



No. 06-128576- -00003-0000

Fecha: 2008-03-13 14:20:14 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Lve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 60

FORMULARIO UNICO DE OPOSICIÓN

25

①

OPOSICIÓN A:

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

②

**SOLICITUD
PUBLICADA**

Numero del expediente: 06-128576
Solicitante: ARTURO JIMENEZ BAYARDO
Apoderado: EMILIO FERRERO
Titulo de la nueva creación o denominación del signo: "UN METODO PARA
PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE"
Gaceta: 583

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: PROCAPS S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: Lugar de Constitución: COLOMBIA BARRANQUILLA	C.E. ☐	Otro ☐
	Teléfono: (571)3719900 Fax: (571)3730818 E-mail:	Cual _____ Número <u>890.106.527-5</u>	
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 104	C.C. ☒	NIT ☐
	Teléfono: (571) 2131213 Fax: (571) 6121979 E-mail: <u>negocios@optimum-co.com</u>	C.E. ☐	Otro ☐
		Cual _____ Número <u>51'975.664</u> TP <u>83823</u>	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

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

Fecha _____

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.

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⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

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Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 06128576
Asunto : Oposición a la solicitud de patente de Invención
titulada "UN MÉTODO PARA PREPARAR UNA
SOLUCIÓN OFTÁLMICA DE LATANOPROST Y
SOLUCIÓN RESULTANTE"
Solicitante : ARTURO JIMENEZ BAYARDO.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 583 del 18 de diciembre de 2007

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 y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley

y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada **"UN MÉTODO PARA PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE"**, cuyo titular es **ARTURO JIMENEZ BAYARDO**, 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 latanoprost. 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

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- 2.1. La solicitud objeto de la presente fue presentada el 22 de diciembre de 2006, reivindicando prioridad bajo la solicitud WO2004MX00034 del 2004-05-26; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 583 del 18 de diciembre de 2007, cuya publicación internacional corresponde a la WO2005115401 del 2005-12-08.
- 2.2. La solicitud colombiana **06128576** objeto de la presente oposición, se refiere a un método para solubilizar el latanoprost para preparar una solución oftálmica acuosa químicamente estable para el tratamiento de diversas afecciones oculares, donde dicho método comprende: a) colocar en un recipiente 5.000 g de latanoprost; b) agregar al recipiente aproximadamente 15 L de una solución que contiene 7.5% de hidroxipropilbetaciclodextrinas, 0.7% de fosfato monobásico de sodio monohidratado, 0.6% de fosfato dibásico de sodio anhidro y 0.2% de hialuronato de sodio, y agitar de 500 a 550 rpm para disolver el latanoprost; c) esperar a que se disuelva por completo y agregar a la solución de 0.005% a 0.02% de cloruro de benzalconio, enjuagando siempre con la misma solución con que se disolvió el latanoprost; y d) agitar hasta que se homogeneice la solución; donde dicho método comprende las siguientes fases: a) solubilizar un agente análogo de prostaglandina, tal como latanoprost; b) preparar una solución acarreadora; y c) mezclar el latanoprost solubilizado y la solución acarreadora, y completar el volumen a 100 L con agua purificada

mientras se agita constantemente por un periodo predeterminado; en el que la fase de solubilización del latanoprost comprende las siguientes etapas: a) colocar 5.000 g de latanoprost en un recipiente de capacidad suficiente y agregar 15 L de una solución que contiene 7.5% de hidroxipropilbetaciclodextrinas, 0.7% de fosfato monobásico de sodio monohidratado, 0.6% de fosfato dibásico de sodio anhidro y 0.2% de hialuronato de sodio, y agitar de 500 a 550 rpm para disolver el latanoprost; y b) esperar a que se disuelva por completo la solución anterior y agregar de 0.005 a 0.02% de cloruro de benzalconio, agitando por aproximadamente 5 minutos para que se homogeneice la solución; en el que la fase de preparación de la solución acarreadora comprende las siguientes etapas: a) en un tanque de acero inoxidable, se vierten 70 litros de agua purificada a $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$; b) se inicia agitación de 500 a 550 rpm y se mantiene constante durante todo el proceso de preparación.

- 2.3. En primera instancia, se debe advertir que las reivindicaciones 16, 17 y 18 se refieren a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- “Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”, los usos no están contemplados como patentables; y, Artículo 20.- “No serán patentables (...) d) los métodos terapéuticos o

quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN que reza “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 afectan la patentabilidad de la presente solicitud:

- D1: US2002103255 publicada el 1º de agosto de 2002. ISR
- D2: WO9729752 publicada el 21 de agosto de 1997. ISR

2.5. Ahora bien, en el documento D1 se describen composiciones oftálmicas que comprende análogos de prostaglandina entre otros los que se cita es el latanoprost, para administración tópica en el tratamiento de glaucoma y de la hipertensión ocular. Este documento D1 con base en la página 5 columna 1 y ejemplos, revela que entre los ingredientes utilizados en las preparaciones oftálmicas se incluyen

conservantes, cosolventes y agentes que incrementan la viscosidad. Entre los conservantes se cita en dicha anterioridad D1 el cloruro de benzalcionio entre los cosolventes polisorbato y ciclodextrinas, entre los agentes que incrementan la viscosidad hidroxipropilmetilcelulosa y ácido hialurónico. Según esta anterioridad D1, se utilizan asimismo sistemas amortiguadores del pH tales como el ácido bórico y fosfato dibásico de sodio, reguladores de la osmolaridad como el cloruro de sodio y agentes antioxidantes como el EDTA disódico. Por lo tanto la materia revelada en la presente carece evidentemente de novedad a luz de la anterioridad D1.

- 2.6. Ahora bien, el documento D2 revela el uso de aceites polietoxilados para mejorar la estabilidad de composiciones con prostaglandinas, preparadas para la administración tópica en el ojo. Según esta anterioridad D2 en la página 10 y ejemplo 1, estas composiciones contienen varios ingredientes en su formulación tales como conservantes, antimicrobianos, agentes que incrementan la tonicidad, agentes reguladores del pH, reguladores de osmolaridad y antioxidantes. En las páginas 12 y 13, esta anterioridad D2 define asimismo la preparación de dichas formulaciones, obteniéndose primero una solución acuosa con todos los ingredientes de la composición hasta completar la disolución y, en recipiente aparte, se prepara la cantidad apropiada de prostaglandina a la que se le añade el vehículo anteriormente preparado. Así las cosas, a la luz de lo visto en

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dicho documento D2 la presente solicitud carece evidentemente de novedad.

2.7. Por lo tanto, este documento objeto de oposición a los ojos de lo que dictan estos documentos D1 y D2, carece evidentemente de NOVEDAD

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06128576 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.9.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 26 de mayo de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1 y D2, un método para solubilizar el latanoprost para preparar una

solución oftálmica acuosa químicamente estable para el tratamiento de diversas afecciones oculares así como la solución acuosa, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.10. 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

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industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"UN MÉTODO PARA PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE"**, cuyo titular es **ARTURO JIMENEZ BAYARDO**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 583 del 18 de diciembre de 2007.

3. PRUEBAS

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

- D1: US2002103255 publicada el 1° de agosto de 2002.
- D2: WO9729752 publicada el 21 de agosto de 1997.

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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:

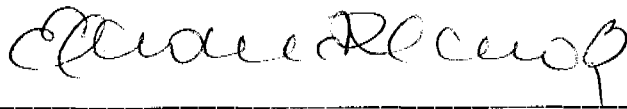
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: EP0308341 publicada el 22 de marzo de 1989.
 - D2: WO0158868 publicada el 16 de agosto de 2001.

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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.



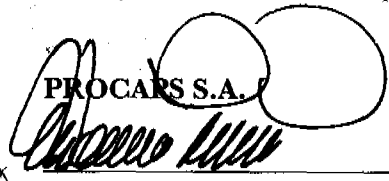
PODER ESPECIAL

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. **06.128.576**, titulada "**UN METODO PARA PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE**", cuyo titular es **ARTURO JIMENEZ BAYARDO**, publicada en la gaceta No. 583 del 18 de Diciembre de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente 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 ____ días del mes de Marzo de 2008.


PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA
2a
David A. Arcieri Gutierrez
Notario Encargado
BOLO DE BARRANQUILLA

[Signature]

Edward R. Lamb

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO 200170000-0

89 15 29

RECIBO OFICIAL DE CAJA : 00 20,134
FECHA : MARZO 13 DE 2000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-128576-00003-0000

La Ley 273 de 1997 y la Ley 2014 Dep. 2020 NULCREACIONE
DE MARCAS Y LEAS COMERCIALES Ley 379 FASE NACIONAL II
LA LEY DE OBSERVACION Folios: 60

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VAL. PAGO
LAD. PROCAPO	CONSIGNACION	BANCO POPULAR	050 00110-6	04084112	07/11/2007	1,534,000.00

CONCEPTO

CONCEPTO	TOTAL CONCEPTO
1. CONCEPTO DE PRESENTACION DE OBSERVACIONES	
12. MARCAS Y LEAS COMERCIALES	261,000.00
TOTAL :	261,000.00

SON: DOSCIENTOS SESENTA Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.



***** Pag. 1
 CAMARA DE COMERCIO
 DE BARRANQUILLA
 03*****

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

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

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

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.".-----

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

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 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

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.

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



***** Pag. 2

CAMARA DE COMERCIO
DE BARRANQUILLA

03*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion 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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-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, d) 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. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) 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; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o in-

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

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

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NIT: 890.106.527-5.

dustrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, 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 o 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 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		
\$*****1,224,500,000	*****1,224,500	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir

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



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apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir 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 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

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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 Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	.*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

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

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PROCAPS S.A.-----

NIT: 890.106.527-5.

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
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

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. 124 del 29 de Marzo de 1999 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 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 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.

C E R T I F I C A

Que 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:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

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 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

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



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MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
 liquidados a la tasa representativa del mercado vigente en el día
 que se realice la respectiva transaccion. Grupo A. WALTER NANAKA
 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, y al señor ANTONIO VARELA DIAZ CC.No.72.004.699,
 para que en nombre y representacion de PROCAPS S.A., suscriban ----
 declaraciones cambiarias, aduaneras y tributarias a que este -----
 obligada la sociedad, en el giro normal de sus negocios y -----
 operaciones sociales, por tanto quedan facultados para firmarlas,
 como tambien los demas documentos relacionados con ellas, -----
 notificarse, aportar y solicitar las pruebas que sean necesarias.
 c.-Otorgar poder especial amplio y suficiente al señor MARLON ----
 TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
 CERRA CC.No.8.715.941, para que en nombre y representacion de ----
 PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
 documento relacionado con los tramites o registros de Comercio ----
 Exterior y o cualquier entidad del Estado que haga sus veces: d)
 Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
 ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
 TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
 representacion de PROCAPS S.A.; endosen los titulos valores de la
 sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
 (1.000.000.000.00) M.L. CUARTO: 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 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: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

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

10015-005-C
 PROCAPS S.A. NIT. 890.321.151-C FORMAS EFICIENTES

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PROCAPS S.A.-----

NIT: 890.106.527-5.

Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

m. l. a. e. a.



US 20020103255A1

(19) **United States**(12) **Patent Application Publication**
Hellberg et al.(10) **Pub. No.: US 2002/0103255 A1**(43) **Pub. Date: Aug. 1, 2002**(54) **USE OF NON-STEROIDAL
ANTI-INFLAMMATORY AGENTS IN
COMBINATION WITH PROSTAGLANDIN FP
RECEPTOR AGONISTS TO TREAT
GLAUCOMA AND OCULAR
HYPERTENSION**(76) **Inventors: Mark R. Hellberg, Highland Village,
TX (US); Jon C. Nixon, Belhaven, NC
(US)****Correspondence Address:
ALCON RESEARCH, LTD.
R&D COUNSEL, Q-148
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099 (US)**(21) **Appl. No.: 10/059,692**(22) **Filed: Jan. 28, 2002****Related U.S. Application Data**(63) Continuation-in-part of application No. 09/575,833,
filed on May 22, 2000, now patented, which is a
continuation-in-part of application No. 08/994,903,
filed on Dec. 19, 1997, now patented.**Publication Classification**(51) **Int. Cl.⁷ A61K 31/558; A61K 31/216;
A61K 31/165**
(52) **U.S. Cl. 514/530; 514/534; 514/617**(57) **ABSTRACT**Disclosed are methods and compositions for the treatment of
glaucoma and ocular hypertension, comprising the admin-
istration of a prostaglandin FP receptor agonist and a pros-
taglandin synthesis inhibitor.

ANEXO 1

Concentrations of Unidentified Radioactivity in Ocular Tissues
Following a Single 0.3% Topical Ocular Dose of ^{14}C -Nepafenac

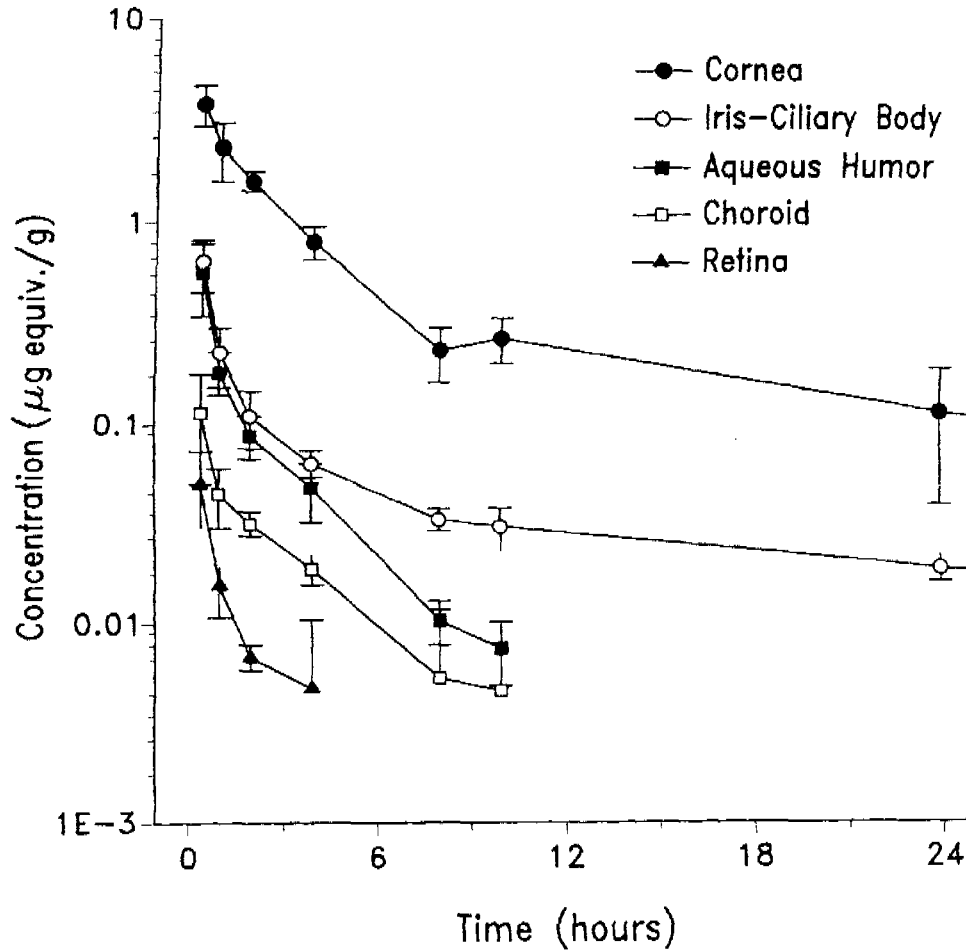


FIG. 1

Maximum Potential Drug Concentration
in Various Ocular Compartments

Compartment	Concentration (μM)
Cornea	200
Iris-Ciliary Body	29
Aqueous Humor	24
Choroid	0.4
Retina	0.2

FIG. 2

99

USE OF NON-STEROIDAL ANTI-INFLAMMATORY AGENTS IN COMBINATION WITH PROSTAGLANDIN FP RECEPTOR AGONISTS TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation-in-part of U.S. application Ser. No. 09/575,833 filed May 22, 2000, now U.S. Pat. No. 6,342,524, which is a continuation-in-part of U.S. application Ser. No. 08/994,903 filed Dec. 19, 1997, now U.S. Pat. No. 6,066,671.

FIELD OF THE INVENTION

[0002] This invention is directed to the use of non-steroidal anti-inflammatory agents, and especially certain non-steroidal cyclooxygenase inhibitors in combination with prostaglandin FP receptor agonists for treating glaucoma and/or ocular hypertension in an individual.

BACKGROUND OF THE INVENTION

[0003] The glaucomas are a heterogeneous group of optic neuropathies characterized by cupping of the optic nerve head, thinning of the retinal nerve fiber layer due to loss of retinal ganglion cells, and specific pathognomonic changes in visual fields. Elevated intraocular pressure (IOP) is a very important risk factor for the development of most common forms of glaucoma (Sommer A, et al., "Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans," *Arch. Ophthalmol.*, 109:1090-1095 (1991)).

[0004] A family history of glaucoma also is an important risk factor for the development of glaucoma. It appears that a significant portion of glaucoma is inherited (or at least the risk for developing glaucoma is inherited) although it is often difficult to establish clear inheritance patterns for most of the glaucomas because of the disease onset late in life and the slowly progressive clinical manifestations of the disease. Despite these problems, a number of families with heritable forms of glaucoma have been identified and these families have been used to map a variety of glaucoma genes (Sheffield, et al., "Genetic Linkage of Familial Open Angle Glaucoma to Chromosome 1q21-q31," *Nature Genetics*, 4:47-50 (1993); Sarfarazi, et al., "Assignment of a Locus (GLC3A) for Primary Congenital Glaucoma (Buphthalmos) to 2p21 and Evidence for Genetic Heterogeneity," *Genomics*, 30:171-177 (1995); Akarsu, et al., "A Second Locus (GLC3B) for Primary Congenital Glaucoma (Buphthalmos) Maps to the 1p36 Region," *Human Molecular Genetics*, 5(8):1199-1203 (1996); Stoilova, et al., "Localization of a Locus (GLC1B) for Adult-Onset Primary Open Angle Glaucoma to the 2cen-q13 Region," *Genomics*, 36:142-150 (1996); Wirtz, et al., "Mapping a Gene for Adult-Onset Primary Open-Angle Glaucoma to Chromosome 3q," *Am. J. Hum. Genet.*, 60:296-304 (1997); Andersen, et al., "A Gene Responsible for the Pigment Dispersion Syndrome Maps to Chromosome 7q35-q36," *Arch. Ophthalmol.*, 115:384-388 (1997). The first glaucoma gene mapped (GLC1A) was in a large family with autosomal dominant inherited juvenile glaucoma (JG). This disease is characterized by an early disease onset (at the age of late teens to early 20s), relatively

high IOPs, and general resistance to conventional pharmacological IOP lowering therapy. The GLC1A gene was mapped by positional cloning and linkage analysis to chromosome 1q22-q25 (Sheffield et al, Id., and a number of other groups have confirmed the 1q location of this juvenile glaucoma gene (Richards, et al., "Mapping of a Gene for Autosomal Dominant Juvenile-Onset Open-Angle Glaucoma to Chromosome 1q," *Am. J. Hum. Genet.*, 54:62-70 (1994); Morissette, et al., "A Common Gene for Juvenile and Adult-Onset Primary Open-Angle Glaucomas Confined on Chromosome 1q," *Am. J. Hum. Genet.*, 56:1431-1442 (1995); Wiggs, et al., "Genetic Linkage of Autosomal Dominant Juvenile Glaucoma to 1q21-q31 in Three Affected Pedigrees," *Genomics*, 21:299-303 (1994); Meyer, et al., "Age-Dependent Penetrance and Mapping of the Locus for Juvenile and Early-Onset Open-Angle Glaucoma on Chromosome 1q (GLC1A) in a French Family," *Hum. Genet.*, 98:567-571 (1996); Graff, et al., "Confirmation of Linkage to 1q21-31 in a Danish Autosomal Dominant Juvenile-Onset Glaucoma Family and Evidence of Genetic Heterogeneity," *Hum. Genet.*, 96:285-289 (1995). Glaucoma due to the GLC1A gene is hereinafter referred to as GLC1A glaucoma or 1 q glaucoma.

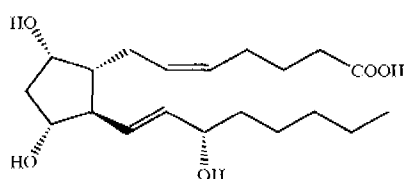
[0005] The GLC1A gene was identified as encoding a 57 kD protein expressed in the trabecular meshwork (TM) (Stone, et al., "Identification of a Gene That Causes Primary Open Angle Glaucoma," *Science*, 275:668-670 (1997). The expression of the GLC1A gene, and the encoded TM protein, is up-regulated by glucocorticoids (Polansky, et al., "In Vitro Correlates of Glucocorticoid Effects on Intraocular Pressure," *Glaucoma Update IV* (1991); and Polansky, et al., "Cellular Pharmacology and Molecular Biology of the Trabecular Meshwork Inducible Glucocorticoid Response Gene Product," *Ophthalmologica*, 211:126-139 (1997). This TM protein is also known as TIGR (trabecular meshwork inducible glucocorticoid response) (Polansky, Id.). The glucocorticoid-induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma (Polansky, Id.).

[0006] The GLC1A gene is expressed in other ocular tissues such as the ciliary epithelium (Ortego, et al., "Cloning and Characterization of Subtracted cDNAs from a Human Ciliary Body Library Encoding TIGR, a Protein Involved in Juvenile Open Angle Glaucoma with Homology to Myosin and Olfactomedin," *FEBS Letters*, 413:349-353 (1997) and the retina (Kubota, et al., "A Novel Myosin-like Protein (Myocilin) Expressed in the Connecting Cilium of the Photoreceptor: Molecular Cloning, Tissue Expression, and Chromosomal Mapping," *Genomics*, 41:360-369 (1997). The gene is referred to by several names including GLC1A (Sheffield, supra; Sunden, et al., "Fine Mapping of the Autosomal Dominant Juvenile Open Angle Glaucoma (GLC1A) Region and Evaluation of Candidate Genes," *Genome Research*, 6:862-869 (1996); Stone, et al., supra, TIGR (Polansky supra; Ortego, supra, and myocilin (Kubota, supra). Mutations in GLC1A are not only responsible for juvenile glaucoma, but also a significant subset of adult onset primary open angle glaucoma (Stone, et al., supra); Adam, et al., "Recurrent Mutations in a Single Exon Encoding the Evolutionarily Conserved Olfactomedin-Homology Domain of TIGR in Familial Open-Angle Glaucoma," *Human Molecular Genetics*, 6(12):2091-2097 (1997). The 1q glaucoma gene (GLC1A) is the subject of Nguyen, et al., U.S. Pat. No. 5,606,043, issued Feb. 25, 1997.

[0007] Ocular inflammation is a condition which generally affects the patient with scratchiness, itchiness and/or red eye. Ocular inflammation can be initiated by various insults. For example, ocular inflammation can result from allergic response to various allergens, trauma to the eye, dry eye and surgical complications. Various anti-inflammatory therapies are currently known for the treatment of inflammation, including the topical administration of non-steroidal anti-inflammatory agents such as diclofenac for ophthalmic inflammation. A number of these therapies, from aspirin to the recently commercialized COX II inhibitors, celecoxib and rofecoxib, are believed to involve, at least in part, inhibition of prostaglandin synthesis. In addition to the treatment of inflammation, several patent applications have disclosed the use of non-steroidal cyclooxygenase inhibitors to treat intraocular pressure (WO 95/17178) through the action of the compounds on trabecular meshwork cells (WO 96/40103 and WO 96/40102). At least some of the beneficial effects of the non-steroidal cyclooxygenase inhibitors are attributed to the inhibition of the expression of myocilin (or TIGR) which is the gene product of GLC1A.

[0008] It is known that trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton (Wilson, et al., "Dexamethasone Induced Ultrastructural Changes in Cultured Human Trabecular Meshwork Cells, *Cur. Eye Res.*, 12:783-793 (1993), and Clark, et al., "Glucocorticoid-Induced Formation of Cross-Linked Actin Networks in Cultured Human Trabecular Meshwork Cells," *Invest. Ophthalmol. Vis. Sci.*, 35:281-294 (1994)) and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises. If this state of elevated intraocular pressure (IOP) is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field. Loss of visual field is the hallmark symptom associated with glaucoma.

[0009] Prostaglandins, which are metabolite derivatives of arachidonic acid, have recently been pursued for possible efficacy in treating glaucoma and lowering IOP. The arachidonic acid cascade is initiated by the conversion of arachidonic acid to prostaglandin G_2 and subsequent conversion to prostaglandin H_2 . Other naturally occurring prostaglandins are derivatives of prostaglandin H_2 . A number of different types of prostaglandins have been discovered including A, B, D, E, F and I-Series prostaglandins. Of interest in the present invention are combinations of compounds which exhibit IOP lowering mechanisms similar to that of $PGF_{2\alpha}$ formula (I):



[0010] The relationship between receptor activation by $PGF_{2\alpha}$ and IOP lowering is not well understood. It is believed that FP receptor activation by $PGF_{2\alpha}$ leads to increased outflow of aqueous humor. Regardless of mechanism, $PGF_{2\alpha}$ and analogs have been shown to lower IOP (Giuffrè, *The Effects of Prostaglandin $F_{2\alpha}$ the Human Eye*, *Graefe's Archive Ophthalmology*, volume 222, pages 139-141 (1985); and Kerstetter et al., *Prostaglandin $F_{2\alpha}$ -1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow*, *American Journal of Ophthalmology*, volume 105, pages 30-34 (1988)). Thus, it has been of interest in the field to develop synthetic $PGF_{2\alpha}$ analogs with IOP lowering efficacy.

[0011] Synthetic $PGF_{2\alpha}$ -type analogs have been pursued in the art (*Graefe's Archive Ophthalmology*, volume 229, pages 411-413 (1991)). Though $PGF_{2\alpha}$ -type molecules lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects include an initial increase in IOP, breakdown of the blood aqueous barrier and conjunctival hyperemia (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, *Current Opinion in Ophthalmology*, volume 4, No. 11, pages 44-50 (1993)). The binding of PGF analogs with the FP receptor may lead to IOP lowering effects, but with fewer or diminished side effects compared to those elicited by the above mentioned $PGF_{2\alpha}$ -type analogs.

[0012] Attempts have been made by Stjernschantz et al. (U.S. Pat. No. 5,422,368), Woodward et al., (U.S. Pat. No. 5,093,329), Chan et al. (WO 92/08465) and Ueno et al. (U.S. Pat. No. 5,151,444) to use structural analogs and derivatives of prostaglandins to reduce selectively or to eliminate altogether the side effects while maintaining the IOP-lowering effect. The contents of the foregoing U.S. patents are by this reference incorporated herein. Commonly assigned U.S. Pat. Nos. 5,510,383; 5,627,209; 5,665,773; 5,721,273; 5,698,733; 5,807,892; 5,814,660; 5,866,602; 5,994,397; 6,025,392; and 6,169,111; and 6,172,109 are also by this reference incorporated herein.

[0013] Even such modified prostaglandins, however, still often exhibit undesirable side effects. Latanoprost, for example (commercially available from Pharmacia, Inc.) is generally not excessively hyperemic, but it is known to cause iridial hyperpigmentation, as well as darkening of the eyelids and lashes in some patients (secondary side effects). Clark, "Current trends in antiglaucoma therapy," *Emerging Drugs*, 4:333-353 (1999). There remains a need, therefore, for a relatively side effect free prostaglandin-based therapy.

[0014] Use of the non-steroidal anti-inflammatory agents diclofenac sodium and fluorometholone in concurrent administration with the prostaglandin analog, latanoprost has been suggested to reduce the amount of flare and cystoid macular edema associated with the use of the prostaglandin analog in glaucoma therapy. Miyake et al., "Latanoprost accelerates disruption of blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakia," *Arch. Ophthalmol.*, 117(1):34-40 (1999). Commonly assigned U.S. Pat. Nos. 5,607,966; 5,750,564; and 5,607,966, which are by this reference incorporated herein, disclose non-steroidal anti-inflammatory agents useful in the treatment of ocular inflammation.

101

SUMMARY OF THE INVENTION

[0015] Certain non-steroidal cyclooxygenase inhibitors and their pharmaceutical formulations are useful for treating GLC1A glaucoma. The invention is also directed to methods for controlling GLC1A glaucoma using the non-steroidal cyclooxygenase inhibitors. A further aspect of the invention lies in the discovery that these non-steroidal anti-inflammatory agents and other prostaglandin synthesis inhibitors may be used in combination with prostaglandin analogs to treat glaucoma with reduced side effects.

BRIEF DESCRIPTION OF DRAWINGS

[0016] FIG. 1 shows nepafenac concentrations in ocular tissues of rabbits following a single topical dose.

[0017] FIG. 2 shows the nepafenac concentration calculated from the data in FIG. 1.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0018] Agents which alter the expression of GLC1A in the glaucomatous eye are expected to lower IOP and thereby prevent or inhibit the glaucomatous optic neuropathy which is being driven by elevated IOP. Glucocorticoids upregulate GLC1A expression in the TM of certain individuals. There have been several reports of elevated levels of the natural glucocorticoid cortisol in the aqueous humor and plasma of glaucoma patients (Schwartz, et al., supra; Rozsival, et al., supra). In addition, certain mutations in GLC1A may alter the expression of GLC1A in the TM tissue of 1q glaucoma patients. Unexpectedly, it has been discovered that certain non-steroidal cyclooxygenase inhibitors inhibit the expression of GLC1A in cultured human TM cells and lower elevated IOP in certain animal models of ocular hypertension. The non-steroidal cyclooxygenase inhibitors act to prevent the expression of GLC1A and the subsequent development of ocular hypertension. While bound by no theories, it is postulated that the secondary side effects of prostaglandin therapy and especially PGF-type prostaglandin therapy, may be attributable to prostaglandin induced prostaglandin synthesis in the eye. The IOP lowering effect of the prostaglandin analogs, however, is believed to result from a direct effect on the target tissue. Thus, in addition to reducing inflammation (flare and cystoid macular edema), prostaglandin synthesis inhibitors, such as the non-steroidal anti-inflammatory agents described herein (whether directly or through an incorporated reference), will ameliorate the undesirable secondary side effects associated with prostaglandin therapy for the treatment of glaucoma, without significantly interfering with the desired IOP lowering.

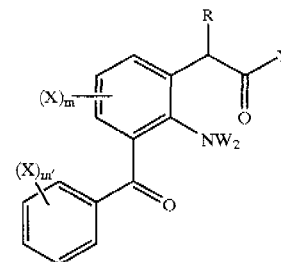
[0019] The present invention is directed, therefore, to methods of treating glaucoma, comprising concurrent or combined administration of therapeutically effective amounts of a prostaglandin analog and a prostaglandin synthesis inhibitor. The preferred methods of the present invention comprise one or more prostaglandin analogs in combination with one or more prostaglandin synthesis inhibitors. Preferred among the prostaglandin analogs are the F-type prostaglandin analogs. Preferred among the prostaglandin synthesis inhibitors are the non-steroidal anti-inflammatory agents, especially those which inhibit PGF synthesis. It will be appreciated, however, that any IOP lowering effective prostaglandin in combination with any

prostaglandin synthesis inhibitor for the treatment of glaucoma is within the scope of the present invention.

[0020] Many non-steroidal cyclooxygenase inhibitors do not readily penetrate the cornea upon topical administration and, therefore, do not reach therapeutic concentrations in the target tissue, whether that be the trabecular meshwork, iridial melanocytes, or some other tissue.

[0021] A series of compounds disclosed in commonly assigned U.S. Pat. No. 5,475,034, which showed no significant non-steroidal anti-inflammatory activity in vitro, exhibit superior corneal penetration leading to improved ocular bioavailability. The estimated concentration within the anterior chamber following topical ocular administration of 0.3% nepafenac to rabbits is 24 μ M (see FIGS. 1 and 2). This concentration, achieved using a simple formulation without penetration enhancers, is in excess of the parent compounds' COX I and COX II IC₅₀s. This enhanced bioavailability provides a significant advantage and is unexpected over other non-steroidal anti-inflammatory drugs as well as amide derivatives of non-steroidal anti-inflammatory drugs. The compounds disclosed in the '034 patent, the contents of which are incorporated herein by reference, are ester and amide derivatives of 3-benzoylphenylacetic acid.

[0022] The compounds set forth in the '034 patent have the following structure:



[0023] R=H, C₁₋₄ (un)branched alkyl, CF₃, SR⁴

[0024] Y=OR', NR'R'

[0025] R'=H (except when Y=OR'), C₁₋₁₀ (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), —(CH₂)_nZ(CH₂)_nA

[0026] n=2-6

[0027] n'=1-6

[0028] Z=nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR³, NR³C(=O), S(O)_n, ClOR³, NR³

[0029] n²=0-2

[0030] R³=H, C₁₋₆ (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below)

[0031] A=H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), —CH₂)_nOR³

[0032] $R''=H, OH, OR'$

[0033] X and X' independently=H, F, Cl, Br, I, OR', CN, OH, S(O)_n2R⁴, CF₃, R⁴, NO₂

[0034] $R^4=C_{1-6}$ (un)branched alkyl

[0035] $m=0-3$

[0036] $m'=0-5$

[0037] $W=O, H$

[0038] Preferred compounds for use as a prostaglandin synthesis inhibitor in the pharmaceutical compositions or methods of the present invention are those of Formula II wherein:

[0039] $R=H, C_{1-2}$ alkyl

[0040] $Y=NR'R''$

[0041] $R=H, C_{1-6}$ (un)branched alkyl, $-(CH_2)_n$, $Z(CH_2)_nA$

[0042] $Z=nothing, O, CHOR^3, NR^3$

[0043] $R_3=H$

[0044] $A=H, OH, (un)substituted$ aryl (substitution as defined by X below)

[0045] X and X' independently=H, F, Cl, Br, CN, CF₃, OR', SR⁴, R⁴

[0046] $R''=H$

[0047] $R^4=C_{1-4}$ (un)branched alkyl

[0048] $m=0-2$

[0049] $m'=0-2$

[0050] $W=H$

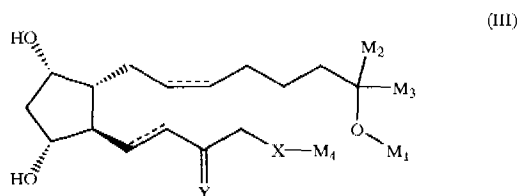
[0051] $n=2-4$

[0052] $n'=0-3$

[0053] The most preferred compounds for use as a prostaglandin synthesis inhibitor in the compositions or methods of the present invention are 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

[0054] For the preferred compound, nepafenac, $W=H, R=H, Y=NH_2, X'=H, X=H, m=3$, and $m'=5$.

[0055] The F-type prostaglandin analogs of the present invention are prostaglandin FP receptor agonists of the following formula (III):



[0056] wherein:

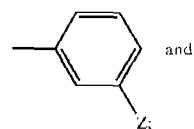
[0057] X is CH₂ or O;

[0058] Y is H and OH or O;

[0059] M_1 is H, C₁₋₁₂ straight-chain or branched alkyl; C₁₋₁₂ straight chain or branched acyl; C₃₋₈ cycloalkyl; a cationic salt moiety; or an acceptable amine moiety;

[0060] M_2 and M_3 are H or taken together are (=O); and

[0061] M_4 is C₃₋₅ alkyl or



[0062] Z is H, Cl or CF₃;

[0063] provided that when M_2 and M_3 taken together are (=O), then M_1 cannot be C₁₋₁₂ straight chain or branched acyl; and when M_2 and M_3 are H, then M_1 cannot be a salt or an amine.

[0064] The following are preferred prostaglandin analogs of formula (III): latanoprost, travoprost, bimatoprost, and UFO-21, as well as, cloprostenol, fluprostenol, 13,14 dihydro-cloprostenol and 13, 14-dihydrofluprostenol and their isopropyl esters and salts. Also preferred is isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate. The most preferred prostaglandin analogs of the present invention are latanoprost, travoprost, and bimatoprost.

[0065] The prostaglandin analogs of the present invention are known and are either commercially available (Cayman Chemical, Ann Arbor, Michigan) or may be prepared by known methods to those skilled in the art. Some of the FP-agonists of the present invention are disclosed in European Patent Publication No. 0 639 563 A2, which is incorporated herein by reference to the extent that it discloses methods of synthesizing or obtaining prostaglandin analogs of the present invention.

[0066] The prostaglandin analogs and prostaglandin synthesis inhibitors of the present invention may be formulated in various pharmaceutical compositions for administering to humans and other mammals as a treatment of glaucoma or ocular hypertension. As used herein, the term "pharmaceutically effective amount" refers to that amount of a prostaglandin analog which lowers IOP when administered to a patient, or that amount of a prostaglandin synthesis inhibitor which reduces secondary side effects of prostaglandin therapy when administered in conjunction with such therapy. The preferred route of administration is topical. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in an ophthalmically acceptable vehicle. As used herein, the term "ophthalmically acceptable vehicle" refers to any substance or combination of substances which are non-reactive with the compounds and suitable for administration to a patient. Solubilizers and stabilizers are deemed to be non-reactive. Preferred are aqueous vehicles suitable for topical application to the patient's eyes.

[0067] In forming compositions for topical administration, the prostaglandin analogs of the present invention are generally formulated as between about 0.00003 to about 0.5 percent by weight (wt %) solutions and the prostaglandin synthesis inhibitors are generally formulated as between about 0.001 to about 1.0 percent by weight (wt %), both in water at a pH between about 4.5 to about 8.0, preferably between about 5.0 and about 7.5. The prostaglandin compounds are preferably formulated as between about 0.0005 to about 0.03 wt % and, most preferably, between about 0.001 and about 0.01 wt %. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution(s) be topically applied by placing one drop in each eye one or two times a day.

[0068] Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents, and viscosity building agents.

[0069] Antimicrobial Preservatives:

[0070] Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Such preservatives are typically employed at a level between about 0.001% and about 1.0% by weight.

[0071] Co-Solvents:

[0072] Prostaglandin analogs, and particularly ester derivatives thereof, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; CREMOPHORE® EL (polyoxyl 35 castor oil); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level between about 0.01% and about 2% by weight.

[0073] Viscosity Agents:

[0074] Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and other agents known to those skilled in the art. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0075] The following examples are illustrative of formulations which can be used according to the present invention, but are not limiting. "PG Synthesis Inhibitor" means one or more non-steroidal anti-inflammatory agents; described by the structure and definition set forth above.

EXAMPLE 1

[0076]

Component	Concentration (wt/vol %)
Nepafenac	0.1
Travoprost	0.004
NCO-40	0.1
Tromethamine	0.12
Boric acid	0.3
Mannitol	4.6
Disodium EDTA (edetate disodium)	0.1
Benzalkonium Chloride Solution	0.01
HCl and/or NaOH	q.s. to pH 7.3-7.4
Purified Water	q.s. to 100%

EXAMPLE 2

[0077]

Component	Concentration (% w/w)
Nepafenac	0.1
Latanoprost	0.005
Carbopol 974P	0.5
Sodium Chloride	0.4
Mannitol	2.4
Tyloxapol	0.1
EDTA	0.01
Benzalkonium Chloride	0.01
NaOH or HCl	q.s. to pH 7.5
Water for injection	q.s. to 100%

EXAMPLE 3

[0078]

Component	Concentration (% w/w)
PG Synthesis Inhibitor	0.01-0.5%
Travoprost	0.0015%
Hydroxypropyl Methylcellulose	0.5%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 5% excess
Disodium EDTA	0.01%
Disodium EDTA	0.2%
Dibasic Sodium Phosphate	q.s. 290-300 Osm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2-7.4
Water	q.s. to 100%

EXAMPLE 4

[0079]

Component	Concentration (% w/w)
PG Synthesis Inhibitor	0.01-0.5%
Latanoprost	0.005%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 10% excess

-continued

Component	Concentration (% w/w)
Disodium EDTA	0.1%
Monobasic Sodium Phosphate	0.03%
Dibasic Sodium Phosphate	0.1%
Sodium Chloride	q.s. 290-300 Osm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2-7.4
Water	q.s. to 100%

EXAMPLE 5

[0080]

Component	Concentration (wt/vol %)
Nepafenac	0.1
Bimatoprost	0.03
NCO-40	0.1
Tromethamine	0.12
Boric acid	0.3
Mannitol	4.6
Disodium EDTA (edetate disodium)	0.1
Benzalkonium Chloride Solution	0.01
HCl and/or NaOH	q.s. to pH 7.3-7.4
Purified Water	q.s. to 100%

EXAMPLE 6

[0081]

Component	Concentration (% w/w)
Nepafenac	0.1
Travoprost	0.004
Carbopol 974P	0.5
Sodium Chloride	0.4
Mannitol	2.4
Tyloxapol	0.1
EDTA	0.01
Benzalkonium Chloride	0.01
NaOH or HCl	q.s. to pH 7.5
Water for injection	q.s. to 100%

EXAMPLE 7

[0082]

Component	Concentration (% w/w)
PG Synthesis Inhibitor	0.01-0.5
Bimatoprost	0.03
Hydroxypropyl Methylcellulose	0.5
Polysorbate 80	0.01
Benzalkonium Chloride	0.01 + 5% excess
Disodium EDTA	0.01
Disodium EDTA	0.2
Dibasic Sodium Phosphate	q.s. 290-300 Osm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2-7.4
Water	q.s. to 100%

EXAMPLE 8

[0083]

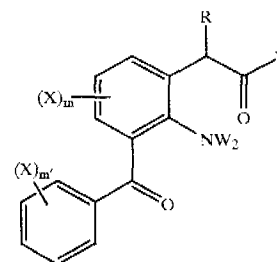
Component	Concentration (% w/w)
PG Synthesis Inhibitor	0.01-0.5
Travoprost	0.004
Polysorbate 80	0.01
Benzalkonium Chloride	0.01 + 10% excess
Disodium EDTA	0.1
Monobasic Sodium Phosphate	0.03
Dibasic Sodium Phosphate	0.1
Sodium Chloride	q.s. 290-300 Osm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2-7.4
Water	q.s. to 100%

[0084] The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

We claim:

1. A method of treating glaucoma, comprising administering to an affected eye a combination of an intraocular pressure lowering effective amount of a prostaglandin FP receptor agonist, and a prostaglandin synthesis inhibiting effective amount of a prostaglandin synthesis inhibitor other than diclofenac or fluorometholone.

2. The method of claim 2, wherein the prostaglandin synthesis inhibitor is a non-steroidal anti-inflammatory agent having the following formula:



R=H, C₁₋₄ (un)branched alkyl, CF₃, SR⁴

Y=OR', NR''R'

R=H (except when Y=OR'), C₁₋₁₀ (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH₂)_nZ(CH₂)_{n'}A

n=2-6

n'=1-6

Z=nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR³, NR³C(=O), S(O)_n, 2, CHOR³, NR³

n²=0-2

$R^3 = H, C_{1-6}$ (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below)

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_n OR^3$

$R'' = H, OH, OR'$

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_n R^4$, CF_3 , R^4 , NO_2

$R^4 = C_{1-6}$ (un)branched alkyl

$m = 0-3$

$m' = 0-5$

W = O, H.

3. The method of claim 2, wherein the prostaglandin FP receptor agonist is selected from the group consisting of latanoprost, travoprost, bimatoprost, unoprostone isopropyl, and $[2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate$, and wherein the prostaglandin synthesis inhibitor is selected from the group consisting of: 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. A topical ophthalmic composition comprising an intraocular pressure lowering effective amount of a prostaglandin FP receptor agonist selected from the group consisting of latanoprost, travoprost, and bimatoprost; a prostaglandin synthesis inhibiting effective amount of nepafenac; and an ophthalmically acceptable vehicle therefore.

* * * * *

ANEXO 2

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US95/17086 (22) International Filing Date: 19 December 1995 (19.12.95) (30) Priority Data: 08/362,677 22 December 1994 (22.12.94) US (71) Applicant: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventor: SCHNEIDER, L., Wayne; 10308 Lisa Jean Drive, Crowley, TX 76036 (US). (74) Agents: RYAN, Patrick, M. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: STORAGE-STABLE PROSTAGLANDIN COMPOSITIONS (57) Abstract The use of polyethoxylated castor oils in prostaglandin compositions greatly enhances the prostaglandin's chemical stability.		

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STORAGE-STABLE PROSTAGLANDIN COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates generally to prostaglandin compositions. In particular, the present invention relates to storage stable, pharmaceutical compositions containing prostaglandins and surfactants. As used herein, the term "prostaglandin" or "PG" shall refer to prostaglandins and derivatives and analogues thereof including pharmaceutically acceptable salts and esters, except as otherwise indicated by context.

Prostaglandins have notoriously low water solubility, and are generally unstable. Attempts have been made to solubilize and stabilize various prostaglandins by complexing them with different cyclodextrins. See, for example: EP 330 511 A2 (Ueno et al.) and EP 435 682 A2 (Wheeler). These attempts have met with varying success.

Surfactants and/or solubilizers have been used with other types of drugs having low water solubility. However, the addition of surfactants and/or solubilizers may enhance or adversely affect the chemical stability of drug compounds. See *Surfactant Systems, Their Chemistry, Pharmacy, and Biology*, (eds. Attwood et al.), Chapman and Hall, New York, 1983, Ch. 11, particularly pp. 698 - 714.

The use of non-ionic surfactants, such as polyethoxylated castor oils, as solubilizing agents is known. See, for example, US 4,960,799 (Nagy).

The use of non-ionic surfactants such as polyethoxylated castor oils in stable emulsions is also known. US 4,075,333 (Josse) discloses stable, intravenous emulsion formulations of vitamins. El-Sayed et al., *Int. J. Pharm.*, 13:303-12 (1983) discloses stable oil-in-water emulsions of an antineoplastic drug. US 5,185,372 (Ushio et al.) discloses topically administrable ophthalmic formulations of vitamin A which are stable preparations in which a non-ionic surfactant is used to form an emulsion of vitamin A in an aqueous medium.

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What is needed is a commercially viable, storage-stable prostaglandin composition.

SUMMARY OF THE INVENTION

5 The present invention is directed to the use of polyethoxylated castor oils in pharmaceutical compositions containing prostaglandins. It has now been unexpectedly discovered that the use of such polyethoxylated castor oils in such compositions enhances the chemical stability of prostaglandins in pharmaceutical compositions. The compositions of the present invention can be administered to the body in a variety of
10 ways. When topically applied to the eye, the compositions of the present invention provide both initial and continual comfort.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the stabilizing effect at different concentrations of a polyethoxylated castor oil in a preserved prostaglandin formulation at pH 5.0.

15 Fig. 2 compares the stabilizing effect of different surfactants in a preserved prostaglandin formulation at pH 5.0.

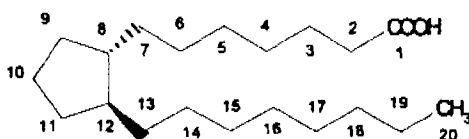
Fig. 3 compares the stabilizing effect of different surfactants in a preserved prostaglandin formulation at pH 7.4.

DETAILED DESCRIPTION OF THE INVENTION

20 Prostaglandin esters are difficult to formulate in storage-stable solutions as they tend to be hydrolytically unstable. In some instances, the parent acids of some prostaglandin esters are also unstable. The pharmaceutical compositions of the present invention, however, are storage stable. These compositions contain a prostaglandin and a stability-enhancing amount of a polyethoxylated castor oil.

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The polyethoxylated castor oils useful in the compositions of the present invention are commercially available, and include those classified as PEG-2 to PEG-200 castor oils, as well as those classified as PEG-5 to PEG-200 hydrogenated castor oils. Such polyethoxylated castor oils include those manufactured by Rhone-Poulenc (Cranbury, New Jersey) under the Alkamuls[®] brand, and those manufactured by BASF (Parsippany, New Jersey) under the Cremophor[®] brand. It is preferred to use the polyethoxylated castor oils classified as PEG-15 to PEG-50 castor oils, and more preferred to use PEG-30 to PEG-35 castor oils. It is most preferred to use those polyethoxylated castor oils known as Cremophor[®] EL and Alkamuls[®] EL-620.

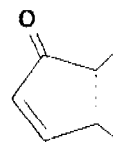
10 The terms "prostaglandin" and "PG" are generally used to describe a class of compounds which are analogues and derivatives of prostanoic acid (1):



(1)

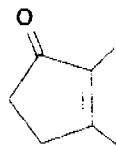
15 PG's may be further classified, for example, according to their 5-membered ring structure, using a letter designation:

Prostaglandins of the A series (PGA's):

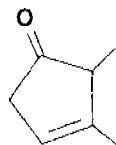


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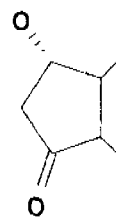
Prostaglandins of the B series (PGB's):



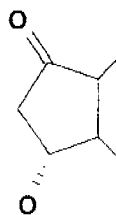
Prostaglandins of the C series (PGC's):



Prostaglandins of the D series (PGD's):

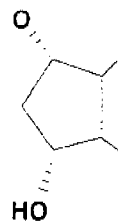


Prostaglandins of the E series (PGE's):



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Prostaglandins of the F series (PGF's):

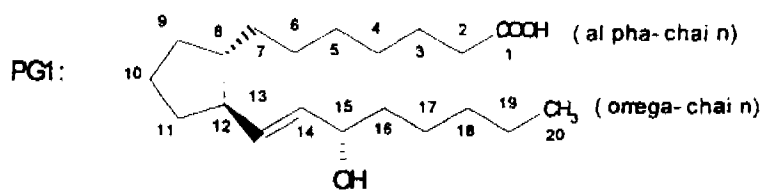


Prostaglandins of the J series (PGJ's):

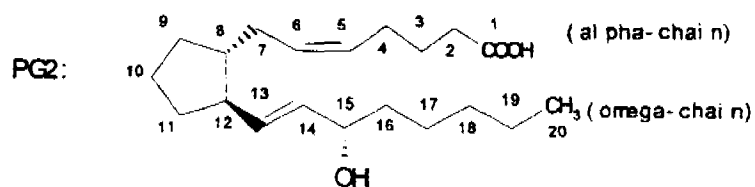


PG's may be further classified based on the number of unsaturated bonds on the side chain:

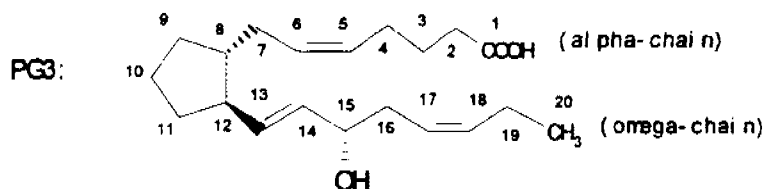
PG₁'s (13,14-unsaturated):



PG₂'s (13,14- and 5,6- unsaturated):



PG₃'s (13,14- 5,6- and 17,18- unsaturated):



The prostaglandins which may be utilized in the present invention include all pharmaceutically acceptable prostaglandins, their derivatives and analogues, and their pharmaceutically acceptable esters and salts. Such prostaglandins include the natural compounds: PGE₁, PGE₂, PGE₃, PGF_{1α}, PGF_{2α}, PGF_{3α}, PGD₂ and PGI₂ (prostacyclin), as well as analogues and derivatives of these compounds which have similar biological activities of either greater or lesser potencies. Analogues of the natural prostaglandins include but are not limited to: alkyl substitutions (e.g., 15-methyl or 16,16-dimethyl), which confer enhanced or sustained potency by reducing biological metabolism or alter selectivity of action; saturation (e.g., 13,14-dihydro) or unsaturation (e.g., 2,3-didehydro, 13,14-didehydro), which confer sustained potency by reducing biological metabolism or alter selectivity of action; deletions or replacements (e.g., 11-deoxy, 9-deoxy-9-methylene), chloro (or halogen) for oxygen (e.g., 9β-chloro), oxygen for carbon (e.g., 3-oxa), lower alkyl for oxygen (e.g., 9-methyl), hydrogen for oxygen (e.g., 1-CH₂OH, 1-CH₂OAcyl) which enhance chemical stability and/or selectivity of action; and ω-chain modifications (e.g., 18,19,20-trinor-17-phenyl, 17,18,19,20-tetranor-16-phenoxy), which enhance selectivity of action and reduce biological metabolism. Derivatives of these prostaglandins include all pharmaceutically acceptable salts and esters, which may be attached to the 1-carboxyl group or any of the hydroxyl groups of the prostaglandin by use of the corresponding alcohol or organic acid reagent, as appropriate. It should be understood that the terms "analogues" and "derivatives" include compounds which exhibit functional and physical responses similar to those of prostaglandins per se.

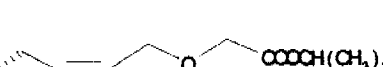
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Specific examples of prostaglandins which are useful in the present invention include the following compounds:

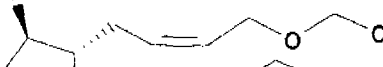
Compound No.

1. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
5 16,17,18,19,20-pentanoic acid;
2. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid isopropyl ester;
3. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid *t*-butyl ester;
- 10 4. (5Z)-(9S,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-
pentanoic acid isopropyl ester;
5. (5Z)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid isopropyl ester;
6. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
15 16,17,18,19,20-pentanoic acid amide;
7. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid N,N-dimethylamide;
8. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid 1-methylcyclohexyl ester;
- 20 9. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid 1-methylcyclopentyl ester;
10. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid cyclopentyl ester;
11. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
25 16,17,18,19,20-pentanoic acid 2,2-dimethylpropyl ester;
12. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid adamantyl ester;
13. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid 2,6-diisopropylphenyl ester;
- 30 14. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-
16,17,18,19,20-pentanoic acid 2,6-dimethylphenyl ester;

- 116 40
15. (5Z, 13E)-(9S,11R,15R)-3-oxa-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester;
 16. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-15-methoxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester;
 17. (5Z)-(9R,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester;
 18. (5E)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester;
 19. (5Z)-(9R,11R)-9-chloro-15-cyclohexyl-11-hydroxy-3-oxa-15-oxo-16,17,18,19,20-pentanoic acid *tert*butyl ester;
 20. (5Z)-(9S,11R,15R)-3-oxa-17-phenyl-9,11,15-trihydroxy-18,19,20-trinor-5-prostenoic acid isopropyl ester;
 21. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-1-(dimethylamino)-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester;
 22. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester;
 23. (9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-3-thia-16,17,18,19,20-pentanoic acid;
 24. Latanoprost (PhXA41);
 25. Cloprostenol isopropyl ester;
 26. (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5-prostenoic acid;
 27. (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5,13-prostadienoic acid;
 28. (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester;
 29. (5Z)-(9S,11R,15S)-15-cyclohexyl-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester;
 30. (5Z, 13E)-(9S,11R,15R)-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid amide;
 31. PGF_{2α} isopropyl ester; and
 32. Fluprostenol isopropyl ester.



 (2)



 (3)

The prostaglandin compositions of the present invention contain one or more polyethoxylated castor oils in an amount effective to enhance the stability of the prostaglandin. As Figure 1 illustrates the stabilizing effect of the polyethoxylated castor oil increases with increasing polyethoxylated castor oil concentration. However, other factors may limit the amount of polyethoxylated castor oil to be utilized in the compositions of the present invention. For example, too much polyethoxylated castor oil should not be used in order to avoid adversely affecting the prostaglandin's pharmacologic activity.

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The compositions of the present invention may be administered to the body in a variety of ways. The compositions may be administered by mouth, by intravenous injection or by topical application to the skin, nose or eyes. Most preferred are compositions prepared for topical administration to the eye.

5 In addition to the above-described principal active ingredients, the compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives, tonicity agents, and buffers. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, 10 Polyquad* and other agents equally well known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.001 and about 1.0 wt%. Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include sodium chloride, potassium chloride, mannitol, dextrose, glycerine and propylene glycol. Such agents, if utilized, will be 15 employed in an amount between about 0.1 and about 10.0 wt%. Examples of suitable buffering agents include acetic acid, citric acid, carbonic acid, phosphoric acid, boric acid, the pharmaceutically acceptable salts of the foregoing, and tromethamine. Such buffers, if utilized, will be employed in an amount between about 0.001 and about 1.0 wt%.

20 The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers and gelling polysaccharides, such as those described in US 4,861,760 (Mazuel et al), US 4,911,920 (Jani et al.), and in commonly assigned US Serial No. 08/108,824 (Lang et al.). The contents of these patents and 25 patent applications relating to the polymers cited above are incorporated herein by reference.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The

compositions are preferably aqueous, have a pH between 3.5 to 8.0 and an osmolality between 260 to 320 milliOsmoles per kilogram (mOsm/kg).

The present invention is also directed to methods of treating glaucoma and other ophthalmic diseases and abnormalities. The methods comprise topically applying to the affected eye(s) of the patient a therapeutically effective amount of a composition according to the present invention. The frequency and amount of dosage will be determined by the clinician based on various clinical factors. The methods will typically comprise topical application of one or two drops (approximately 30 microliters) of a liquid composition, or an equivalent amount of a solid or semi-solid dosage form, to the affected eye one to two times per day.

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EXAMPLE

The following topically administrable ophthalmic formulations are representative of the compositions of the present invention.

INGREDIENT	FORMULATION (wt%)		
	A	B	C
Compound 2	0.01	—	0.01
Compound 3	—	0.01	—
Cremophor [®] EL <i>polyethylene glycol</i>	0.5	0.5	0.5
Sodium Acetate <i>polyethylene glycol</i> (Trihydrate)	0.07	0.07	—
Tromethamine	—	—	0.12
Boric Acid	—	—	0.3
Mannitol	4.6	4.6	4.6
Disodium EDTA	0.1	0.1	0.1
Benzalkonium Chloride	0.01	0.01	0.01
NaOH and/or HCl	q.s. to pH 5	q.s. to pH 5	q.s. to pH 7
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

Preparation of Formulations A-C:

To a clean glass vessel of appropriate size was added approximately 75% of the batch volume of water. To this was sequentially added sodium acetate, tromethamine, boric acid, mannitol, EDTA, benzalkonium chloride and Cremophor[®] EL so that there was complete dissolution of one ingredient prior to the addition of the next ingredient. Next the pH of the solution was adjusted using NaOH and/or HCl, and the water was added to bring the volume to 100%.

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In a separate clean glass vessel, the appropriate quantity of prostaglandin was added, followed by the appropriate quantity of the vehicle whose preparation was described above. The vessel was then tightly capped and sonicated in an ultrasonic bath for one hour or alternatively stirred with a magnetic stir bar overnight, until the prostaglandin was completely dissolved. The resulting solution was then sterile filtered (0.2 micron filter) into sterile containers. These containers were then aseptically plugged, capped and labelled.

The stabilizing effect of polyethoxylated castor oils in the compositions of the present invention was evaluated according to the following procedure. (X)

1. Pipet the required quantity of 1% w/v prostaglandin ethanolic stock solution into 1.5 mL high performance liquid chromatograph (HPLC) sample vials.
2. Dry the sample vials under a stream of helium.
3. Add 1 mL of the appropriate vehicle (or HPLC mobile phase for standards).
4. Sonicate the vials one hour to dissolve the prostaglandin.
5. Run initial HPLC assays.
6. Place the HPLC sample vials into 20cc scintillation vials with several mLs of deionized water and cap tightly. (Note: This prevents loss due to evaporation.) Standards are stored with HPLC mobile phase in the scintillation vial.
7. Place the vials in the appropriate controlled temperature ovens and reassay periodically by HPLC. Standards are stored in a refrigerator.
8. HPLC Data Analysis: Divide Sample Peak Area by Standard Peak Area and multiply by 100 to obtain Percent of Standard for each sample at each time point.
9. Plot Percent of Standard versus time on a semilogarithmic graph. Fit a monoexponential equation to the data. The slope times 2.303 is the apparent first-order degradation rate constant for each plot (Note: The factor of 2.303 converts common logarithm to natural logarithm).

422 46 122

Figure 1 demonstrates the effect of increasing polyethoxylated castor oil concentration in Formulation A. The chemical stability of a given concentration of prostaglandin is increased as the concentration of Cremophor® EL is increased.

Figure 2 demonstrates the superior stabilizing effect of the polyethoxylated castor oils, Cremophor® EL and Alkamuls® EL-620, over Polysorbate 80 in a type A Formulation (pH = 5.0).

Figure 3 demonstrates the superior stabilizing effect of the polyethoxylated castor oils, Cremophor® EL and Alkamuls® EL-620, over Polysorbate 80 in a type C formulation (pH = 7.4).

The data shown in Figures 1-3 were generated using a Phenomenex 250 X 4.6 mm HPLC column with Spherisorb® 10 ODS(2) packing. The mobile phase was 50/50 acetonitrile/0.1 % phosphoric acid at pH 3 with NaOH, 5mM tetrabutylammonium hydroxide, and 5 mM sodium dodecylsulfate. The flow rate was 2 mL/minute, the detection was 190 - 192 nm UV, and the injection quantity was 25 mcL.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

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23What is claimed is:

1. A pharmaceutical composition comprising a prostaglandin, a polyethoxylated castor oil in an amount effective to enhance the chemical stability of the prostaglandin, and a pharmaceutically acceptable vehicle.
2. The composition of Claim 1 wherein the polyethoxylated castor oil is present at a concentration between about 0.02 wt% and about 20.0 wt%.
3. The composition of Claim 2 wherein the polyethoxylated castor oil is present at a concentration between about 0.1 wt% and about 5.0 wt%.
4. The composition of Claim 3 wherein the polyethoxylated castor oil is present at a concentration between about 0.5 wt% and about 2.0 wt%.
5. The composition of Claim 1 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-2 to PEG-200 castor oils and PEG-5 to PEG-200 hydrogenated castor oils.
6. The composition of Claim 5 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-15 to PEG-50 castor oils.
7. The composition of Claim 6 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-30 to PEG-35 castor oils.
8. The composition of Claim 1 wherein the prostaglandin is selected from the group consisting of (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9S,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15S)-9-chloro-15-

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cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid amide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid N,N-dimethylamide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclohexyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclopentyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid cyclopentyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,2-dimethylpropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid adamantyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,6-diisopropylphenyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,6-dimethylphenyl ester; (5Z, 13E)-(9S,11R,15R)-3-oxa-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-15-methoxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9R,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5E)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R)-9-chloro-15-cyclohexyl-11-hydroxy-3-oxa-15-oxo-16,17,18,19,20-pentanoic acid *tert*butyl ester; (5Z)-(9S,11R,15R)-3-oxa-17-phenyl-9,11,15-trihydroxy-18,19,20-trinor-5-prostenoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-1-(dimethylamino)-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-3-thia-16,17,18,19,20-pentanoic acid; latanoprost (PhXA41); cloprostenol isopropyl ester; (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5-prostenoic acid; (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5,13-prostadienoic acid; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9S,11R,15S)-

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15-cyclohexyl-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z, 13E)-(9S,11R,15R)-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid amide; PGF_{2α} isopropyl ester; and fluprostenol isopropyl ester.

5 9. The composition of Claim 8 wherein the prostaglandin is selected from the group consisting of: (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9S,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid amide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid N,N-dimethylamide; and (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclohexyl ester.

10 10. The composition of Claim 9 wherein the prostaglandin is selected from the group consisting of (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester and (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester.

11. The composition of Claim 1 wherein the prostaglandin is present at a concentration between about 0.0001 wt% and about 0.1 wt%.

12. The composition of Claim 1 wherein the composition is a topically administrable ophthalmic composition.

13. A method of enhancing the chemical stability of pharmaceutical prostaglandin composition comprising adding a polyethoxylated castor oil to the composition.

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14. The method of Claim 13 wherein the polyethoxylated castor oil is present at a concentration between about 0.02 wt% and about 20.0 wt%.

15. The method of Claim 14 wherein the polyethoxylated castor oil is present at a concentration between about 0.1 wt% and about 5.0 wt%.

16. The method of Claim 15 wherein the polyethoxylated castor oil is present at a concentration between about 0.5 wt% and about 2.0 wt%.

17. The method of Claim 13 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-2 to PEG-200 castor oils and PEG-5 to PEG-200 hydrogenated castor oils.

18. The method of Claim 17 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-15 to PEG-50 castor oils.

19. The method of Claim 18 wherein the polyethoxylated castor oil is selected from the group consisting of: PEG-30 to PEG-35 castor oils.

20. The method of Claim 13 wherein the prostaglandin is selected from the group consisting of: (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9S,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid amide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid N,N-dimethylamide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclohexyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-

11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclopentyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid cyclopentyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,2-dimethylpropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid adamantyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,6-diisopropylphenyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 2,6-dimethylphenyl ester; (5Z, 13E)-(9S,11R,15R)-3-oxa-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-15-methoxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9R,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5E)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R)-9-chloro-15-cyclohexyl-11-hydroxy-3-oxa-15-oxo-16,17,18,19,20-pentanoic acid *tert*butyl ester; (5Z)-(9S,11R,15R)-3-oxa-17-phenyl-9,11,15-trihydroxy-18,19,20-trinor-5-prostenoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-1-(dimethylamino)-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11-hydroxy-3-thia-16,17,18,19,20-pentanoic acid; latanoprost (PhXA41); cloprostenol isopropyl ester; (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5-prostenoic acid; (5Z)-(9S,11R,15R)-1-decarboxy-1-(pivaloyloxy)methyl-9,11,15-trihydroxy-16-[(3-chlorophenyl)oxy]-17,18,19,20-tetranor-5,13-prostadienoic acid; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9S,11R,15S)-15-cyclohexyl-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z, 13E)-(9S,11R,15R)-9,11,15-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid amide; PGF_{2α} isopropyl ester; and fluprostenol isopropyl ester.

21. The method of Claim 20 wherein the prostaglandin is selected from the group

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consisting of: (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester; (5Z)-(9S,11R,15R)-15-cyclohexyl-3-oxa-9,11,15-trihydroxy-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid amide; (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid N,N-dimethylamide; and (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid 1-methylcyclohexyl ester.

22. The method of Claim 21 wherein the prostaglandin is selected from the group consisting of (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid isopropyl ester and (5Z)-(9R,11R,15R)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanoic acid *t*-butyl ester.

23. The method of Claim 13 wherein the prostaglandin is present at a concentration between about 0.0001 wt% and about 0.1 wt%.

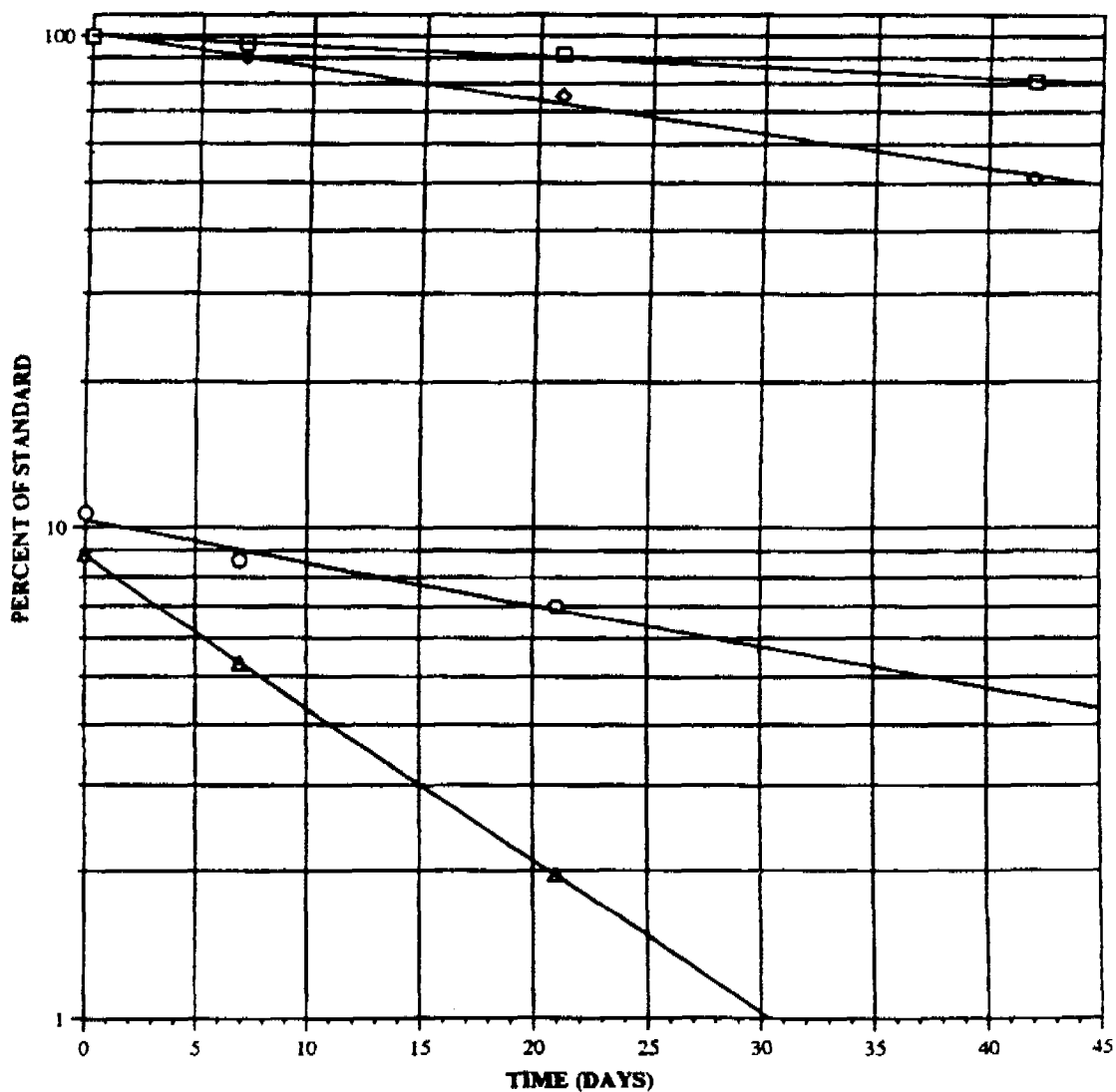
24. The method of Claim 13 wherein the composition is a topically administrable ophthalmic composition.

25. A method for the treatment of glaucoma and ocular hypertension, comprising the topical administration to an affected eye of a composition comprising a prostaglandin, a polyethoxylated castor oil, and an ophthalmically acceptable vehicle, wherein the polyethoxylated castor oil is present in an amount effective to chemically stabilize the prostaglandin.

Figure 1.

**Stability of Compound No. 2. at 65°C in pH 5.0
Preserved Vehicle with Cremophor® EL.**

- 5% Cremophor® EL / 0.01 % Compound No. 2.
- ◇ 0.5% Cremophor® EL / 0.01 % Compound No. 2.
- 0.5% Cremophor® EL / 0.001 % Compound No. 2.
- △ 0.05% Cremophor® EL / 0.001 % Compound No. 2.



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30**Figure 2.**

**Stability of 0.01% Compound No. 2. at 55°C in pH 5.0
Preserved Vehicle with the indicated Surfactant.**

- 0.5% Cremophor® EL
- △ 0.5% Alkamuls® EL-620
- ◇ Polysorbate 80

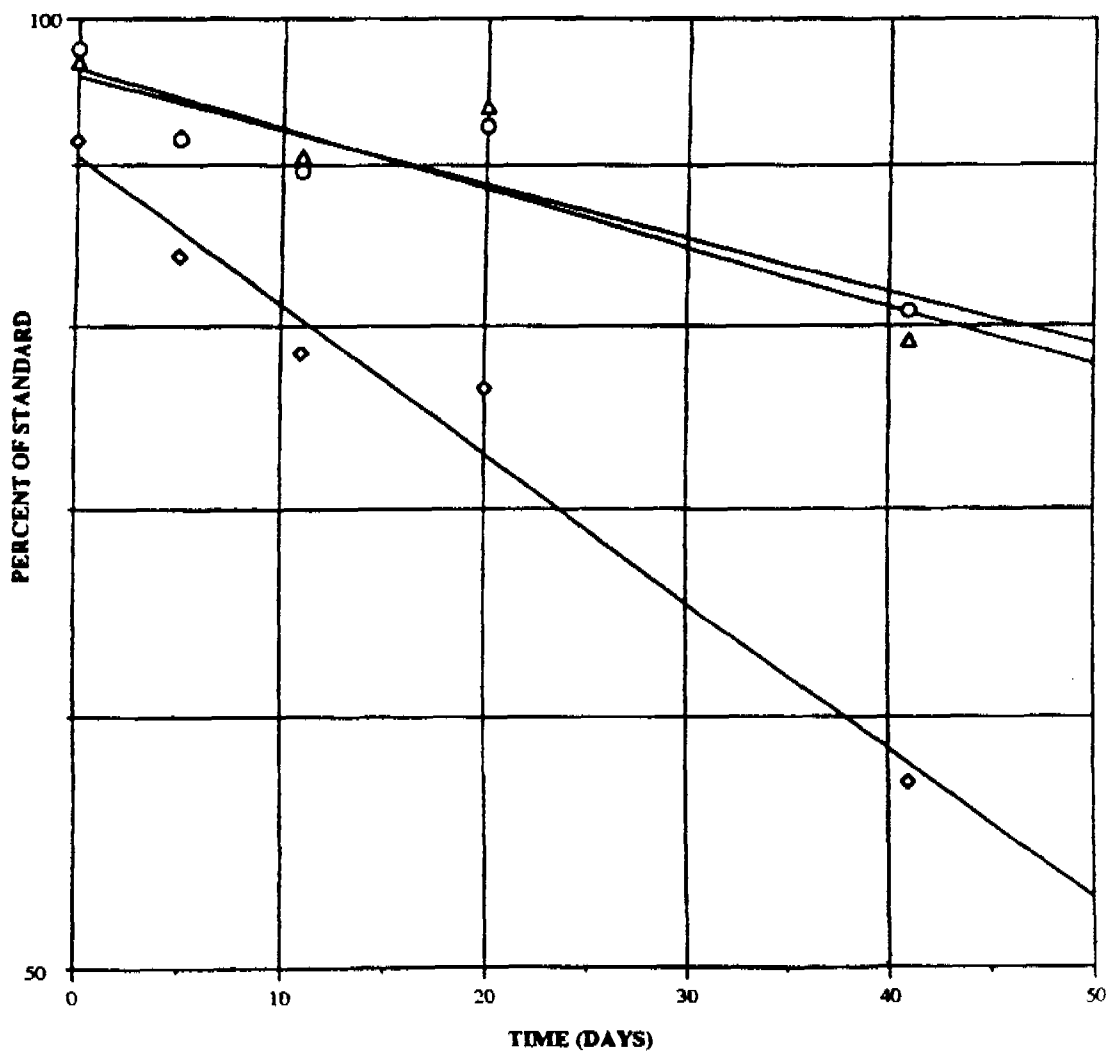
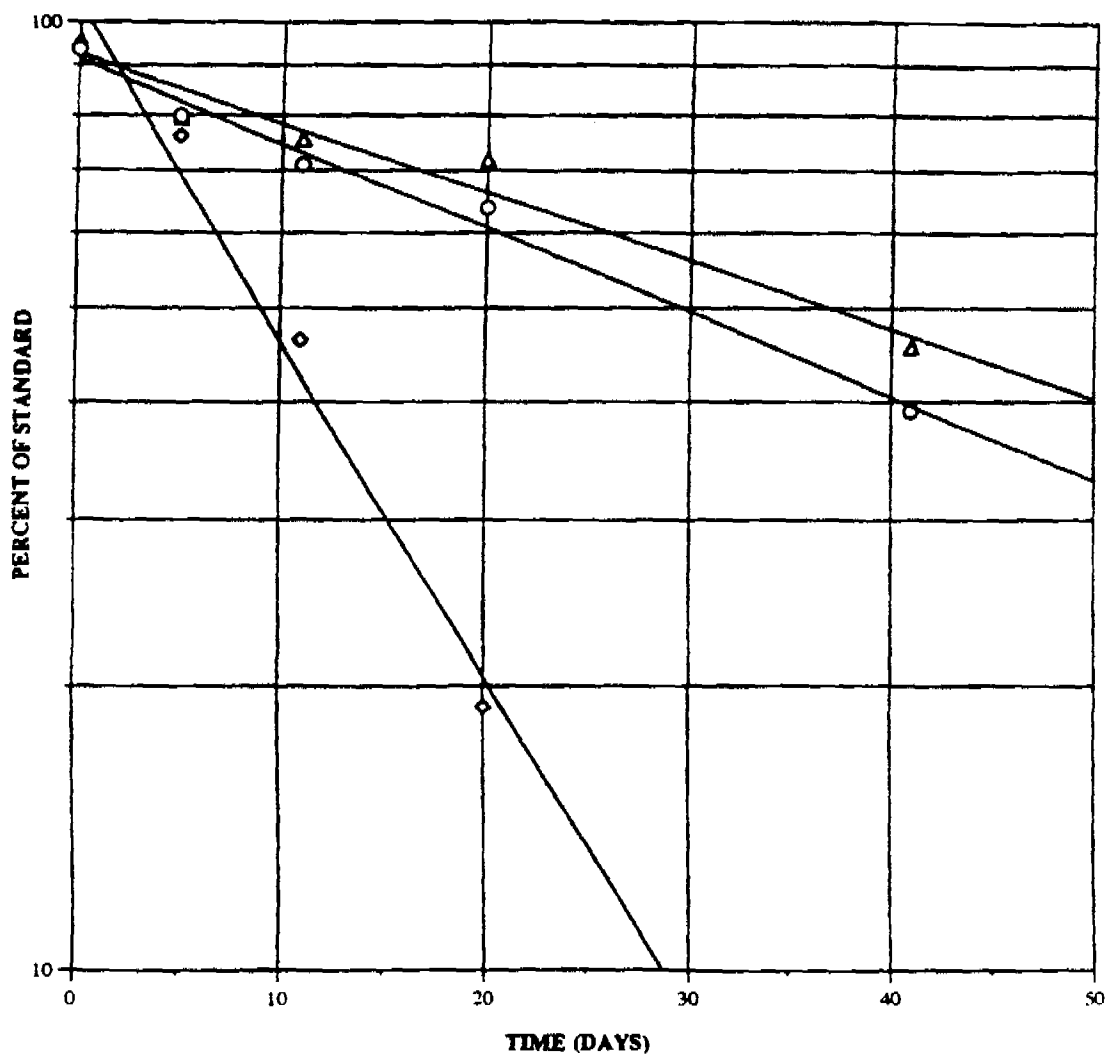


Figure 3.

**Stability of 0.01% Compound No. 2. at 55°C in pH 7.4
Preserved Vehicle with the indicated Surfactant.**

- 0.5% Cremophor® EL
- △ 0.5% Alkamuls® EL-620
- ◇ 0.5% Polysorbate 80



SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

Int: nal Application No
PCT/US 95/17086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K47/44 A61K39/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 667 160 (ALCON LAB INC) 16 August 1995 see claims; tables 1,3,4 ---	1-25
X	EP,A,0 407 148 (GREEN CROSS CORP ;TAISHO PHARMA CO LTD (JP)) 9 January 1991 see page 3, line 41 - line 46; claims ---	1-7, 11-19
P,A	EP,A,0 645 145 (SQUIBB BRISTOL MYERS CO) 29 March 1995 see claims 1,4 ---	1-7, 11-19
X	EP,A,0 132 027 (TAISHO PHARMA CO LTD ;GREEN CROSS CORP (JP)) 23 January 1985 see page 5, line 15 - line 25 ---	1-7, 11-19

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

12 June 1996

Date of mailing of the international search report

21.06.96

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Berte, M

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 95/17086

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 418 004 (GREEN CROSS CORP ;TAISHO PHARMA CO LTD (JP)) 20 March 1991 see page 3, line 41 - line 46 ---	1-7, 11-19
A	DATABASE EMBASE ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL AN=79232832, XP002005367 see abstract & ARCH. OPHTHALMOL., vol. 97, no. 9, 1979, pages 1703-1706, FOSTER C.S. ET AL.: "INTRAOCULAR PENETRATION OF MICONAZOLE IN RABBITS." ---	1-7, 11-19
A	INT. J. PHARM. (1983), 13(3), 303-12 CODEN: IJPHDE;ISSN: 0378-5173, 1983, XP002005366 EL-SAYED, ABDEL AZIZ A. ET AL: "Solubilization and stabilization of an investigational antineoplastic drug (NSC no. 278214) in an intravenous formulation using an emulsion vehicle" cited in the application ---	1-7, 11-19
P,X	WO,A,95 05163 (PHARMOS CORP) 23 February 1995 see page 1, line 6 see page 9, line 31 - page 10, line 11 see page 11, line 15 see page 19, line 17 - line 30; claims 1,20,23,26 -----	1-7

INTERNATIONAL SEARCH REPORT

134-58
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International application No.

PCT/US95/17086

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US95/17086

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Remark : Although claims 25 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/17086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0667160	16-08-95	AU-B- 7913894 CA-A- 2138181	22-06-95 16-06-95
EP-A-0407148	09-01-91	JP-A- 4066540 JP-B- 6069966 CA-A- 2020368 DE-D- 69021289 DE-T- 69021289 ES-T- 2076320 US-A- 5445812	02-03-92 07-09-94 06-01-91 07-09-95 21-03-96 01-11-95 29-08-95
EP-A-0645145	29-03-95	AU-B- 7427394 BE-A- 1007987 CA-A- 2132936 CN-A- 1107367 CZ-A- 9402349 FI-A- 944448 HU-A- 68687 JP-A- 7179362 NO-A- 943583 PL-A- 305240 US-A- 5504102 ZA-A- 9407482	13-04-95 05-12-95 30-03-95 30-08-95 12-04-95 30-03-95 28-07-95 18-07-95 30-03-95 03-04-95 02-04-96 15-05-95
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EP-A-0418004	20-03-91	JP-A- 3101622 CA-A- 2024965 DE-D- 69021304 DE-T- 69021304 ES-T- 2075161 US-A- 5091417	26-04-91 12-03-91 07-09-95 18-01-96 01-10-95 25-02-92
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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 06-128576

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18** DE **DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **14** DE **MARZO DEL 2008**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI X

NO

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°:
10354

ASUNTO:	Radicación PCT N°	06-128576
	Trámite	011
	Evento	379
	Actuación	440
	Folios	012

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021