, at least, Dexamethasone-17-acetate (CAS RN: 1177-87-3), Dexamethasone Disodium Phosphate (CAS RN: 2392-39-4), Dexamethasone Valerate (CAS RN: 14899-36-6), Dexametha-

sone-21-isonicotinate (CAS RN: 2265-64-7), Dexamethasone Palmitate (CAS RN: 33755-46-3), Dexamethasone Propionate (CAS RN: 55541-30-5), Dexamethasone Acefurate (CAS RN: 83880-70-0), Dexamethasone-21-galactoside (CAS RN: 92901-23-0), dexamethasone 21-thiopivalate, dexamethasone 21-thiopentanoate, dexamethasone 21-thiol-2-methyl-butanoate, dexamethasone 21-thiol-3-methyl-butanoate, dexamethasone 21-thiohexanoate, dexamethasone 21-thiol-4-methyl-pentanoate, dexamethasone 21-thiol-3,3-dimethyl-butanoate, dexamethasone 21-thiol-2-ethyl-butanoate, dexamethasone 21-thiooctanoate, dexamethasone 21-thiol-2-ethyl-hexanoate, dexamethasone 21-thiononanoate, dexamethasone 21-thiodecanoate, dexamethasone 21-p-fluorothiobenzoate or a combination thereof. Dexamethasone derivatives are also described in U.S. Pat. No. 4,177,268.

[0029] Suitable topical anesthetics for the compositions and methods of the invention include, at least, proparacaine, lidocaine, tetracaine or a derivative or combination thereof.

[0030] The compositions of the present invention can be administered as solutions, suspensions, emulsions (dispersions), gels, creams, or ointments in a suitable ophthalmic vehicle.

[0031] In any of the compositions of this disclosure for topical administration, such as topical administration to the eye, the mixtures are preferably formulated as 0.01 to 2.0 percent by weight solutions in water at a pH of 5.0 to 8.0 (figures relate to combined presence of povidone-iodine and dexamethasone). This pH range may be achieved by the addition of buffers to the solution. We have found that, surprisingly, the formulation of the present invention is stable in buffered solutions. That is, there is no adverse interaction between the buffer and the iodine or other component that would cause the composition to be unstable. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye 1 to 24 times daily. For example, the solution may be applied 1, 2, 4, 6, 8, 12, 18 or 24 times a day.

Antimicrobial Preservative

[0032] As an optional ingredient, suitable antimicrobial preservatives may be added to prevent multi-dose package contamination. Such agents may include benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, EDTA, sorbic acid, Onamer M, other agents known to those skilled in the art, or a combination thereof. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

Co-Solvents/Surfactants

[0033] The compositions of the invention may contain an optional co-solvent. The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents/surfactants include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g. Pluronic F-68, F-84 and P-103), cyclodextrin, tyloxapol, other agents known to those skilled in the art, or a combination

but compounds A10B01, A15B01 and A20B01 resulted in complete inactivation of the virus.

Example 6

Human Eye Irritation Studies

[0078] All volunteers were examined before testing and found to have healthy eyes with no signs of disease. 1.0% PVP-Iodine solution alone was made and tried in 15 healthy volunteers. Side effects of treatment were immediately reported. The side effects found included mild pain, discomfort, tearing, and redness. This is consistent because the literature has previously indicated that 1% PVP-iodine is unsuitable for use because of irritation that is unacceptable to the patient (e.g., U.S. Pat. No. 5,126,127). From the reported side effects, it is clear that a regiment of multiple applications to the volunteers would be intolerable.

[0079] The solution of A10B01, containing 1% PVP-I and 0.1% dexamethasone, was tested by seven healthy volunteers. Administration was by eye drop. It was surprisingly found that the solution was tolerable to the eye (does not burn) and was comfortable at a range of pH. Specifically, the formulation of pH 5.9 formulation is comfortable upon instillation into the eye. One person used the solution as an eye drop four times a day for a period of 3 days with no adverse side effects. Other pH values, such as pH 6 to 8, are obtainable either by adjusting the pH alone, with a suitable chemical such as sulfuric acid or sodium hydroxide, or by the addition of a suitable buffer.

[0080] All volunteers were examined by physicians immediately after the trial period and in further follow-up examinations after a period of time. Further, volunteers were contacted by physicians at one month, two months and three months after trial and no adverse effects were reported for any of the volunteers.

We claim:

1. An ophthalmic composition suitable for topical administration to an eye, effective for treatment and/or prophylaxis of a microorganism infection or a disorder of at least one tissue of the eye, comprising

- a) povidone-iodine in a concentration between 0.01% and 10%, and
- b) An anti-inflammatory, a steroid, or a combination thereof.

2. The ophthalmic composition of claim 1 wherein said povidone-iodine is between 0.1% and 2.5% by weight.

3. The ophthalmic composition of claim 1 wherein said povidone-iodine is between 0.5% and 2% by weight.

4. The ophthalmic composition of claim 1 wherein a total weight of said povidone-iodine, said anti-inflammatory, and said steroid is between 0.1% and 4.5% in said solution.

5. The ophthalmic composition of claim 1 wherein said anti-inflammatory agent is selected from the group consisting of ketotifen fumarate, diclofenac sodium, flurbiprofen sodium, ketorlac tromethamine, suprofen, celecoxib, naproxen, rofecoxib, and a combination thereof.

6. The ophthalmic composition of claim 1 wherein said steroid is at a concentration of between 0.01 and 10%.

7. The ophthalmic composition of claim 1 wherein said steroid is at a concentration of between 0.05 and 2%.

8. The ophthalmic composition of claim 1 wherein said steroid is selected from the group consisting of dexametha-

sone, dexamethasone alcohol, dexamethasone sodium phosphate, and salts, esters, and derivatives and combinations thereof.

9. The ophthalmic composition of claim 1 wherein said steroid is selected from the group consisting of fluomethalone acetate, fluomethalone alcohol, lotoprendol etabonate, medrysone, prednisolone, prednisone, prednisolone acetate, prednisolone sodium phosphate, rimexolone, hydrocortisone, hydrocortisone acetate, Iodoxamide tromethamine and a combination thereof.

10. The ophthalmic composition of claim 1 wherein said composition further comprises a topical anesthetic which relieves pain.

11. The ophthalmic composition of claim 10 wherein said topical anesthetic is selected from the group consisting of proparacaine, lidocaine, tetracaine and a combination thereof.

12. The ophthalmic composition of claim 1 wherein said composition further comprises a penetration enhancer which enhances the penetration of povidone-iodine into the tissues of the eye.

13. The ophthalmic composition of claim 12 wherein said penetration enhancer is a topical anesthetic.

14. The ophthalmic composition of claim 1 wherein said composition further comprises an antimicrobial preservative.

15. The ophthalmic composition of claim 14 wherein said antimicrobial preservative is selected from the group consisting of benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, EDTA, sorbic acid, Onamer M and a combination thereof.

16. The ophthalmic composition of claim 14 wherein said antimicrobial preservative is at a concentration of about 0.001% to 1.0% by weight in said solution.

17. The ophthalmic composition of claim 1 wherein said composition further comprises a co-solvent/surfactant.

18. The ophthalmic composition of claim 17 wherein said co-solvent/surfactant is selected from the group consisting of polysorbate 20, polysorbate 60, polysorbate 80, Pluronic F-68, Pluronic F-84, Pluronic P-103, cyclodextrin, tyloxapol and a combination thereof.

19. The ophthalmic composition of claim 17 wherein said co-solvent/surfactant is at a concentration of about 0.01% to 2% by weight in said composition.

20. The ophthalmic composition of claim 1 wherein said composition further comprises viscosity increasing agent.

21. The ophthalmic composition of claim 20 wherein said viscosity increasing agent is selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, and a combination thereof.

22. The ophthalmic composition of claim 20 wherein said viscosity increasing agent is at a concentration of about 0.01% to 2% by weight in said solution.

23. The ophthalmic composition of claim 1, wherein said composition is in the form of a solution, suspension, emulsion, ointment, cream, gel, or a controlled-release/sustain-release vehicle.

24. The ophthalmic composition of claim 1, wherein said microorganism is selected from the group consisting of bacteria, viruses, fungi, and amoebae.

25. The ophthalmic composition of claim 24 wherein said bacteria is mycobacteria.

26. The ophthalmic composition of claim 1 wherein said eye disorder is selected from the group consisting of a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

27. The ophthalmic composition of claim 1 wherein said prophylaxis is prophylaxis of infection following corneal abrasion or ocular surgery.

28. The ophthalmic composition of claim 1, comprising:
0.5 to 2% (w/w) polyvinylpyrrolidone-iodine complex;
0.05 to 2% (w/w) steroid;
0.005% to 0.02% (w/w) EDTA;
0.01 to 0.5% (w/w) sodium chloride;
0.02 to 0.1% (w/w) tyloxapol;
0.5% to 2% (w/w) sodium sulfate; and
0.1 to 0.5% (w/w) hydroxyethylcellulose;
wherein said steroid is selected from the group consisting of dexamethasone, prednisolone, prednisone, acetate forms thereof, and sodium phosphate forms thereof.

29. The ophthalmic composition of claim 1, comprising:
1.0% (w/w) polyvinylpyrrolidone-iodine complex;
0.1% (w/w) steroid;
0.01% (w/w) EDTA;
0.3% (w/w) sodium chloride salt;
0.05% (w/w) tyloxapol;
0.2% (w/w) sodium sulfate; and
0.25% (w/w) hydroxyethylcellulose

wherein said steroid is selected from the group consisting of dexamethasone, prednisolone, prednisone, acetate forms thereof, and sodium phosphate forms thereof.

30. The ophthalmic composition of claim 1 wherein said composition retains 90% of its polyvinylpyrrolidone-iodine and 90% of its steroid after a period of 3 months in a lighted environment.

31. The ophthalmic composition of claim 1 wherein said composition retains 90% of its polyvinylpyrrolidone-iodine and 90% of its steroid after a period of 1 year in a lighted environment.

32. The ophthalmic composition of claim 1 wherein said composition is an aqueous solution.

33. A method for treating and/or prophylaxis of an eye disorder or a microorganism infection of at least one tissue of the eye comprising the step of administering one of more doses of an ophthalmic composition of claim 1 to said eye.

34. The method of claim 33 wherein said prophylaxis is prophylaxis of infection following corneal abrasion or ocular surgery.

35. The method of claim 33 wherein said eye disorder is selected from the group consisting of a microorganism infection of at least one tissue of the eye, conjunctivitis, corneal abrasion, ulcerative infectious keratitis, epithelial keratitis, stromal keratitis and herpesvirus-related keratitis.

36. The method of claim 33, wherein said microorganism is a bacteria, virus, fungi, or amoebae.

37. The method of claim 36 wherein said bacteria is mycobacteria.

38. The method of claim 33 wherein the sum of said povidone-iodine, said anti-inflammatory, and said steroid is between 0.001 mg to 5 mg per dose.

39. The method of claim 33 wherein each dose is between 10 microliters to 200 microliters.

40. The method of claim 33 wherein each dose is between 50 microliters to 80 microliters.

41. The method of claim 33 wherein said administering comprises administering said solution to said eye one to four times a day.

42. The method of claim 33 wherein said administering comprises administering said solution to said eye one to twenty-four times a day.

43. The method of claim 33 further comprising the step of storing the composition for at least one month, at least three months, at least six months, or at least 1 year before said administration step.

44. The method of claim 43 wherein said storing is in a lighted environment.

* * * * *

Anexo 2



US006328991B1

(12) **United States Patent**
Myhling

(10) **Patent No.: US 6,328,991 B1**
(45) **Date of Patent: *Dec. 11, 2001**

(54) **COMPOSITION AND METHOD FOR PREVENTION OF SEXUALLY TRANSMITTED DISEASES, INCLUDING AIDS**

(76) **Inventor:** John Myhling, P.O. Box 141, Rhinebeck, NY (US) 12572

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** 09/451,362

(22) **Filed:** Nov. 30, 1999

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/140,794, filed on Oct. 21, 1993, now Pat. No. 5,527,534, which is a continuation-in-part of application No. 07/964,494, filed on Oct. 21, 1992, now abandoned.

(51) **Int. Cl.⁷** A61F 6/06; A61F 6/14; A61M 31/00

(52) **U.S. Cl.** 424/430; 424/DIG. 15; 514/841; 514/843; 514/960; 514/975; 128/830; 128/832; 128/833; 604/55

(58) **Field of Search** 424/430, DIG. 15; 514/841, 843, 967, 975; 128/830, 832, 833; 604/55

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,070,889 * 12/1991 Leveen et al. 128/830
5,527,534 * 6/1996 Myhling 424/430

* cited by examiner

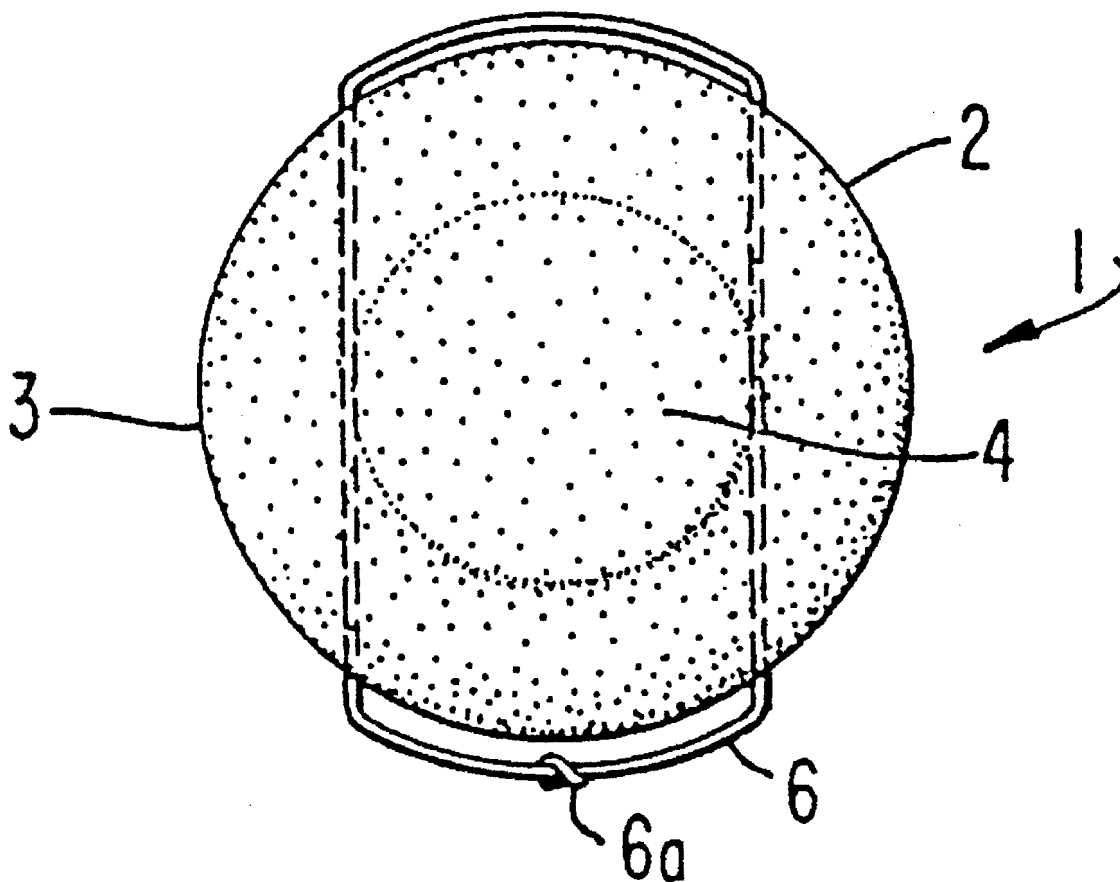
Primary Examiner—Carlos A. Azpuru

(74) *Attorney, Agent, or Firm*—Levisohn, Lerner, Berger & Langsam

(57) **ABSTRACT**

A chemical composition, method and product for administration into the vaginal canal. The composition, method and product are effective in preventing the spread of sexually transmitted diseases, including the spread of AIDS.

27 Claims, 3 Drawing Sheets



COMPOSITION AND METHOD FOR
PREVENTION OF SEXUALLY
TRANSMITTED DISEASES, INCLUDING
AIDS

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 08/140,794, filed Oct. 21, 1993 and issuing as U.S. Pat. No. 5,527,534 on Jun. 18, 1996, which is a continuation-in-part of U.S. application Ser. No. 07/964,494 filed Oct. 21, 1992 (abandoned).

FIELD OF THE INVENTION

The invention relates to a composition of active pharmaceutical agent for administration into the vaginal canal to prevent the spread and transmission of Sexually Transmitted Diseases. The present invention also relates to a composition for administration into the vaginal canal to prevent the transmission of HIV, and the spread of AIDS.

The invention also relates to a method of administration of an active pharmaceutical agent via the vaginal cavity and to a sponge capable of delivering such agent into the vaginal canal during insertion of the sponge, while the sponge is resident in the vagina and during removal from the vagina.

The present invention also relates to vaginal sponges for the topical or systemic, sustained release of a wide range of active pharmaceutical compounds. And the invention relates to sterile, packaged vaginal sponges containing predetermined dosages of active pharmaceuticals which sponges can be conveniently inserted and removed by the user without compromising the predetermined dosage and without waste or mess.

THE PRIOR ART

Sexually Transmitted Diseases

The term "Sexually Transmitted Disease" (STD) is a relatively new one that has gradually replaced the term "Venereal Disease." This terminology has expanded not only the awareness of infectious diseases transmitted through sexual contact, but now describes an expanded array of diseases.

Venereal diseases originally encompassed five traditional infections: Gonorrhea, Syphilis, Chancroid, Lymphogranuloma Venereum, and Granuloma Inguinale. The term STD today includes more than twenty specific organisms and syndromes, including HIV, Chlamydia Trachomatis, Genital Herpes, Genital Warts and Cervical Neoplasia. Thus, the use of the term STD has grown in its scope, and now encompasses a large number of sexually transmitted infections. These include Acquired Immunodeficiency Syndrome (AIDS), Acute Urethral Syndrome or Cystitis, Bacterial Vaginosis Vulvovaginitis, Candidiasis, Cervical Intraepithelial Neoplasia, Chancroid, Chlamydia, Cytomegalovirus infections, Enteric infections, Genital Warts, Gonorrhea, Granuloma Inguinale, Hepatitis B, Herpes Genitalis, Human Papillomavirus (HPV), Lymphogranuloma venereum (LGV), Molluscum Contagiosum, Mucopurulent Cervicitis, Nongonococcal Urethritis, Pediculosis Pubis, Pelvic Inflammatory Disease (PID), Scabies, Syphilis, Trichomoniasis and Vulvovaginitis.

STDs are getting worse both in magnitude and severity. A large and growing number of pathogens have been implicated as causative agents. To name a few of the causative agents currently known, Acquired Immunodeficiency Syndrome is caused by Human Immunodeficiency Virus (HIV). Acute Urethral Syndrome is caused by *E. coli*, *C.*

trachomatis, *N. gonorrhea* and other gram-negative bacteria. Cervical Intraepithelial Neoplasia (CIN) has been associated with human papilloma virus (HPV), and the Herpes Simplex Virus. Chancroid is caused by *Hemophilus Ducreyi*. Chlamydia, one of the most common bacterial STD infections in the United States, is caused by *Chlamydia trachomatis*. Cytomegalovirus infections are caused by a DNA virus of the Herpes virus group. Enteric infections, which are outside, but are related to STDs, are caused by many sexually transmissible bacteria, viruses and protozoa, and by other organisms that produce disease, and are carried in the gastrointestinal tract. Genital Warts are caused by the human papillomavirus (HPV), a small DNA virus belong to the papillomavirus group. Gonorrhea is caused by *Neisseria Gonorrhea*, a gram-negative diplococcus. Granuloma Inguinale is caused by the gram-negative bacteria *Calymmatobacterium granulomatis*. Hepatitis B is caused by Hepatitis B virus (HBV), a DNA virus with multiple antigenic components. Herpes Genitalis is caused by the Herpes Simplex II virus (HSV). Lymphogranuloma venereum (LGV) is caused by immuno-types L I, L II, or L III of *Chlamydia Trachomatis*. Molluscum Contagiosum is caused by the Molluscum Contagiosum virus, the largest DNA virus of the poxvirus group. Mucopurulent Cervicitis is caused by Chlamydia and Gonorrhea. Nongonococcal Urethritis (NGU) is caused by Chlamydia of the D to K immunotypes. Pediculosis Pubis, which, strictly speaking is not a true sexually transmitted disease, is caused by a pubic or crab louse, an ectoparasite. Pelvic Inflammatory Disease (PID) is caused by Gonorrhea, Chlamydia, and other anaerobic bacteria and gram-negative rods, such as *E. coli* and *Mycoplasma homines*. Scabies is caused by *Sarcoptes scabiei*, a female mite approximately 0.4 mm long. (Although not a true STD disease it is commonly found among those with other STD infections). Syphilis is caused by *Treponema Pallidum*, a spirochete. Vulvovaginitis is caused by *Trichomonas Vaginalis*.

As can be seen from the foregoing, a broad variety of microorganisms can potentially enter the vaginal tract through sexual intercourse, and result in a sexually transmitted disease. These microorganisms include bacteria, viruses, fungi, protozoa, and yeasts among others. The health consequences which can result from the contraction of a sexually transmitted disease can be severe, and extremely debilitating. The risk of contracting AIDS through sexual intercourse, for example, is a major concern for many individuals.

From a health care perspective, numerous other sexually transmitted diseases, as provided, for example, in the listing above, are likewise a potential concern. Accordingly, there is a need in the prior art for a chemical composition or medication for administration into the vaginal canal to prevent the transmission and spread of sexually transmitted diseases, including AIDS.

Thus, there is need for suitable and effective microbicides which would kill microorganisms in the vaginal canal before they can cause infection. In addition, there is also a need for effective contraceptive agents and preparations for use before or during sexual intercourse, as well.

The Vaginal Sponge

One of the primary concerns encountered when medication is to be administered to an individual is that the medication reach the targeted area of treatment and be maintained in that targeted area. For example, when treating vaginal disorders it is often desirable that medication be applied for extended period of time to remote regions of the vaginal canal or cervix. These regions are not readily

accessible by conventional vaginal suppositories due to their size and shape. Moreover, because of the structure and nature of the vaginal canal, inserted suppositories often do not stay in place or, upon melting, may drain out of the vagina substantially reducing the effectiveness of the medication. Vaginal foams formed by delivering foam-forming materials into the vagina are short lived and hence are unsuitable for sustained release of active agents. Moreover, both vaginal suppositories and vaginal foams are very messy to use. Use of tampons and other similar devices have not proved successful because of their configuration and the nature of their compositions.

Physical swabbing and douching can cleanse the vaginal canal, but neither can provide sustained release of active agents.

Contraceptive vaginal foam sponges have been previously proposed but even those currently in commercial use do not provide for a predetermined level of sustained release of spermicide and medicaments over a given period of time.

Clinical studies have indicated that young women using oral contraceptives may increase their risk of developing breast and cervical cancers in midlife. Whether this type of contraception is dangerous is debateable but it is recognized that the "pill" interferes with the hormonal balance of the user. Multiple and considerable side effects from the use of oral contraceptives have been observed in many women.

Many attempts to find safer and more effective contraceptive methods which reduce or eliminate side effects have been made. A 24-hour vaginal contraceptive sponge has been commercially marketed. The device comprises a polyurethane sponge disc having a central recess and containing 1,000 milligrams of a spermicide known as nonoxynol-9, which is generically known as nonylphenoxypoly(ethyleneoxy)-ethanol.

While the contraceptive sponge has met with some success in the market place, its usage has been accompanied by drawbacks. Use of the device requires that the spermicide be activated by adding tap water to the sponge and requires manual manipulation of the sponge. Such procedures present numerous disadvantages:

- (a) It is virtually impossible to accurately measure the volume of water coming out of a standard faucet, therefore the spermicide is often diluted to less than an effective amount or is insufficiently diluted. Application of the uniform effective amount of active spermicide is unpredictable because it depends on the amount of water run through the sponge.
- (b) The tap water may contain contaminants, including bacteria that destroy or impair the sterility of the contraceptive sponge.
- (c) The water may contain contaminant chemicals, such as chlorine and fluorides, that may interfere and react with the therapeutic agents contained in the contraceptive sponge.
- (d) The contraceptive sponge cannot be immediately inserted or used after removal from its package, i.e., the sponge does not contain active spermicide but requires activation with water.

U.S. Pat. No. 5,070,899 ('899 patent) describes bactericidal, viricidal polyurethane sponges containing iodine or chlorhexidine and a spermicide surfactant. It is used as a contraceptive. The purpose of the iodine is to provide protection against toxic shock syndrome. The patent does not discuss how the active ingredients are released nor does it attempt to address the medical or contraceptive applications for which it is allegedly used.

U.S. Pat. No. 4,393,871 ('871 patent) relates to the administration of medicaments. The medicament or spermicide enters the '871 product in the solution which makes the foam sponge. Thus when the resulting device is molded, cured and dried, the medicament is incorporated therein and must be reactivated into a foam by the use of tap water before application. There is no hermetically sealed sterile package to prevent intrusion of foreign organisms.

The '871 sponge is said to be reusable like a diaphragm for many repeated applications and thus is not sterile after its first use. The release of foam carrying the active ingredient is problematic because the foam must be agitated to create the foam.

There is no water release of activated spermicide because the water level used to create the foam is blocked in the foam structure.

The amount of water originally added to the '871 system is not controlled or consistent and is only sufficient to generate initial foaming. The cells of the foam cannot be saturated, or partially saturated with liquid to provide liquid release during use because to do so will cause complete disintegration of the sponge in the vaginal cavity.

An alternative sponge-type contraceptive, packaged in a hermetically sealed, air tight foil packet has also been proposed in Gero, U.S. Pat. Nos. 4,693,705 ("705 patent") and 4,692,143 ("143 patent"). The spermicide is preactivated and carried in a solvent of distilled water impregnated into the sponge so that the sponge can be used upon removal from its packet. The contraceptive contains no more than approximately 1650 milligrams of solution per sponge and does not release the spermicide in the vaginal canal. The sponge is merely a blocking device and does not provide for sustained release of the activated solution.

The '705 and '143 patents teach that a solution is injected in the foam. The solution is, however, totally "blocked" because the size and construction of the sponge and the amount of solution introduced therein are such that no release of fluid from the sponge is possible. Solution release is not described nor is sustained release described for prolonged medicinal action.

Long Felt Need in the Art

There is currently a need in the art for a broad spectrum microbiocide for administration into the vaginal canal to prevent the transmission and spread of microorganisms which can cause a sexually transmitted disease. There is also a particular need in the art for a microbiocide effective in preventing the transmission of HIV, and thereby, reducing the spread of Acquired Immune Deficiency Syndrome (AIDS).

There is also a need in the art for a vaginal device that can deliver an active agent, such as medication, to areas within the vagina and/or into the bloodstream via the tissue of the vaginal canal and be maintained within the vagina for a prolonged period of time. There is a further need for a removable vaginal device which releases a spermicide or other active agent throughout the vaginal canal while being inserted and removed and which will release from the device a spermicide or other active agent for a prolonged period of time upon normal body movements of the wearer.

Objects of the Invention

It is an object of the present invention to provide a chemical composition which acts as a microbiocide to kill a broad spectrum of microorganisms which can become introduced into the vaginal canal during sexual intercourse.

It is a further object of the present invention to provide a chemical composition which is effective in preventing the spread and transmission of the HIV virus during sexual intercourse.

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tissue and removes debris. Microorganisms that may have been deposited through sexual intercourse or otherwise, after introduction of the sponge, are further contacted and destroyed. Moreover, when the user applies normal muscular pressure, sometimes known as "Kegel Exercises", additional amounts of liquid are released. In certain applications, muscle contraction can and does provide a well of liquid at the external os of the cervical canal. Normal capillary action of tissue will raise the liquid into the cervical canal providing protection against microorganisms, sperm, and debris.

Packaging

It is important to maintain the concentration of active in the liquid and for the liquid within the foam to be free of mechanical pressure. Thus the foam sponge must be sealed against humidity to secure the integrity of the therapeutic dose level. Any diminution of the predetermined concentration of active or the amount of carrier may defeat the purpose of the invention. The foam must be packaged to avoid crushing and prerelease of solution by mechanical or atmospheric pressure.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in terms of a preferred embodiment in the accompanying drawing in which:

FIG. 1 is a top plan view of a vaginal sponge according to the invention;

FIG. 2 is a side elevational view of the sponge of FIG. 1;

FIG. 3 is a side elevational view of the sponge of FIG. 1 in a hermetically sealed container; and

FIG. 4 is a schematic view, in section of the sponge of FIG. 1 in place in the vagina.

FIG. 5 is a cross-sectional view of a vaginal device, in the process of being inserted into the vaginal canal. The device will, in the preferred embodiment, contain a chemical composition therein, as described at greater length hereafter.

DESCRIPTION OF A PREFERRED EMBODIMENT

Broadly, the sponge of the invention is a truncated sphere with two parallel opposed planar surfaces. Each of the planar surfaces has a diameter between 30% and 50% of the sphere diameter and preferably they are between 30% and 45% thereof. Desirably the planes are of equal size.

The advantages of such a configuration are manifold. The shape ensures that the surface of the sponge is fully curved as it enters and contacts the vagina, it provides a gliding action which follows the contours of the vaginal tissue, it conforms to the vaginal cavity, it is adjustable so that it seats in women having varied vaginal anatomies and in its seating position is sensitive to muscular pressures which cause release of the liquid contained therein.

Referring to the drawing, the sponge 1 of the invention comprises a spheroidal polyurethane foam sponge 2 having a spheroidal body 3 and opposed flattened portions 4, 5. Preferably, the sponge 2 is in the form of a sphere with parallel flats at each pole. Sponge 2 is symmetrical about a plane parallel to flats 4, 5 passing midway through body 3. Secured to body 3 in a conventional manner is a loop of string or cord 6 having a knot 6a.

Sponge 1 is contained in a hermetically sealed container 7 having a removable lid 7a. Sponge 1 contains a solution of a desired active agent and hence is hermetically sealed in container 7 to prevent loss of the solution.

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Preferably the loop of string 6 extends through the body 3 and passes tightly about the rear of the body 3, with a portion depending from the front. If desired, the loop of string 6 can be substituted by a simple length of string or dispensed with entirely.

Sponge 1 may be from about 1 ¼ to about 3 inches in diameter. When used as a contraceptive sponge, a useful diameter is preferably 1 ¾ to 2 ½ inches. Suitably, the distance between the flats may be from about 1 to about 2 inches, preferably about 1 to about 1 ½ inches. Preferably, the flats 4, 5 are circles of about ¾ to 1 ¼ inch diameter, most preferably about 1 inch.

Suitably, the sponge 1 has a volume of from about 2 to about 5 cubic inches and contains from about 125,000 to about 15,600,000 open reticulated cells per cubic inch. Preferably, the sponge 1 is formed from polyether polyol derived polyurethane foam.

The sponge 1 is inserted into the vagina by being held by the fingers against the body 3, with the flats 4, 5 disposed horizontally. The sponge is lightly compressed, but under such conditions the liquid contained with the sponge is not released. Such pressure does bring solution to the outer edges of the sponge 1, which provides excellent lubrication for its entry into the vagina.

As the sponge 1 is directed to its seating position in the vagina shown in FIG. 4, the vaginal wall tissue is gently pushed away from its normally closed position to one following the shape of the sponge 1. The sponge 1 is thus further squeezed to release liquid so as to provide for the complete bathing of the expanded tissue surface leaving behind a liquid film of active agent throughout the entire vaginal cavity.

Upon reaching the entrance to the fornix 10, a relatively open cavity appears. The expelling pressure of the vaginal walls assisted by the lubricating action of the sponge deposits the sponge 1 into the full fornix cavity 10.

As seen in FIG. 4, the cervix 11 may be an intrusion prohibiting direct access of the sponge 1 to the full fornix cavity 10. The sponge 1 being resilient, lubricated, and designed with its curved body 3, then gently follows the fornix tissue under the cervix 11 and proceeds to the posterior wall 12 of the fornix 10. In this position, the external os 14 is completely blocked.

The sponge 1 will have been compressed in varying degrees depending upon the individual size of the user. In virtually most instances it will be compressed from its original size to an average compressed size of about ¾ inches as measured between flats 4, 5. The sponge retains its original diameter. The compressed size of the sponge will fully accommodate the size of the individual user.

The sponge is compressible to about ¼ inch thickness. This does not occur upon insertion because the vaginal tissues of the vaginal floor 13 and the cervical cavity 3 expand. The fornix wall tissue is supple and will move to accommodate the size of the device without creating such compression to prematurely release its liquid reservoir.

The sponge 1 may be impregnated with a solution containing a stabilizing or swelling agent, such as sodium carboxymethylcellulose, which assists in creating outward pressure on the sponge to restore it to its original shape. Such pressure provides for maintenance of the sponge in its seated position during and after releasing liquid. The fit created by the tissue compression and the sponge expansion will provide for contact with all tissue. In its seating position, the sponge 1 will prevent passage and blocks sperm and semen from entering in and around the entire fornix tissue, as well as providing a double blocking action at the entrance to the fornix.

For removal of the sponge 1 from the vaginal fornix, the user may grasp the looped cord 6 and pull downward, or use her fingers to grasp the sponge 1 itself. The knot 6 a may be used as a locating adjunct to the end of the cord 6.

The method of using the sponge delivery system of the present invention may be defined as follows:

- (a) removing the sponge 1 carrying the liquid containing active agent from sealed air-tight packet 7;
- (b) immediately inserting the sponge into the vaginal fornix;
- (c) blocking the cervix and the entrance to the fornix with the sponge and thereby providing a liquid gasket seal between the walls of the fornix and the peripheral diameter of the sponge; and
- (d) providing for repeated release of liquid over a period of 24 hours by applying muscular and tissue pressure upon the sponge by Kegel exercises or similar muscular pressure.

When the system is used as a contraceptive sponge, it may be inserted in anticipation of, during and after coitus for a 24 hour period, but should not be removed less than 6 hours after coitus.

As a contraceptive, the spermicide may comprise between 4 and 10 percent by volume of nonylphenoxypoly-(ethyleneoxy)-ethanol, and 0.125 to 0.250 percent of an anti-toxic shock syndrome agent. In addition, benzethonium chloride may be used in combination with the spermicide to produce a synergistic reaction for sperm immobilization. The anti-toxic shock syndrome agent is active to kill staphylococcus aureus whose toxins cause toxic shock syndrome.

The invention is further illustrated by the following examples.

EXAMPLE 1

Table 1 below provides a topical spermicide contraceptive formulation providing for sexually transmitted disease protection. The spermicide formulation is prepared by mixing the ingredients together. A polyether-polyol derived polyurethane sponge of 2 ¼ inches in diameter having about 100 cells per lineal inch and a density of about 3 pounds per cubic foot and a tensile strength of about 18-20 psi was impregnated with 6,500 milligrams of solution to provide a sponge weighing 8,200 milligrams, the dry weight of the sponge being 1,700 milligrams.

The freely releasable amount of liquid reservoir is 4,800 milligrams. In this instance, 1,000 milligrams of solution are deposited on the wall tissue to the vagina upon insertion and another 1,000 milligrams are deposited upon removal. The other 2,800 milligrams are made available for sustained release during the period of use.

TABLE 1

Ingredient	Function of Ingredients	Composition %	Mg.
Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9)	Spermicide	2.500	162.50
Pectin	Vaginal Deodorant	0.500	32.50
Glycine	PH adjuster	0.500	32.50
Povidone-Iodine	Bactericide anti-TSS agent	0.300	19.50

TABLE 1-continued

Ingredient	Function of Ingredients	Composition %	Mg.
Sodium-Carboxymethyl-cellulose	Swelling agent	0.160	10.40
Benzalkonium Chloride	Bactericide, anti-fungal, anti-yeast and anti-mold agent	0.150	9.75
Distilled Water	Solvent	95.890	6,232.85
TOTAL		100.000%	6,500.00 mg

This embodiment provides a broad spectrum of protection from a variety of microorganisms. The combination of the three active ingredients Nonoxynol-9, Benzalkonium Chloride, and Povidone Iodine is a preferred combination for providing a safe, effective means of protection from sexually transmitted diseases. In addition, this chemical composition is a highly effective formulation for preventing the sexual transmission of AIDS.

With respect to the prevention of AIDS, the formulation's effectiveness rests both in destroying both free virus and virus-infected cells. Both free virus and infected cells in bodily fluids can cause the spread of HIV and AIDS through sexual intercourse. During unprotected sexual intercourse, male infected cells can and do survive in the female reproductive tract, and act as reservoirs and factories for virus production. Thus, the present formulation's effectiveness in destroying both free virus and infected cells, while also providing a broad spectrum microbiocide to prevent transmission of a large variety of sexually transmitted diseases, is an important advantage.

The Nonoxynol-9 in the present formulation is a spermicide and microbiocide in its own right. It is a nonionic surfactant mixture which can be prepared, for example, by reacting Nonylphenol with Ethelene Oxide. It was first determined to be an effective spermicide agent in approximately 1940. It is a highly stable compound, soluble in water, and is used as a non-ionic surfactant, detergent, emulsifier, wetting agent, dispersant and stabilizer.

Since the 1970s, evidence from laboratories has lent support to the prophylactic use of Nonoxynol-9 against some STDs. It has been determined that viral, bacterial and parasitic entities are destroyed in the laboratory under certain conditions, but the compound is very selective. Chlamydia and the candida albicans fungi, for example, are not inhibited. Although gonorrhea and C. trachomatis were observed to respond to Nonoxynol-9 when compared against a placebo, not all of their varieties were destroyed.

Investigation of Nonoxynol-9 against HIV in a number of studies determined that its working mechanism would destroy the free HIV virus, but that this chemical agent was ineffective against virus in cells in male semen. Moreover, although this compound is toxic to many microorganisms, it has little or no effect upon others. For example, Nonoxynol-9 has is ineffective against E. Coli and Staph. aureus, both very serious vaginal intruders.

Thus, with respect to the prevention of AIDS, Nonoxynol-9 is used in the present formulation to disrupt the "free" infectious virus when applied at a non-toxic dosage. It will not however, destroy all viruses, as many viruses are present in cells where Nonoxynol 9's working mechanism does not penetrate. This distinction is an important one, since, when it comes to combatting AIDS, unlike strategies used to fight other human viruses (such as measles

virus, poliovirus and hepatitis virus), blocking free-virus entry without removal of the infected cell viruses will not lead to disease prevention.

The second component of the chemical composition, Benzalkonium Chloride, is also a microbiocide and spermicide. It is an active microbiocide against bacteria, some fungi, protozoa, bacterial spores and viruses.

With respect to AIDS, in the present formulation Benzalkonium Chloride has an effective spectrum against the infected cells transferring HIV, in particular, infected cells in male semen. This chemical agent has a direct working mechanical action complementing the activity of Nonoxynol-9. Benzalkonium Chloride's properties allow it to penetrate the cell membranes of a large number of viral and bacterial entities. Once having penetrated, it destroys the metabolic functions of the cell. It destroys the nucleic acids contained in the cells, and specifically the metabolism of DNA, as well as RNA production therein. It further destroys the intracellular enzymes required for cell metabolism. As a result, it is an important second component of the microbiocide composition. In addition to having properties as an active chemical agent, the Benzalkonium Chloride is also used in the formulation as a preservative.

The Povidone Iodine in the present formulation completes the three elements of the microbiocide "triad." In the form commonly encountered, it is an Iodine-Polyvinylpyrrolidone complex. It is a yellowish brown powder fully soluble in water, having a pH of 2.0. Its low pH assists in reducing the total pH of the aqueous chemical microbiocide composition to under 4.0. Furthermore, the Povidone Iodine has an topical anti-infective action that broadens the microbiocide spectrum of the preparation. Povidone Iodine is also an excellent preservative.

In the prior art, Povidone Iodine has been used for pre- and post-operative prepping of operative sites, the treatment of burns, including third-degree burns, and treatment of decubitus and stasis ulcers.

One of its major applications is to provide prompt and soothing symptomatic relief of vaginal irritation, itching and soreness with no irritation to vaginal tissue. It rapidly reduces the aerobic and anaerobic bacteria count, offering comfort from annoying vaginal symptoms and their odor. It is currently used as a treatment for vaginitis conditions, and is used as a cleansing douche. It has a low surface tension with a uniform wetting action which makes it ideal for penetrating into the deep vaginal crypts and crevices. It is active in the presence of blood, pus or vaginal secretions. It is nonirritating to all vaginal mucosa.

Its excellent action as a broad-spectrum microbiocide makes it a useful compound for the disinfection of wounds and for antiseptic treatment of lacerations, abrasions and the disease lesions associated with sexually transmitted disease infections. It destroys both gram-positive and gram-negative bacteria (including antibiotic resistant strains), fungi, protozoa, yeasts and viruses. Its broad spectrum activity covers most commonly occurring skin bacteria.

Its inclusion in the present formulation completes the spectrum of coverage required for STD prevention. Of considerable importance, it is useful against staphylococcus aureus, the entity whose toxins produce toxic-shock syndrome. The Povidone Iodine also provides the preservative required for the solution when encapsulated in a sponge and placed in a hermetically sealed package. The Povidone Iodine further contributes to the present formulations effectiveness as a composition which is microbiocidal, and not merely bacteriostatic.

The need to supplement the working spectrum of Nonoxynol-9 and Benzalkonium Chloride for specifically fungicidal agents, and bacterial agents not within their spectrums, has required addition of this agent. The addition of Povidone Iodine provides free iodine, which is a most useful microbiocide in treating the vaginal infections caused by trichomonas, gonococcus, monilia and chlamydia. This also assists in lowering the incidence of the carcinoma of the cervix, which is now known to be a manifestation of the sexually transmitted papilloma virus, which is destroyed. The iodine content also destroys the highly prevalent genital herpes virus Type-II.

Iodine is a useful bacteriocidal substance because of its non-toxicity when used in low concentrations. There is no bacterial resistance to iodine. Because it has the ability to preform its microbiocide action in the presence of blood, proteins and other vaginal secretions, it provides a total menstrual-cycle protection against STDs.

Consequently, each of the components of the present formulation acts together to form an effective broad spectrum microbiocide, useful in combatting sexually transmitted diseases in general, and AIDS in particular. No cross reactivity between the chemical agents, either inhibiting their effectiveness in combination, or producing unwanted compounds or results, has been observed. Furthermore, the combination has been found to be both safe and non-irritating during use. In combination the toxicity and effects of this chemical composition are safely within the parameters of FDA criteria for an over the counter (OTC) preparation.

Although the levels listed in the table above are those currently preferred, alternative levels for use of these chemical agents are as follows: Nonoxynol-9: 2.0%-8.0%; Benzalkonium Chloride: 0.05%-0.3%; and, Povidone Iodine: 0.15%-2.0%. Although the Benzalkonium levels could be increased to approximately 2.0%, this is not preferred. In an alternate embodiment, Benzethonium Chloride could be substituted for Benzalkonium Chloride at the same levels.

As an active ingredient for use as a spermicide, Benzethonium Chloride is also effective by itself, at these levels, or in combination with Benzalkonium Chloride. Benzethonium Chloride as a spermicide may be used at a preferred level of 0.15%, or in combination with Benzalkonium Chloride at levels of 0.15% for each.

The addition of the Apple Pectin is useful to provide an deodorant function effective in destroying vaginal odor. The Glycine is utilized as a pH reducer which very effectively assists the Povidone Iodine to reduce the Nonoxynol-9 and Benzalkonium Chloride pH levels down to a formula pH of 3.9. The Sodium Carboxymethyl Cellulose is added to increase the viscosity of the solution to create a more stable foaming application.

EXAMPLE 2

Table 2 below sets forth an alternative formulation useful in the invention.

TABLE 2

Ingredient	Function of Ingredients	Composition %	Mg.
Nonylphenoxypoly-(Ethyleneoxy)-Ethanol(nonoxynol-9)	Spermicide	8.000	162.50
Benzethonium chloride	Bactericide	0.150	9.75

-continued

c) Tensile strength, psi	22 pounds
d) Elongation percent	200%
e) Tear Strength lb/inch (minimum)	4.5 pounds
f) Absorption (Saturation Value) foam weight	19 to 20 times

The Shape of the Sponge

The shape of the sponges is as described in Example 3. The weight of each sponge is 2.382 grams.

The Medication

MBVC-SPONGE

The solution has the following formula:

	Milligrams Per Sponge
Distilled Water	6,325.0
Povidone Iodine - U.S.P.	30.0
A gram positive and gram negative disinfectant	
Glycerophosphoric Acid	35.0
A PH adjuster	
Pectin - Natural Apple U.S.P. Deodorant	35.0
Glycine - PH Reducer	40.0
Hydroxypropyl Methyl-Cellulose	35.0
Viscosity control Agent	
Total Solution Fill per Sponge	6,500.0

YVC-SPONGE

The solution has the following formula:

	Milligrams Per Sponge
Clotrimazole - Anti Fungal Agent	65.0
Distilled Water - Solvent	6,215.0
Povidone Iodine - Anti Fungal - Bacteria Agent	30.0
Pectin - Natural Apple - U.S.P. - Deodorant	35.0
Glycine - PH Reducer	100.0
Benzalkonium Chloride	15.0
Hydroxypropyl Methyl-Cellulose	40.0
Emulsifying Agent - Thickener	
Total Product Fill per Sponge	6,500.0

NVCC-SPONGE

The solution has the following formula:

	Milligrams Per Sponge
Nonoxynol-9 - Detergent Cleanser	100.0
Distilled Water - Solvent	6,275.0
Povidone Iodine - Bactericide/Fungicide	30.0
Benzalkonium Chloride	10.0
Pectin - Natural Apple - U.S.P. - Deodorant	35.0
Glycine - pH Adjuster	35.0
Hydroxypropyl Methyl-Cellulose	15.0
Total Solution per Sponge	6,500.0

The Fill

The sponges have an unfilled weight of 1,800 mgs and the amount of blocked solution for each is 1,800 mgs.

Upon entry into the vagina and positioning, each will release 1000 mgs of solution. In its seating position and upon removal it can release an additional 3,700 mg. In total each sponge can release 4,700 mg of active solution in the vagina.

The recommended use is as follows:

MBVC-Sponge—One application each day at bedtime, removal in the morning, for seven days.

MBVC-Sponge—One application at bedtime, removal in the morning, for seven days.

NVCC-Sponge—When required, to be used for 20 minutes and removed, or inserted at bedtime and removed the following morning as desired.

Packaging

The sponges are packaged as described in Example 3.

What is claimed is:

1. A chemical composition for administration into the vaginal canal to prevent the transmission of sexually transmitted diseases, said composition comprising:

(a) Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9);

(b) Benzalkonium Chloride; and,

(c) Povidone Iodine.

2. A chemical composition as claimed in claim 1, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.5% of said chemical composition, said Benzalkonium Chloride comprises approximately 0.15% of said chemical composition, and said Povidone Iodine comprises approximately 0.3% of said chemical composition.

3. A chemical composition as claimed in claim 1, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.0–8.0% of said chemical composition, said Benzalkonium Chloride comprises approximately 0.05–2.0% of said chemical composition, and said Povidone Iodine comprises approximately 0.15–2.0% of said chemical composition.

4. A chemical composition as claimed in claim 1, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises 2.0–8.0% of said chemical composition, said Benzalkonium Chloride comprises 0.05–0.3% of said chemical composition, and said Povidone Iodine comprises 0.15–2.0% of said chemical composition.

5. A chemical composition as claimed in claim 1, wherein said composition is located within a vaginal device for placement in the vaginal canal.

6. A chemical composition for administration into the vaginal canal, said composition comprising,

(a) Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9);

(b) Benzethonium Chloride; and,

(c) Povidone Iodine.

7. A chemical composition as claimed in claim 6, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.5% of said chemical composition, said Benzethonium Chloride comprises approximately 0.15% of said chemical composition, and said Povidone Iodine comprises approximately 0.3% of said chemical composition.

8. A chemical composition as claimed in claim 6, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.0–8.0% of said chemical composition, said Benzethonium Chloride comprises approximately 0.05–2.0% of said chemical composition, and

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said Povidone Iodine comprises approximately 0.15–2.0% of said chemical composition.

9. A chemical composition as claimed in claim 6, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises 2.0–8.0% of said chemical composition, said Benzethonium Chloride comprises 0.05–0.3% of said chemical composition, and said Povidone Iodine comprises 0.15–2.0% of said chemical composition.

10. A chemical composition as claimed in claim 1, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.0–8.0% of said chemical composition.

11. A chemical composition as claimed in claim 1, wherein said Benzalkonium Chloride comprises approximately 0.05–0.3% of said chemical composition.

12. A chemical composition as claimed in claim 1, wherein said Povidone Iodine comprises approximately 0.15–2.0% of said chemical composition.

13. A chemical composition as claimed in claim 6, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.0–8.0% of said chemical composition.

14. A chemical composition as claimed in claim 6, wherein said Benzethonium Chloride comprises approximately 0.05–0.3% of said chemical composition.

15. A chemical composition as claimed in claim 6, wherein said Povidone Iodine comprises approximately 0.15–2.0% of said chemical composition.

16. A chemical composition as claimed in claim 5, wherein said vaginal device comprises a vaginal sponge.

17. A chemical composition as claimed in claim 6, wherein said chemical composition is applied to a vaginal device for placement in the vaginal canal.

18. A chemical composition as claimed in claim 17, wherein said vaginal device comprises a vaginal sponge.

19. A chemical composition as claimed in claim 3, wherein said composition is provided in a vaginal sponge.

20. A method for preventing transmission and spread of a sexually transmitted disease, comprising:

placing a chemical composition in the vaginal canal, said chemical composition comprising Nonylphenoxypoly-

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(Ethyleneoxy)-Ethanol, Benzalkonium Chloride, and Povidone Iodine.

21. A method as claimed in claim 20, wherein said Nonylphenoxypoly-(Ethyleneoxy)-Ethanol (Nonoxynol-9) comprises approximately 2.0–8.0% of said chemical composition, said Benzalkonium Chloride comprises approximately 0.05–2.0% of said chemical composition, and said Povidone Iodine comprises approximately 0.15–2.0% of said chemical composition.

22. A method as claimed in claim 20, wherein said chemical composition is provided in a vaginal device for insertion into the vaginal canal.

23. A method as claimed in claim 20, wherein said composition is used for the prevention of Acquired Immunodeficiency Syndrome (AIDS).

24. A method as claimed in claim 20, wherein said sexually transmitted disease is a disease selected from the group consisting of: Acquired Immunodeficiency Syndrome (AIDS), Acute Urethral Syndrome, Bacterial Vaginosis, Vulvovaginitis, Candidiasis, Cervical Intraepithelial Neoplasia, Chancroid, Chlamydia, Cytomegalovirus infections, Enteric infections, Genital Warts, Gonorrhea, Granuloma Inguinale, Hepatitis B, Herpes Genitalis, Human Papillomavirus (HPV), Lymphogranuloma venereum (LGV), Molluscum Contagiosum, Mucopurulent Cervicitis, Nongonococcal Urethritis, Pediculosis Pubis, Pelvic Inflammatory Disease (PID), Scabies, Syphilis, Trichomoniasis and Vulvovaginitis.

25. A method for preventing contraception, comprising: placing a device in the vaginal canal, wherein said device has a chemical composition applied thereto, said chemical composition comprising spermicidal chemical agents, said chemical agents comprising Benzethonium Chloride.

26. A method as claimed in claim 25, wherein said composition comprises approximately 0.15% of said Benzethonium Chloride.

27. A method as claimed in claim 25, wherein said composition comprises approximately 0.05–2.0% of said Benzethonium Chloride.

* * * * *

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 11 002094

Asunto : Oposición a la solicitud de patente de Invención titulada
"POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS"

Solicitante : FORESIGHT BIOTHERAPEUTICS INC

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 634 del 21 de noviembre de 2011

Yo, *ELIANA ISaura MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad 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 *"POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS"*, cuyo titular es FORESIGHT BIOTHERAPEUTICS INC, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

solicitud también incluye agregar a una preparación oftálmica PVP-I en una cantidad suficiente para preservar la preparación oftálmica.

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: US2007219170 publicada el 20 de septiembre de 2007.
- D2: US6328991 publicada el 11 de diciembre de 2001.

2.4 Así entonces, el documento D1, se refiere a una composición oftálmica tópica compuesta de 0,01% a 10,0% de povidona yodada combinada con un fármaco anti-inflamatorio esteroide o no esteroide. Esta solución según la invención es útil en el tratamiento de infecciones activas de al menos un tejido del ojo (por ejemplo, la conjuntiva y la córnea) de causas bacterianas, micobacterianas, virus, hongos, o amebiana, así como tratamiento para prevenir tales infecciones en entornos clínicos apropiados (abrasión corneal por ejemplo, la profilaxis post-operatorio, post-LASIK/LASEK profilaxis y, el documento uno menciona que la solución es eficaz en la prevención de la infección e inflamación oftálmica es pacientes post-operatorios. Adicionalmente, de forma particular en la descripción, Dicho documento D1 enseña de forma particular en los párrafos 0007, 0013, 0025, 0032, 0043 y 0075 una preparación oftálmica conservada que comprende: a) una povidona-yodada (PVP-I) a una concentración suficiente para tratar infecciones de la conjuntiva y de la córnea y b) al menos un miembro seleccionado del grupo que

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 **POVIDONA YODADA**. 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 11 de enero de 2011, reivindicando prioridad bajo la solicitud US20080129222 del 2008-06-12; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **Nº 634 del 21 de noviembre de 2011**, cuya publicación internacional corresponde a la WO2009151619 del 2009-12-17.
- 2.2. La solicitud colombiana **11 002094** objeto de la presente oposición, se refiere a una preparación oftálmica preservada que comprende Povidona yodada (PVP-I) en una concentración suficiente para preservar la preparación oftálmica, y por lo menos un miembro seleccionado del grupo que consiste de un compuesto esteroideal anti-inflamatorio, un compuesto no esteroideal anti-inflamatorio, un compuesto antibacteriano, un compuesto antialérgico, y un compuesto anti-glaucoma. La

consiste en compuestos anti-inflamatorios esteroideos y compuestos anti-inflamatorios no esteroideos.

2.5. Consecuentemente, el documento D2 que se refiere a una composición química, el método y los productos para la administración en el canal vaginal, revela de forma particular en las columnas 1 y 19 una composición farmacéutica que comprende PVP-I (Povidona yodada), que actúa como un excelente conservante, y en la que la PVP-I proporciona una acción anti-infectiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 en combinación con el documento D2, carece de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 002094 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA DE ALTURA INVENTIVA Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 12 de junio de 2008, a partir del documento D1 en combinación con D2, un experto en la materia puede llegar de manera evidente a combinar la preparación oftálmica conservada enseñada en el Documento D1, con la propiedad conservante de PVP-I revelada en el documento D2 para desarrollar una mejora de la

preparación oftálmica conservada donde la povidona-yodo (FVP-I) proporciona una propiedad conservante un y una característica antimicrobiana, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *“POVIDONA YODADA, UN PRESERVATIVO ALTERNATIVO NOVEDOSO PARA COMPOSICIONES OFTALMOLOGICAS”*, cuyo titular es FORESIGHT BIOTHERAPEUTICS INC, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 634 del 21 de noviembre de 2011.

3. PRUEBAS

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

- D1: US2007219170 publicada el 20 de septiembre de 2007.
- D2: US6328991 publicada el 11 de diciembre de 2001.

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

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

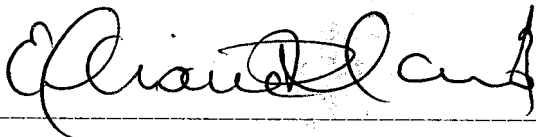
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

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: US2007219170 publicada el 20 de septiembre de 2007.
 - D2: US6328991 publicada el 11 de diciembre de 2001.

6. NOTIFICACIONES

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

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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