

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.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

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



RECIBO DE CAJA

No. 11 - 107708

Bogotá D.C., Noviembre 02 de 2011 - 15:51:23

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S. NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	430324134	01/11/2011	3.040.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable:

Recibo de Caja Aplicado al Expediente No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-121549- -00003-0000

Fecha: 2011-12-16 11:24:46 Dep. 2020 DIR. NUEVASCR
Tra. 11 PATENTE IYII Eve: 378 FASE NACIONAL I
Act. 400 OPOSIOBSERVTER Folios: 33

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: Info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Noviembre 2 de 2011 - 15:51:24



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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

Referencia : Expediente N° 10 121549.
Asunto : Oposición a la solicitud de patente de Invención titulada
*"COMPOSICIONES DE KETOROLAC TROMETAMINA
PARA TRATAR O PREVENIR EL DOLOR OCULAR"*
Solicitante : ALLERGAN INC
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial
N° 632 del 20 de septiembre de 2011

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"COMPOSICIONES DE KETOROLAC TROMETAMINA PARA TRATAR O PREVENIR EL DOLOR OCULAR"*, cuyo titular es **ALLERGAN INC**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la

ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular KETOROLAC. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 30 de septiembre de 2010, reivindicando prioridad bajo la solicitud US20080067925 del 2008-03-03; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 632 del 20 de septiembre de 2011, cuya publicación internacional corresponde a la WO2009111418 del 2009-09-11.

2.2. La solicitud colombiana 10 121549 objeto de la presente oposición, se refiere a una solución oftálmica tópica acuosa que comprende keterolac trometamina, carboximetilcelulosa y ningún preservante, donde la ketorolac trometamina está presente en una concentración de aproximadamente 0.40 - 0.45 por ciento en peso/volumen, y en donde la carboximetilcelulosa es una combinación de carboximetilcelulosa de media y alta viscosidad.

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

- D1: US2008039398 publicada el 14 de febrero de 2008.

2.4. Así pues, el documento D1 proporciona composiciones para el tratamiento y / o prevenir los signos y síntomas asociados con el ojo seco y / o irritación ocular, y los métodos de uso de las mismas. Dichas composiciones se presentan en formulaciones oftálmicas que se sienten cómodo tras la instilación en el ojo; dicho



documento D1 de forma particular en el ejemplo 1 y el párrafo [0062] describe una composición ocular de ketorolaco trometamina en composición de lágrimas artificiales (Refresh TM) a base de CMC, que contiene un preservativo.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de ALTURA INVENTIVA.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 121549 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.8. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 03 de marzo de 2008, a partir del documento D1 por si solo, un experto en la materia basado en la constante necesidad de mejorar, y sabiendo que disminuir los preservativos es una forma de mejora conocida, puede llegar de manera evidente a una solución oftálmica tópica acuosa que comprende ketorolac trometamina, carboximetilcelulosa y ningún preservante, donde la ketorolac trometamina está presente en una concentración de aproximadamente 0.40 - 0.45 por ciento en peso/volumen, y en donde la carboximetilcelulosa es una combinación de carboximetilcelulosa de media y alta viscosidad; sobre lo cual se busca protección en el capítulo reivindicatorio.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada **"COMPOSICIONES DE KETOROLAC TROMETAMINA PARA TRATAR O PREVENIR EL DOLOR OCULAR"**, cuyo titular es ALLERGAN INC, solicitud

Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N°
632 del 20 de septiembre de 2011.

3. PRUEBAS

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

- D1: US2008039398 publicada el 14 de febrero de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

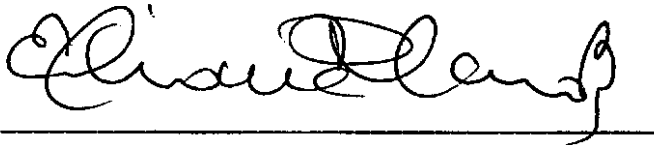
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
 2. Documento que acredita al representante legal de **LABORATORIOS
SYNTHESIS S.A.S.**
 3. Recibo de caja del respectivo pago de tasa.
 4. Copias de los documentos:
- D1: US2008039398 publicada el 14 de febrero de 2008.

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.

9

PODER ESPECIAL

Yo, **ORLANDO MUÑOZ MARTINEZ**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 10 121.549, titulada "**COMPOSICIONES DE KETOROLAC TROMETAMINA PARA TRATAR O PREVENIR EL DOLOR OCULAR**", cuyo titular **ALLERGAN, INC** publicada en la gaceta No. 632 del 20 de septiembre de 2011.

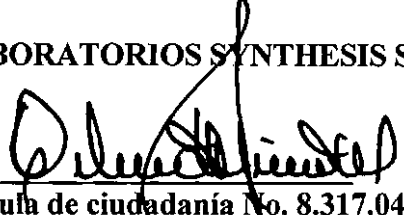
Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados.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

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

Dado y Firmado en Bogotá (Colombia) a los 07 días del mes de diciembre de 2011.

LABORATORIOS SYNTHESIS S.A.S.




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



DILIGENCIA DE RECONOCIMIENTO

REPUBLICA DE COLOMBIA

Compareció ante el Notario 18 del Circulo de Bogotá, Orlando Montez

MARTÍNEZ

quien exhibió la C.C. 8317044

Expedida en Medellín y

dictó que la firma y huella que

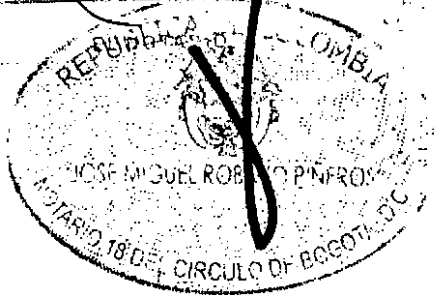
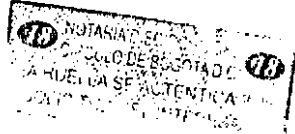
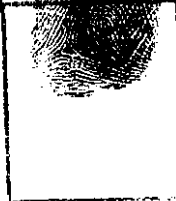
aparecen en el presente documento

son suyas y que el contenido del mismo

es cierto.

07 DIC 2011

[Signature]



[Signature]



QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301
5942	7-X -1.996	1A.STAFE BTA	11- X- 1.996 NO.558.222
6305	24-X--1.996	1A.STAFE BTA	07-XI--1.996 NO.561.207
6929	25-XI-1.996	1A.STAFE BTA	12-XII-1.996 NO.565.961
787	19-II-1.997	1A.STAFE BTA	25-II -1.997 NO.575.141



01



* 1 1 3 2 4 7 6 3 3 *

CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

2 DE DICIEMBRE DE 2011 HORA 11:17:51

R033215763

PAGINA: 2 de 5

* * * * *

1024

28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837
139	2011/06/07	0000	BOGOTA D.C.	2011/06/20	01489422
146	2011/10/24	0000	BOGOTA D.C.	2011/11/30	01531828

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA

~~EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS~~
GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER
CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR
DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS
NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL
TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL
TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O
ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA
EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTORES
AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

**** CAPITAL AUTORIZADO ****

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

**** CAPITAL SUSCRITO ****

VALOR : \$20,362,200,000.00
NO. DE ACCIONES : 20,362,200.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL PAGADO ****

VALOR : \$20,362,200,000.00
NO. DE ACCIONES : 20,362,200.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ
DOS SUPLENTE DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS
FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUEL.

CERTIFICA:

**** NOMBRAMIENTOS ****

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE
2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL
LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE
2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL
LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE
2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL
LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

PICART LAURENZ FRANCISCO JAVIER

C.E. 00000000E399661

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A
SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA
REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS
LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN
DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS



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* * * * *

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFIENDA LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS. A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C.

~~ADELANTE CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE~~
MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D.
RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO
DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA
GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS
Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS
INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE
CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F.
SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G.
OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y
EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS,
RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE
NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE
DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A
CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR
SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR
TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR,
RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y
EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE
FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS
DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES
O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR
Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS,
COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE
RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS
QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR
NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS
AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA
VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR,
CONCILIAR, TRANSIGIR Y MODIFICAR. L. ELEVAR PETICIONES Y SOLICITAR
INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M.
PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES.
N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA
REPÚBLICA DE COLOMBIA.

CERTIFICA:

** REVISOR FISCAL **

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

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	

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

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010,
INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX,
FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL SUPLENTE	

PRADA SANCHEZ NUBIA MARCELA	C.C. 000001032358923
-----------------------------	----------------------

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE
2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO
IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	

DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134
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CERTIFICA:



* 1 1 3 2 4 7 6 3 5 *

PAGINA: 4 de 5

* * * * *

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,



01



* 1 1 3 2 4 7 6 3 6 *

14

CAMARA DE COMERCIO DE BOGOTA

SEDE SALITRE

2 DE DICIEMBRE DE 2011 HORA 11:17:51

R033215763

PAGINA: 5 de 5

* * * * *

VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

Handwritten signature
2

ANEXO



US 20080039398A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2008/0039398 A1**

(43) **Pub. Date: Feb. 14, 2008**

Ousler, III et al.

(54) **FORMULATIONS AND METHODS FOR TREATING DRY EYE**

(60) Provisional application No. 60/761,945, filed on Jan. 25, 2006.

(76) Inventors: George W. Ousler III, North Andover, MA (US); Matthew Jonathan Chapin, Amesbury, MA (US); Mark B. Abelson, Andover, MA (US)

Publication Classification

(51) Int. Cl.

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A61K 38/00 (2006.01)
A61K 31/01 (2006.01)
A61K 31/045 (2006.01)
A61K 31/21 (2006.01)
A61P 27/04 (2006.01)
A61K 31/40 (2006.01)
A61K 31/715 (2006.01)
A61K 31/717 (2006.01)

(21) Appl. No.: 11/890,030

(52) U.S. Cl. 514/12; 514/413; 514/57; 514/648; 514/738; 514/762

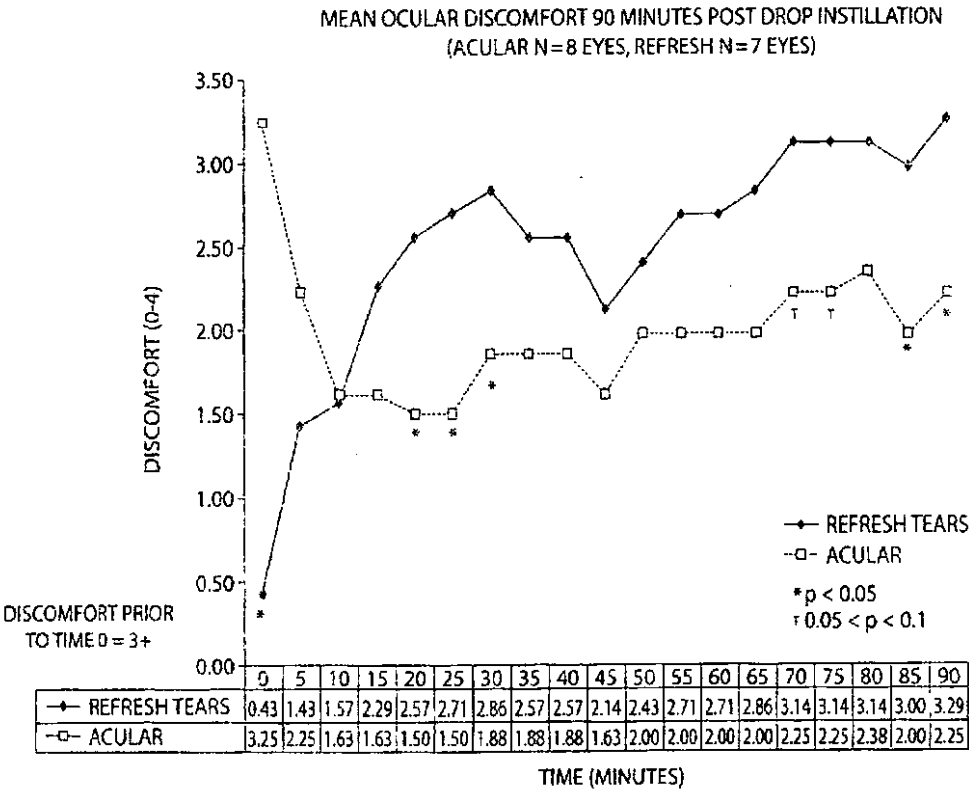
(22) Filed: Aug. 2, 2007

Related U.S. Application Data

(57) **ABSTRACT**

(63) Continuation-in-part of application No. 11/820,461, filed on Jun. 18, 2007, which is a continuation-in-part of application No. 11/807,147, filed on May 24, 2007, which is a continuation-in-part of application No. 11/698,778, filed on Jan. 25, 2007.

The present invention provides compositions for treating and/or preventing signs and symptoms associated with dry eye and/or ocular irritation, and methods of use thereof. Such compositions are provided in novel ophthalmic formulations that are comfortable upon instillation in the eye.



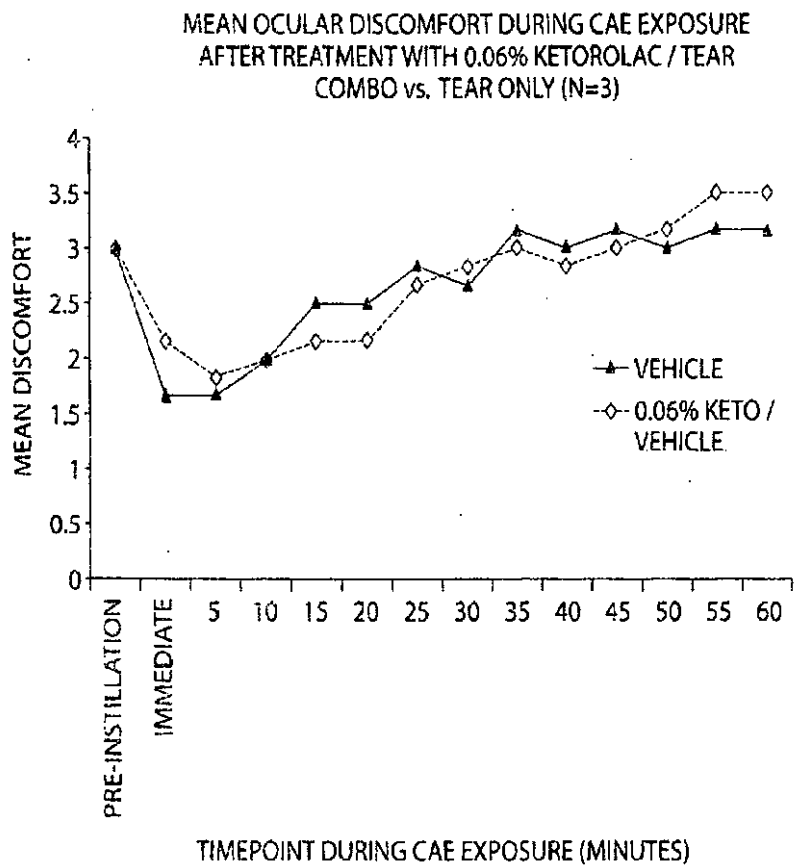


Fig. 9

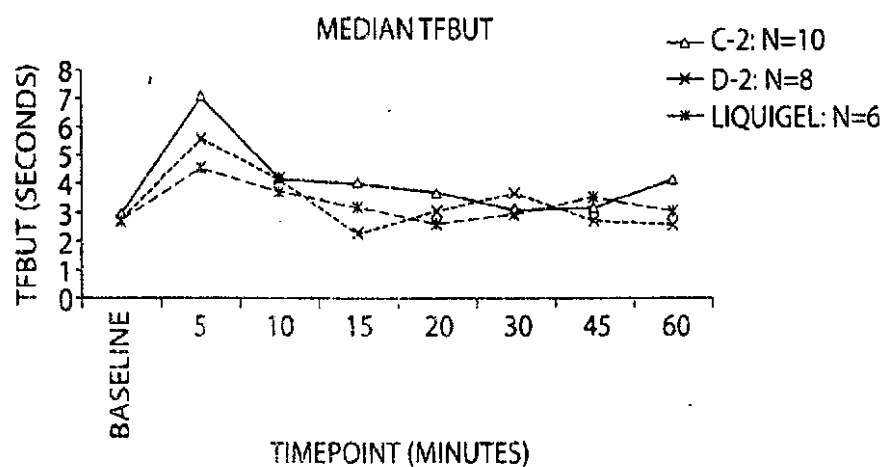


Fig. 10

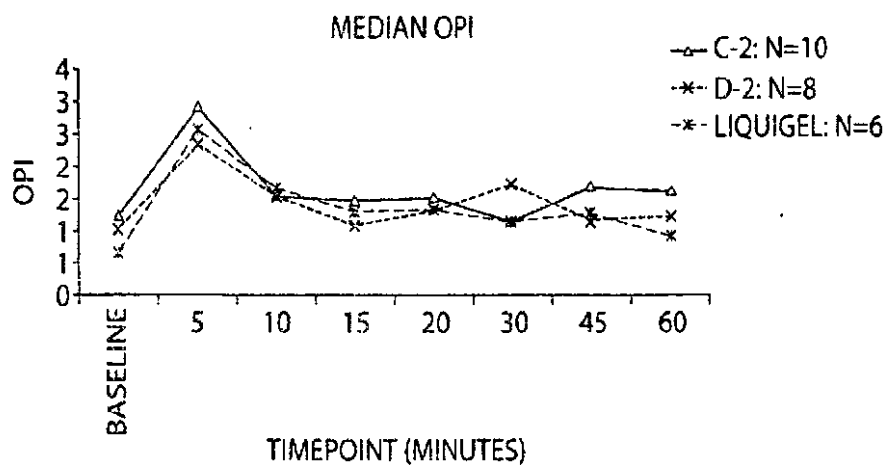


Fig. 11

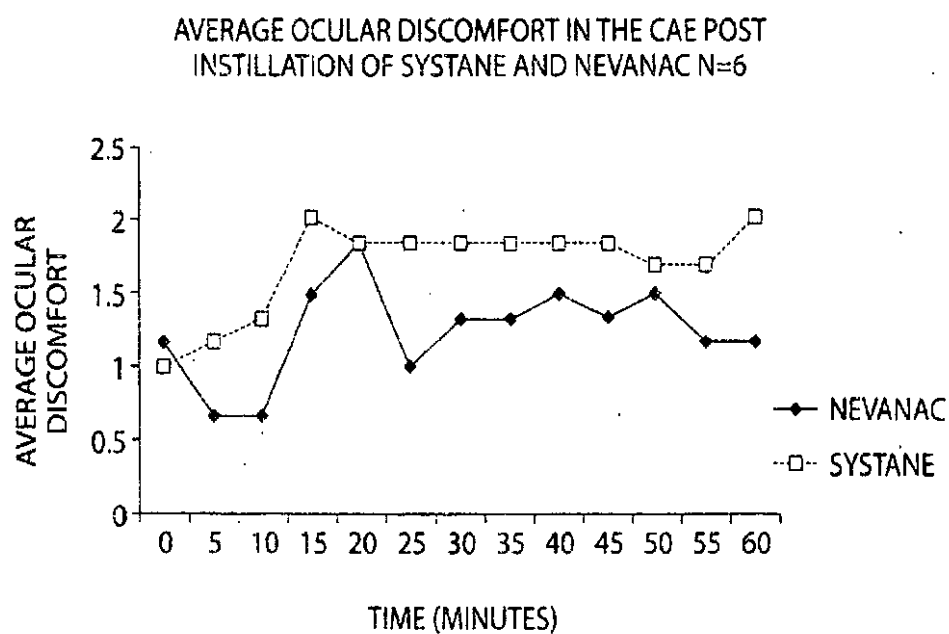


Fig. 12

FORMULATIONS AND METHODS FOR TREATING DRY EYE

RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 11/820,461, filed Jun. 18, 2007, which is a continuation-in-part of U.S. Ser. No. 11/807,147, filed May 24, 2007, which is a continuation-in-part of U.S. Ser. No. 11/698,778, filed Jan. 25, 2007, which claims the benefit of U.S. Provisional Application No. 60/761,945, filed Jan. 25, 2006, the contents of which are each hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The invention relates generally to compositions for the treatment of ocular disorders, and more particularly to compositions comprising a tear substitute, or one or more components thereof, and a second agent for the treatment of acute or chronic dry eye disease. The invention further relates to materials and methods for the administration of compositions comprising a tear substitute, or one or more components thereof and a second agent.

BACKGROUND OF THE INVENTION

[0003] Dry eye disease is an ocular disease affecting approximately 10-20% of the population. This disease progressively affects larger percentages of the population as it ages, with the majority of these patients being women. In addition, almost everyone experiences ocular irritation, or the symptoms and/or signs of dry eye as a condition, from time to time under certain circumstances, such as prolonged visual tasking (e.g. working on a computer), being in a dry environment, using medications that result in ocular drying, etc.

[0004] In individuals suffering from dry eye, the protective layer of tears that normally protects the ocular surface is compromised, a result of insufficient or unhealthy production of one or more tear components. This can lead to exposure of the surface of the eye, ultimately promoting desiccation and damage of surface cells. Signs and symptoms of dry eye include but are not limited to keratitis, conjunctival and corneal staining, redness, blurry vision, decreased tear film break-up time, decreased tear production, tear volume, and tear flow, increased conjunctival redness, excess debris in the tear film, ocular dryness, ocular grittiness, ocular burning, foreign body sensation in the eye, excess tearing, photophobia, ocular stinging, refractive impairment, ocular sensitivity, and ocular irritation. Patients may experience one or more of these symptoms. The excess tearing response may seem counterintuitive, but it is a natural reflex response to the irritation and foreign body sensation caused by the dry eye. Some patients may also experience ocular itching due to a combination of ocular allergy and dry eye symptoms.

[0005] There are many possible variables that can influence a patient's signs or symptoms of dry eye including levels of circulating hormones, various autoimmune diseases (e.g. Sjögren's syndrome and systemic lupus erythematosus), ocular surgeries including PRK or LASIK, many medications, environmental conditions, visual tasking such as computer use, ocular fatigue, contact lens wear, and mechanical influences such as corneal sensitivity, partial lid

closure, surface irregularities (e.g. pterygium), and lid irregularities (e.g. ptosis, entropion/ectropion, pinguecula). Environments with low humidity, e.g., those that cause dehydration, can exacerbate or cause dry eye symptoms, such as sitting in a car with the defroster on or living in a dry climate zone. In addition, visual tasking can exacerbate symptoms. Tasks that can greatly influence symptoms include watching TV or using a computer for long periods of time where the blink rate is decreased.

[0006] There are a number of products for the treatment of dry eye commercially available. However, such products provide only temporary relief of acute symptoms, are suitable for short term use only, and/or cause ocular discomfort upon installation in the eye. For example, artificial tears and ointments may provide temporary relief of dry eye, but do little to arrest or reverse any damaging conditions. For more severe cases of dry eye, in which the cornea is inflamed, anti-inflammatory agents are sometimes prescribed. Topical corticosteroids (in eye drops) are safe for short-term use to combat inflammation, but can cause side effects, including but not limited to decreased wound healing, cataract, and in some cases, increased risk of elevated intra-ocular pressure in patients, when used for a long time. Likewise, non-steroidal anti-inflammatory drugs (NSAIDs) in their current ophthalmic dosage forms are approved for short term use only, e.g., inflammation and pain associated with post-ocular-surgery, and may result in corneal damage in patients predisposed to such conditions, delayed wound healing after repeated dosing, or ocular discomfort. (see e.g., Congdon et al., *J Cataract Refract Surg.* 2001 April; 27(4):622-31; Flach A., *Tr Am Ophthal Soc* 2001; 99:205-212).

[0007] Commercial cyclosporin-A (Restasis®-Allergan) is the first approved therapeutic agent for the treatment of dry eye, and is suitable for long term use. However, the primary side effect cited on the package insert is ocular burning and stinging upon instillation, and Restasis® was only shown to be effective in only 17% of patients. To improve patient discomfort during the induction phase of cyclosporin therapy, clinicians may prescribe topical corticosteroids or NSAIDs (in eye drop form) in conjunction with cyclosporin-A (see e.g., Schechter B., *J Ocul Pharmacol Ther.* 2006 April; 22(2):150-4). However, such agents in their current ophthalmic dosage forms should only be used during the initiation of cyclosporin treatment, due to the potential adverse effects of damage to the cornea, delayed wound healing, and discomfort associated with such dosage forms. As such, there exists a need for an ocular therapy for the treatment of acute or chronic dry eye disease which is comfortable upon instillation in the eye, and at a safe dose particularly suitable for long term use. The present invention meets this need and other needs.

SUMMARY OF THE INVENTION

[0008] The present invention provides ophthalmic formulations suitable for the treatment of acute or chronic dry eye disease which contain a combination of ingredients capable of acting synergistically to relieve ocular discomfort and prolong the integrity of the tear film. In particular, the formulations described herein provide an NSAID suitable for ophthalmic use in a comfortable ophthalmic formulation when instilled in the eye. Specifically provided are ophthalmic formulations comprising one or more components of a tear substitute and a low dose amount of NSAID effective

to treat and/or prevent signs and symptoms associated with dry eye disease, suitable for intermittent and/or repeated long term use for the treatment of chronic dry eye disease.

[0009] In some embodiments, the ophthalmic formulations of the invention comprise a low dose amount of an NSAID selected from the group consisting of: ketorolac tromethamine (also referred to herein as ketorolac), indomethacin, flurbiprofen sodium, nepafenac, bromfenac, suprofen and diclofenac. Other suitable NSAIDs may be used.

[0010] In one embodiment of the invention, the low dose amount of NSAID in the ophthalmic formulation of the invention is about 0.10% to about 0.30%, more preferably about 0.15% to about 0.30%, even more preferably about 0.15% to about 0.26% ketorolac tromethamine. In another embodiment the low dose amount of NSAID is about 0.01% to about 0.10%, preferably about 0.03% to about 0.08%, more preferably about 0.040% to about 0.065% indomethacin. In another embodiment, the low dose amount of NSAID is about 0.009 to about 0.024% flurbiprofen sodium. In another embodiment, low dose amount of NSAID is about 0.03% to about 0.08% nepafenac. In yet another embodiment, low dose amount of NSAID is about 0.027% to about 0.072% bromfenac. In another embodiment, low dose amount of NSAID is about 0.3% to about 0.8% suprofen. In yet another embodiment, the low dose amount of NSAID is about 0.01% to about 0.08% diclofenac.

[0011] In some embodiments, the ophthalmic formulations of the invention comprise a tear substitute comprising an active ingredient, which may include without limitation: a polyol, a dextran, a water soluble protein, a carbomer, a gum, a cellulose derivative, or combinations thereof. Other suitable tear substitute components known in the art may be used in the formulations of the invention. Suitable cellulose derivatives for use in the ophthalmic formulations of the invention include, without limitation, hydroxypropylmethyl cellulose (HPMC), carboxymethyl cellulose (CMC) sodium, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, or combinations thereof. In preferred embodiments, the cellulose derivative is hydroxypropylmethyl cellulose and/or carboxymethyl cellulose sodium.

[0012] In a preferred embodiment, the viscosity of the tear substitute, or one or more components thereof, is in a range which optimizes efficacy of supporting the tear film while minimizing blurring, lid caking, etc. Preferably, the viscosity of the tear substitute, or one or more components thereof, ranges from about 30-150 centipoise (cpi), preferably about 30-130 cpi, more preferably about 50-120 cpi, even more preferably about 70-120 cpi. In some embodiments, the viscosity of the tear substitute, or one or more components thereof, ranges from about 50-90 cpi.

[0013] In some embodiments, the invention features an ophthalmic formulation comprising a combination of a tear substitute component having a viscosity of about 50 cpi, and a low dose amount of an NSAID, useful for the treatment and/or prevention of the signs and/or symptoms of dry eye disease. In one preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.2% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 50 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.25% ketoro-

lac tromethamine and a tear substitute, or one or more components thereof, having a viscosity of about 50 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.05% nepafenac, and a tear substitute, or one or more components thereof, having a viscosity of about 50 cpi. In yet another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.045% bromfenac, and a tear substitute, or one or more components thereof, having a viscosity of about 50 cpi.

[0014] In other embodiments, the invention features an ophthalmic formulation comprising a combination of a tear substitute component having a viscosity of about 70 cpi, and a low dose amount of an NSAID, useful for the treatment and/or prevention of the signs and/or symptoms of dry eye disease. In one preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.2% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 70 cpi. In another preferred embodiment, the invention features an ophthalmic formulation comprising a combination of 0.25% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 70 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.05% nepafenac, and a tear substitute, or one or more components thereof, having a viscosity of about 70 cpi. In yet another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.045% bromfenac, and a tear substitute, or one or more components thereof, having a viscosity of about 70 cpi.

[0015] In still other embodiments, the invention features an ophthalmic formulation comprising a combination of a tear substitute component having a viscosity of about 85 cpi, and a low dose amount of an NSAID, useful for the treatment and/or prevention of the signs and/or symptoms of dry eye disease. In one preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.2% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 85 cpi. In another preferred embodiment, the invention features an ophthalmic formulation comprising a combination of 0.25% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 85 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.05% nepafenac, and a tear substitute, or one or more components thereof, having a viscosity of about 85 cpi. In yet another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.045% bromfenac, and a tear substitute, or one or more components thereof, having a viscosity of about 85 cpi.

[0016] In yet another embodiment, the invention features an ophthalmic formulation comprising a combination of a tear substitute component having a viscosity of about 100 cpi, and a low dose amount of an NSAID, useful for the treatment and/or prevention of the signs and/or symptoms of dry eye disease. In one preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.2% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 100 cpi. In another preferred embodiment, the invention features an ophthalmic formulation comprising a com-

combination of 0.25% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 100 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.05% nepafenac, and a tear substitute, or one or more components thereof, having a viscosity of about 100 cpi. In yet another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.045% bromfenac, and a tear substitute, or one or more components thereof, having a viscosity of about 100 cpi.

[0017] In another embodiment, the invention features an ophthalmic formulation comprising a combination of a tear substitute component having a viscosity of about 120 cpi, and a low dose amount of an NSAID, useful for the treatment and/or prevention of the signs and/or symptoms of dry eye disease. In one preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.2% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 120 cpi. In another preferred embodiment, the invention features an ophthalmic formulation comprising a combination of 0.25% ketorolac tromethamine, and a tear substitute, or one or more components thereof, having a viscosity of about 120 cpi. In another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.05% nepafenac, and a tear substitute, or one or more components thereof, having a viscosity of about 120 cpi. In yet another preferred embodiment, the ophthalmic formulation of the invention comprises a combination of 0.045% bromfenac, and a tear substitute, or one or more components thereof, having a viscosity of about 120 cpi.

[0018] Also featured are methods of improving, relieving, treating, preventing, or otherwise decreasing ocular discomfort, and methods for increasing tear film break-up time and/or the ocular protection index (as described further herein) for the treatment and prevention of the signs and symptoms associated with dry eye and/or eye irritation by administration of the formulations of the invention. In one embodiment, the method for treating dry eye and/or eye irritation comprises the steps of a) determining a first measurement of the tear film break-up time (TFBUT) and/or ocular protection index (OPI), and/or non-invasive tear film break-up time and/or ocular discomfort in a subject; (b) administering an ophthalmic formulation of the invention to the subject; (c) determining a second measurement of the TFBUT and/or OPI and/or non-invasive tear film break-up time and/or ocular discomfort in a subject; wherein an increase in the second measurement of TFBUT and/or OPI and/or non-invasive tear film break-up time and/or ocular discomfort as compared to the first measurement indicates the ophthalmic formulation is efficacious in treating the subject.

[0019] An additional feature is the use of an NSAID in the manufacture of a comfortable ophthalmic formulation for instillation into the eye, wherein said formulation comprises a low dose amount of an NSAID suitable for ophthalmic use and one or more tear substitute components. Also featured are ophthalmic formulations that are comfortable upon instillation in the eye comprising a low dose amount of an NSAID suitable for ophthalmic use and one or more tear substitute components, wherein the tear substitute compo-

nent is selected from the group consisting of hydroxypropylmethyl cellulose (HPMC) and carboxymethyl cellulose (CMC) sodium, or a combination thereof.

[0020] Further, featured are kits for the shipping, storage or use of the formulations, as well the practice of the methods. Other features and advantages of the invention will become apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is a graph depicting a comparison of the efficacy of Acular® (ketorolac tromethamine 0.5%, also referred to herein as "Acular" or "ketorolac") and Refresh® artificial tears on reducing ocular discomfort in patients exposed to a controlled adverse environment (CAE).

[0022] FIG. 2 is a graph depicting the efficacy of a combination of Acular® (ketorolac tromethamine 0.5%) and a hydroxypropylmethyl cellulose based artificial tear (1:1 dilution, final concentration ketorolac tromethamine 0.25%), as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0023] FIG. 3 is a graph depicting the efficacy of a combination of Acular LS® (ketorolac tromethamine 0.4%) and an artificial tear having a viscosity of about 50 cpi (1:1 dilution, final concentration ketorolac tromethamine 0.2%), as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0024] FIG. 4 is a graph depicting the efficacy of a combination of Nevanac® (nepafenac 0.1%) and an artificial tear having a viscosity of about 50 cpi (1:1 dilution, final concentration nepafenac 0.05%), as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0025] FIG. 5 is a graph depicting the efficacy of a combination of Xibrom® (bromfenac 0.09%) and an artificial tear having a viscosity of about 50 cpi (1:1 dilution, final concentration bromfenac 0.045%), as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0026] FIG. 6 is a graph depicting the efficacy of a combination of Voltaren® (diclofenac 0.1%) and an artificial tear having a viscosity of about 50 cpi (1:1 dilution, final concentration diclofenac 0.05%), as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0027] FIG. 7 is a graph depicting the efficacy of an ophthalmic formulation comprising ketorolac tromethamine 0.25% and an artificial tear having a viscosity of about 70 cpi, as compared to the artificial tear alone, on reducing ocular discomfort in reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0028] FIG. 8 is a graph depicting the efficacy of an ophthalmic formulation comprising ketorolac tromethamine 0.125% and an artificial tear having a viscosity of about 70 cpi, as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0029] FIG. 9 is a graph depicting the efficacy of an ophthalmic formulation comprising ketorolac tromethamine 0.05% and an artificial tear having a viscosity of about 70 cpi, as compared to the artificial tear alone, on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

[0030] FIG. 10 is a graph depicting a comparison of the efficacy of three different ophthalmic formulations; 1) 0.25% ketorolac tromethamine and a hydroxymethylpropyl cellulose based artificial tear having a viscosity of approximately 50 cpi (depicted as C-2); 2) 0.25% ketorolac tromethamine and a hydroxymethylpropyl cellulose based artificial tear having a viscosity of approximately 50 cpi (depicted as D-2); and 0.5% ketorolac (Acular®) diluted 1:1 with a carboxymethyl cellulose based artificial tear having a viscosity of approximately 80 cpi (final concentration of 0.25% ketorolac, depicted as Liquigel); on increasing tear film break-up time (TFBUT), using procedures for measuring TFBUT over 60 minutes following dosing.

[0031] FIG. 11 is a graph depicting a comparison of the efficacy of three different ophthalmic formulations; 1) 0.25% ketorolac and a hydroxymethylpropyl cellulose based artificial tear having a viscosity of approximately 50 cpi (depicted as C-2); 2) 0.25% ketorolac and a hydroxymethylpropyl cellulose based artificial tear having a viscosity of approximately 50 cpi (depicted as D-2); and 0.5% ketorolac (Acular®) diluted 1:1 with a carboxymethyl cellulose based artificial tear having a viscosity of approximately 80 cpi (final concentration of 0.25% ketorolac, depicted as Liquigel); on increasing the Ocular Protection Index (OPI) over 60 minutes following dosing.

[0032] FIG. 12 is a graph depicting the efficacy of a combined formulation of Nevanac® (nepafenac 0.1%) and Systane® artificial tear solution (1:1 dilution, final concentration nepafenac 0.1%) (depicted as NEVANAC) as compared to Systane® artificial tear alone (depicted as SYSTANE) on reducing ocular discomfort in patients exposed to a CAE, over a 60 minute timecourse.

DETAILED DESCRIPTION OF THE INVENTION

[0033] For convenience, before further description of the present invention, certain terms employed in the specification, examples, and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art.

[0034] The term "acute" as used herein denotes a condition having a rapid onset, and symptoms that are severe but short in duration.

[0035] The term "analgesic" as used herein denotes a compound/formulation for the management of intermittent and/or chronic physical discomfort, suitable for long term use.

[0036] The term "anesthetic" or "anesthesia" as used herein denotes a compound/formulation for the management of acute physical pain, suitable for short term, temporary use, which has an effect that produces numbing or decreased sensitivity in the body part/organ to which the compound/formulation is administered (e.g., decreased corneal sensitivity of the eye).

[0037] The term "aqueous" typically denotes an aqueous composition wherein the carrier is to an extent of >50%, more preferably >75% and in particular 290% by weight water.

[0038] The term "chronic" as defined herein is meant a persistent, lasting condition, or one marked by frequent recurrence, preferably a condition that persists/recurs for greater than 3 months, more preferably greater than 6 months, more preferably greater than 12 months, and even more preferably greater than 24 months.

[0039] The term "comfortable" as used herein refers to a sensation of physical well being or relief, in contrast to the physical sensation of pain, burning, stinging, itching, irritation, or other symptoms associated with physical discomfort.

[0040] The term "comfortable ophthalmic formulation" as used herein refers to an ophthalmic formulation which provides physical relief from symptoms associated with dry eye disease and/or ocular discomfort, and only causes an acceptable level of pain, burning, stinging, itching, irritation, or other symptoms associated with ocular discomfort, when instilled in the eye, which are less than those seen with dosing with current concentrations on the market.

[0041] The term "dry eye" as used herein, refers to inadequate tear production and/or abnormal tear composition. Causes of dry eye disease as defined herein include but are not limited to the following: idiopathic, congenital alacrima, xerophthalmia, lacrimal gland ablation, and sensory denervation; collagen vascular diseases, including rheumatoid arthritis, Wegener's granulomatosis, and systemic lupus erythematosus; Sjögren's syndrome and autoimmune diseases associated with Sjögren's syndrome; abnormalities of the lipid tear layer caused by blepharitis or rosacea; abnormalities of the mucin tear layer caused by vitamin A deficiency; trachoma, diphtheric keratoconjunctivitis; mucocutaneous disorders; aging; menopause; and diabetes. Dry eye signs and/or symptoms as defined herein may also be provoked by other circumstances, including but not limited to the following: prolonged visual tasking; working on a computer; being in a dry environment; ocular irritation; contact lenses, LASIK and other refractive surgeries; fatigue; and medications such as isotretinoin, sedatives, diuretics, tricyclic antidepressants, antihypertensives, oral contraceptives, antihistamines, nasal decongestants, beta-blockers, phenothiazines, atropine, and pain relieving opiates such as morphine.

[0042] The phrase "effective amount" is an art-recognized term, and refers to an amount of an agent that, when incorporated into a pharmaceutical composition of the present invention, produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. In certain embodiments, the term refers to that amount necessary or sufficient to eliminate, reduce or maintain (e.g., prevent the spread of) a sign and/or symptom of dry eye and/or eye irritation, or prevent or treat dry eye and/or eye irritation. The effective amount may vary depending on such factors as the disease or condition being treated, the particular composition being administered, or the severity of the disease or condition. One of skill in the art may empirically determine the effective amount of a particular agent without necessitating undue experimentation.

[0043] As used herein, the term "NSAID" means an ophthalmologically acceptable nonsteroidal anti-inflammatory

tory drug or a pharmaceutically acceptable salt thereof. The term "low dose NSAID" means an amount of an ophthalmologically acceptable nonsteroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, which reduces ocular discomfort without producing anesthesia, and which would be expected to have reduced adverse effects associated with current FDA approved formulations of NSAIDs marketed for the treatment of acute ocular inflammation and pain, including without limitation, corneal damage, delayed wound healing, and ocular discomfort.

[0044] A "patient," "subject," or "host" to be treated by the subject method refers to either a human or non-human animal, such as a primate, mammal, and vertebrate

[0045] The phrase "pharmaceutically acceptable" is art-recognized and refers to compositions, polymers and other materials and/or salts thereof and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0046] The phrase "pharmaceutically acceptable carrier" is art-recognized, and refers to, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any supplement or composition, or component thereof, from one organ, or portion of the body, to another organ, or portion of the body, or to deliver an agent to the surface of the eye. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the patient. In certain embodiments, a pharmaceutically acceptable carrier is non-pyrogenic. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; (21) gums such as HP-guar; (22) polymers; and (23) other non-toxic compatible substances employed in pharmaceutical formulations.

[0047] The term "pharmaceutically acceptable salts" is art-recognized, and refers to relatively non-toxic, inorganic and organic acid addition salts of compositions of the present invention or any components thereof, including without limitation, therapeutic agents, excipients, other materials and the like. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like.

Examples of suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc and the like. Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For purposes of illustration, the class of such organic bases may include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines such as mono-, di-, and triethanolamine; amino acids, such as arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; (trihydroxymethyl)aminoethane; tromethamine, and the like. See, e.g., J. Pharm. Sci., 66: 1-19 (1977).

[0048] The term "preventing," when used in relation to a condition, such as dry eye and/or eye irritation, is art-recognized, and refers to administration of a composition which reduces the frequency of, or delays the onset of, signs and/or symptoms of a medical condition in a subject relative to a subject which does not receive the composition.

[0049] As used herein, the terms "tear substitute" and "artificial tear" may be used interchangeably, and each refers to one or more molecules or compositions, which lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build up, or otherwise provide temporary relief of dry eye signs and/or symptoms and conditions upon ocular administration, including without limitation a polymer (e.g., a cellulosic polymer), an ocular surface protectant, a demulcent, or other component found on the FDA monograph for tear substitutes. The term "tear substitute component" refers to one or more components thereof.

[0050] The term "treating" is an art-recognized term which refers to reducing or ameliorating at least one sign and/or symptom of any condition or disease.

[0051] 1. Pharmaceutical Compositions

[0052] The invention features novel pharmaceutical compositions comprising an effective amount of an NSAID and one or more tear substitute components in a pharmaceutically acceptable carrier. The NSAID component provides relief of or prevention of ocular discomfort, and the one or more tear substitute components provide ocular surface protection via enhancement of the tear film (as evident by increased tear film break up time). An effective amount of the formulations may be used to treat and/or prevent signs and symptoms associated with dry eye and/or general eye irritation, and can also be used to treat another eye disorder if it contains a drug for that disorder. Such formulations provide a comfortable ophthalmic formulation when instilled in the eye and have enhanced efficacy and duration of action over formulations of NSAIDs that are not combined with such agents. Preferably, the effective amount of NSAID present in the formulations of the present invention is sufficient to reduce the discomfort associated with chronic dry eye and/or ocular irritation, but is below that level which would cause an anesthetic effect.

[0053] The extraordinary efficacy of these formulations is attributed to, among other things, the synergistic effect of the combination of ingredients in them. The combination of an NSAID and tear substitute, or one or more components thereof, act synergistically to treat signs and symptoms of

dry eye, which has never been previously contemplated to be accomplished in one product containing the two separate ingredients. The tear substitute component(s) enhances the integrity of the tear film thereby providing protection of the ocular surface (e.g., by increasing the tear film break-up time and/or the ocular protection index). The NSAID reduces ocular discomfort associated with dry eye. As such, the compositions of the invention are comfortable upon instillation into the eye, and may be used for relief of acute or chronic dry eye disease, and are particularly suitable for both intermittent and long term use. The concentration of the NSAID is at a level that is sufficient to reduce discomfort, without creating an anesthetic effect. The concentration of the NSAID in combination with the tear substitute component(s) also is at a level which would be expected to have reduced adverse effects associated with current FDA approved formulations of NSAIDs marketed for the treatment of acute ocular inflammation and pain, including without limitation, corneal damage, delayed wound healing, and ocular discomfort. As such, the comfortable ophthalmic formulations described herein will treat signs and symptoms of dry eye, increase patient compliance in the use of such formulations for the treatment and/or prevention of signs and symptoms associated with dry eye disease and/or ocular discomfort.

[0054] Exemplary NSAIDs suitable for use in the compositions of the invention include, but are not limited to, agents that inhibit the cyclooxygenase (COX)-1 and/or -2 enzyme, including but not limited to propionic acids such as naproxen, flurbiprofen, oxaprozin, ibuprofen, ketoprofen, fenoprofen; ketorolac tromethamine (and the other compounds described as being ophthalmologically effective in U.S. Pat. No. 4,454,151 to Waterbury, issued Jun. 12, 1984, the pertinent portions of which are incorporated herein by reference); acetic acid derivatives such as sulindac, indomethacin, and etodolac; phenylacetic acids such as diclofenac (and the other compounds described as being ophthalmologically effective in U.S. Pat. No. 4,960,799 to Nagy, issued Oct. 2, 1990, the pertinent portions of which are incorporated herein by reference), bromfenac, and suprofen; arylacetic prodrugs such as nepafenac, and amfenac; salicylic acids, such as aspirin, salsalate, difunisal, choline magnesium trisalicylate (CMT); para-aminophenol derivatives such as acetaminophen; naphthylalkanones such as nabumetone; enolic acid derivatives such as piroxicam and meloxicam; femanates such as mefenamic acid, meclofenamate and flufenamic acid; pyrroleacetic acids such as tolmetin; and pyrazolones such as phenylbutazone; COX-2 selective inhibitors such as celecoxib, valdecoxib, parecoxib, etoricoxib, and luanicoxib; including all esters and pharmaceutically acceptable salts thereof.

[0055] The compositions of the invention comprise a low dose NSAID in an amount effective to relieve acute or chronic corneal discomfort without causing anesthesia or damage to the cornea upon repeated, long term administration. Anesthesia can be measured in the eye using methods known in the art, such as Cochet-Bonnet testing, or other type of esthesiometer. "Low dose NSAID" as used herein refers to a dose lower than current FDA approved ophthalmic NSAID formulations marketed for the treatment of acute ocular inflammation, e.g., inflammation associated with post-ocular surgery. For example, dosages of ophthalmic NSAID formulations currently marketed for the treatment of acute ocular inflammation and pain are as

follows: ketorolac tromethamine 0.5% (Acular®), ketorolac tromethamine 0.4% (Acular LS®), diclofenac 0.1% (Voltaren®), bromfenac 0.09% (Xibrom®), nepafenac 0.1% (Nevanac®), flurbiprofen 0.03% (Ocufen®), and suprofen 1%. Preferably, the low dose NSAID in the pharmaceutical compositions of the invention is about 10-80%, more preferably about 30-80%, even more preferably about 40-65% of the dose of ophthalmic NSAID formulations marketed for the treatment of acute ocular inflammation.

[0056] The pharmaceutical ophthalmic formulations of the invention typically contain an effective, low dosage amount, e.g., 0.001% to 1% wt/vol, preferably about 0.003% to 0.8% of an active ingredient (e.g., the NSAID), suitable for short and long term use for the treatment of acute or chronic conditions. The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. For example, effective amounts of ketorolac tromethamine (also referred to herein as ketorolac) range from about 0.04% to about 0.3%, preferably about 0.10% to about 0.3%, more preferably about 0.15% to about 0.30%, even more preferably about 0.15% to about 0.26%; effective amounts of flurbiprofen range from about 0.003% to about 0.024%, preferably about 0.009% to about 0.024%, more preferably about 0.012% to about 0.0195%; effective amounts of nepafenac range from about 0.01% to about 0.08%, preferably about 0.03% to about 0.08%, more preferably about 0.04% to about 0.065%; effective amounts of suprofen range from about 0.3% to about 0.8%, more preferably about 0.4% to about 0.65%; effective amounts of bromfenac range from about 0.009% to about 0.072%, preferably about 0.027% to about 0.072%, more preferably about 0.036% to about 0.059%; effective amounts of diclofenac range from about 0.01% to about 0.08%, preferably about 0.03% to about 0.08%, more preferably about 0.04% to about 0.065%; and effective amounts of indomethacin range from about 0.01% to about 0.1%, preferably about 0.03% to about 0.08%, more preferably about 0.04% to about 0.065%.

[0057] A variety of tear substitute components are known in the art and include, but are not limited to: polyols such as, glycerol, glycerin, polyethylene glycol 300, polyethylene glycol 400, polysorbate 80, propylene glycol, and ethylene glycol; polyvinyl alcohol, povidone, and polyvinylpyrrolidone; cellulose derivatives such hydroxypropyl methyl cellulose (also known as hypromellose), carboxymethyl cellulose sodium, hydroxypropyl cellulose, hydroxyethyl cellulose, and methyl cellulose; dextrans such as dextran 70; water soluble proteins such as gelatin; carbomers such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P; and gums such as HP-guar, or combinations thereof.

[0058] Many tear substitutes containing such components are commercially available, which include, but are not limited to cellulose esters such as Bion Tears®, Celluvisc®, GenTeal®, OccuCoat®, Refresh®, Teagen II®, Tears Naturale®, Tears Naturale®, Tears Naturale Free®, and Ther-aTears®; and polyvinyl alcohols such as Akwa Tears®, HypoTears®, Moisture Eyes®, Murine Lubricating®, Systane® Lubricant Eye Drops, and Visine Tears®. Tear substitutes may also be comprised of paraffins, such as the commercially available Lacri-Lube® ointments. Other commercially available ointments that are used as tear substitutes include Lubrifresh PM®, Moisture Eyes PM® and Refresh PM®.

[0059] In a preferred embodiment, the tear substitute, or one or more components thereof, is an aqueous solution having a viscosity in a range which optimizes efficacy of supporting the tear film while minimizing blurring, lid caking, etc. Preferably, the viscosity of the tear substitute, or one or more components thereof, ranges from 30-150 centipoise (cpi), preferably 30-130 cpi, more preferably 50-120 cpi, even more preferably 70-120 cpi. In some embodiments, the viscosity of the tear substitute, or one or more components thereof, ranges from about 50-90 cpi.

[0060] In some embodiments, the tear substitute, or one or more components thereof is buffered to a pH 5.0 to 9.0, preferably pH 5.5 to 8.5, more preferably pH 6 to 8, with a suitable salt (e.g., phosphate salts). In some embodiments, the tear substitute further comprises one or more ingredients, including without limitation, glycerol, propyleneglycerol, glycine, sodium borate, magnesium chloride, and zinc chloride.

[0061] In one preferred embodiment of the invention, the tear substitute comprises hydroxypropylmethyl cellulose. For example, without limitation, a tear substitute which comprises hydroxypropyl methyl cellulose is GenTeal® lubricating eye drops. GenTeal® (CibaVision-Novartis) is a sterile lubricant eye drop containing hydroxypropylmethyl cellulose 3 mg/g and preserved with sodium perborate. Other examples of an HPMC-based tear are provided. Preparation and use of one such tear is described in U.S. Pat. No. 6,806,364, which is expressly incorporated by reference herein in its entirety. This tear contains 0.2 to 2.5 (e.g., 0.5 to 0.8) percent by weight of hydroxypropylmethyl cellulose, 0.045 to 0.065 (e.g., 0.05 to 0.06) percent by weight a calcium salt, and 0.14 to 1.4 (e.g., 0.3 to 1.2) percent by weight a phosphate salt. This tear has a viscosity of 20 to 150 (e.g., 50 to 90) centipoise and is buffered to a pH 5.5 to 8.5 (e.g., 6 to 8) with a phosphate salt or other suitable salts. It may further contain one or more of the following ingredients: 0.5 to 1.0 percent by weight glycerol, 0.5 to 1.0 percent by weight propyleneglycerol, 0.05 to 0.05 percent by weight glycine, 0.006 to 0.08 percent by weight sodium borate, 0.025 to 0.10 percent by weight magnesium chloride, and 0.001 to 0.01 percent by weight zinc chloride.

[0062] In another preferred embodiment, the tear substitute comprises carboxymethyl cellulose sodium. For example, without limitation, the tear substitute which comprises carboxymethyl cellulose sodium is Refresh® Tears. Refresh® Tears is a lubricating formulation similar to normal tears, containing a mild non-sensitizing preservative, stabilised oxychloro complex (Purite™), that ultimately changes into components of natural tears when used.

[0063] In certain embodiments, the one or more tear substitute components acts as the pharmaceutical carrier(s).

[0064] In certain embodiments, the pharmaceutical compositions of the invention may comprise combinations of at least two NSAIDs and one or more tear substitute components. In other embodiments, the topical formulations of the invention may comprise one or more anti-allergenic agents and a combination of one or more tear substitute components.

[0065] The pharmaceutical compositions of the invention described above may additionally comprise other active ingredients, including, but not limited to, vasoconstrictors,

anti-allergenic agents, anti-infectives, steroids, anesthetics, anti-inflammatories, analgesics, dry eye agents (e.g. secretagogues, mucomimetics, polymers, lipids, antioxidants), etc., or be administered in conjunction (simultaneously or sequentially) with pharmaceutical compositions comprising other active ingredients, including, but not limited to, vasoconstrictors, anti-allergenic agents, anti-infectives, steroids, anesthetics, anti-inflammatories, analgesics, dry eye agents (e.g. secretagogues, mucomimetics, polymers, lipids, antioxidants), etc.

[0066] For example, the NSAID/tear substitute compositions of the invention may be used in combination with another pharmaceutical composition, such as a prescription drug like Restasis™ (cyclosporine ophthalmic emulsion, 0.05%). It may be used simultaneously with another pharmaceutical composition, or in sequence. For example, the NSAID/tear substitute compositions of the invention may be administered to a subject in the ramp up period before another administered pharmaceutical begins to be effective in the subject. In certain embodiments, the NSAID/tear substitute compositions of the invention may be used in a manner such that they serve as a replacement for a prescription drug like Restasis™.

[0067] The NSAIDs and other active ingredients of the pharmaceutical compositions may be in the form of a pharmaceutically acceptable salt.

[0068] Preferably, the pharmaceutical compositions according to the present invention will be formulated as solutions, suspensions, ointments, gels, sustained release formulation, and other dosage forms for topical administration or for sustained release delivery. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid compositions, or those appropriate for sustained release.

[0069] Any of a variety of carriers may be used in the formulations of the present invention including water, mixtures of water and water-miscible solvents, such as C₁-to C₇-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. The concentration of the carrier is, typically, from 1 to 100000 times the concentration of the active ingredient.

[0070] Additional ingredients that may be included in the formulation include tonicity enhancers, preservatives, solubilizers, stabilizers, non-toxic excipients, demulcents, sequestering agents, pH adjusting agents, co-solvents and viscosity building agents.

[0071] For the adjustment of the pH, preferably to a physiological pH, buffers may especially be useful. The pH of the present solutions should be maintained within the range of 4.0 to 8.0, more preferably about 4.0 to 6.0, more

preferably about 6.5 to 7.8. Suitable buffers may be added, such as boric acid, sodium borate, potassium citrate, citric acid, sodium bicarbonate, TRIS, and various mixed phosphate buffers (including combinations of Na_2HPO_4 , NaH_2PO_4 and KH_2PO_4) and mixtures thereof. Generally, buffers will be used in amounts ranging from about 0.05 to 2.5 percent by weight, and preferably, from 0.1 to 1.5 percent.

[0072] Tonicity is adjusted if needed typically by tonicity enhancing agents. Such agents may, for example be of ionic and/or non-ionic type. Examples of ionic tonicity enhancers are alkali metal or earth metal halides, such as, for example, CaCl_2 , KBr , KCl , LiCl , NaI , NaBr or NaCl , Na_2SO_4 or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. The aqueous solutions of the present invention are typically adjusted with tonicity agents to approximate the osmotic pressure of normal lachrymal fluids which is equivalent to a 0.9% solution of sodium chloride or a 2.5% solution of glycerol. An osmolality of about 225 to 400 mOsm/kg is preferred, more preferably 280 to 320 mOsm.

[0073] In certain embodiments, the formulations of the invention additionally comprise a preservative. A preservative may typically be selected from a quaternary ammonium 30 compound such as benzalkonium chloride, benzoxonium chloride or the like. Benzalkonium chloride is better described as: N-benzyl-N-(C_8 - C_{18} alkyl)-N,N-dimethylammonium chloride. Examples of preservatives different from quaternary ammonium salts are alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, sodium perborate, sodium chlorite, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorhexidine or polyhexamethylene biguanide, sodium perborate, Germal 11 or sorbic acid. Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride or its derivative such as Polyquad (see U.S. Pat. No. 4,407,791), alkyl-mercury salts and parabens. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi.

[0074] In other embodiments, the formulations of this invention do not include a preservative. Such formulations would be useful for patients with dry eye, patients who wear contact lenses, or those who use several topical ophthalmic drops and/or those with an already compromised ocular surface (e.g. dry eye) wherein limiting exposure to a preservative may be more desirable.

[0075] The formulation of the invention may additionally require the presence of a solubilizer, in particular if the active or the inactive ingredients tends to form a suspension or an emulsion. A solubilizer suitable for an above concerned composition is for example selected from the group consisting of tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, a cyclodextrin (for example alpha-, beta- or gamma-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl-alpha-, beta-

or gamma-cyclodextrin, mono- or dimaltosyl-alpha-, beta- or gamma-cyclodextrin or panosyl-cyclodextrin), polysorbate 20, polysorbate 80 or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL® or Cremophor RH40®. Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is selected from tyloxapol and from a cyclodextrin. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.

[0076] The formulations may comprise further non-toxic excipients, such as, for example, emulsifiers, wetting agents or fillers, such as, for example, the polyethylene glycols designated 200, 300, 400 and 600, or Carbowax designated 1000, 1500, 4000, 6000 and 10000. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from approximately 0.0001 to approximately 90% by weight.

[0077] Other compounds may also be added to the formulations of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

[0078] 2. Packaging

[0079] The formulations of the present invention may be packaged as either a single dose product or a multi-dose product. The single dose product is sterile prior to opening of the package and all of the composition in the package is intended to be consumed in one or several applications to one or both eyes of a patient. The use of an antimicrobial preservative to maintain the sterility of the composition after the package is opened is generally unnecessary. The formulations, if an ointment formulation, may be packaged as appropriate for an ointment, as is known to one of skill in the art.

[0080] Multi-dose products are also sterile prior to opening of the package. However, because the container for the composition may be opened many times before all of the composition in the container is consumed, the multi-dose products must have sufficient antimicrobial activity to ensure that the compositions will not become contaminated by microbes as a result of the repeated opening and handling of the container. The level of antimicrobial activity required for this purpose is well known to those skilled in the art, and is specified in official publications, such as the United States Pharmacopoeia ("USP") and other publications by the Food and Drug Administration, and corresponding publications in other countries. Detailed descriptions of the specifications for preservation of ophthalmic pharmaceutical products against microbial contamination and the procedures for evaluating the preservative efficacy of specific formulations are provided in those publications. In the United States, preservative efficacy standards are generally referred to as the "USP PET" requirements. (The acronym "PET" stands for "preservative efficacy testing.")

[0081] The use of a single dose packaging arrangement eliminates the need for an anti-microbial preservative in the compositions, which is a significant advantage from a medical perspective, because conventional antimicrobial agents utilized to preserve ophthalmic compositions (e.g., benzalkonium chloride) may cause ocular irritation, particularly in patients suffering from dry eye conditions or pre-existing ocular irritation, or patients using multiple preserved products. However, the single dose packaging arrangements currently available, such as small volume plastic vials prepared by means of a process known as "form, fill and seal", have several disadvantages for manufacturers and consumers. The principal disadvantages of the single dose packaging systems are the much larger quantities of packaging materials required, which is both wasteful and costly, and the inconvenience for the consumer. Also, there is a risk that consumers will not discard the single dose containers following application of one or two drops to the eyes, as they are instructed to do, but instead will save the opened container and any composition remaining therein for later use. This improper use of single dose products creates a risk of microbial contamination of the single dose product and an associated risk of ocular infection if a contaminated composition is applied to the eyes.

[0082] While the formulations of this invention are preferably formulated as "ready for use" aqueous solutions, alternative formulations are contemplated within the scope of this invention. Thus, for example, the active ingredients, surfactants, salts, chelating agents, or other components of the ophthalmic solution, or mixtures thereof, can be lyophilized or otherwise provided as a dried powder or tablet ready for dissolution (e.g., in deionized, or distilled) water. Because of the self-preserving nature of the solution, sterile water is not required.

[0083] 3. Methods of Use

[0084] The invention features methods of treating and/or preventing the signs and symptoms associated with dry eye and/or eye irritation in a subject comprising use of the novel formulations described above. For example, a method of treating and/or preventing dry eye and/or eye irritation may comprise administering to the eye surface of the subject in need thereof a formulation comprising an effective amount of at least one NSAID and a tear substitute, or one or more components thereof, in a pharmaceutically acceptable carrier.

[0085] Provided also are methods of increasing the tear film break-up time (TFBUT) of a subject's tear film, comprising administering to the eye surface of the subject in need thereof a formulation comprising an effective amount of at least one NSAID and a tear substitute, or one or more components thereof, in a pharmaceutically acceptable carrier.

[0086] Provided also are methods of increasing the ocular protection index (OPI) of a subject's eye, comprising administering to the eye surface of the subject in need thereof a formulation comprising an effective amount of at least one NSAID and a tear substitute, or one or more components thereof, in a pharmaceutically acceptable carrier.

[0087] Provided also are methods for improving, treating, relieving, inhibiting, preventing, or otherwise decreasing ocular discomfort in a subject comprising administering to

the eye surface of the subject in need thereof a formulation comprising an effective amount of at least one NSAID and a tear substitute, or one or more components thereof, in a pharmaceutically acceptable carrier.

[0088] Additionally provided are methods for decreasing the adverse effects associated with the administration of an NSAID to the eye; comprising administering to the eye surface of the subject in need thereof a formulation comprising an effective amount of at least one NSAID and a tear substitute, or one or more components thereof. Examples of an adverse effect associated with the administration of an NSAID to the eye include but are not limited to corneal damage, delayed wound healing, and ocular discomfort.

[0089] The effective amount of NSAIDs in the formulation will depend on absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the compound from the formulation, and will be suitable for short or long term use for the treatment of acute or chronic conditions, respectively. It is to be noted that dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Typically, dosing will be determined using techniques known to one skilled in the art.

[0090] The dosage of any compound of the present invention will vary depending on the symptoms, age and other physical characteristics of the patient, the nature and severity of the disorder to be treated or prevented, the degree of comfort desired, the route of administration, and the form of the supplement. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the formulations of the present invention may be readily determined by techniques known to those of skill in the art or as taught herein.

[0091] An effective dose or amount, and any possible effects on the timing of administration of the formulation, may need to be identified for any particular formulation of the present invention. This may be accomplished by routine experiment as described herein. The effectiveness of any formulation and method of treatment or prevention may be assessed by administering the formulation and assessing the effect of the administration by measuring one or more indices associated with the efficacy of the NSAID composition and with the degree of comfort to the patient, as described herein, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment or by comparing the post-treatment values of these indices to the values of the same indices using a different formulation.

[0092] The precise time of administration and amount of any particular formulation that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determine the optimum time and/or amount of administra-

tion, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

[0093] The combined use of several NSAIDs formulated into the compositions of the present invention may reduce the required dosage for any individual component because the onset and duration of effect of the different components may be complimentary. In such combined therapy, the different NSAIDs may be delivered together or separately, and simultaneously or at different times within the day.

[0094] Efficacy of the formulations and compositions of the invention in treating and preventing the signs and symptoms associated with dry eye disease and/or ocular irritation may be assessed by measuring changes in tear film break-up time, changes in ocular protection index, and level of ocular comfort. An increase in tear film break-up time and/or ocular protection index in a subject, following administration of the formulations and compositions of the invention as compared to TFBUT and/or OPI prior to administration, indicates that the formulation is effective in treating and preventing signs and symptoms associated with dry eye disease and/or ocular irritation. TFBUT may be measured using various methods, including but not limited to illumination of the eye following instillation of sodium fluorescein in the eye, or equivalents thereof. An increase in ocular comfort or decrease in ocular discomfort in a subject following administration of the formulations and compositions of the invention as compared to ocular comfort level prior to administration, indicates that the formulation is effective in treating and preventing signs and symptoms associated with dry eye disease and/or ocular irritation. Ocular comfort level may be assessed by various methods, including but not limited to subjective scales (for example but not limited to, standardized subjective scales that determine ocular discomfort as mild, moderate, severe, or 0, 1, 2, 3, 4, etc., or other appropriate scale), reflexive response (e.g., flinch-reflex), and physiological response, including but not limited to changes in heart rate, blood pressure, and perspiration levels.

[0095] 4. Kits

[0096] In still another embodiment, this invention provides kits for the packaging and/or storage and/or use of the formulations described herein, as well as kits for the practice of the methods described herein. Thus, for example, kits may comprise one or more containers containing one or more ophthalmic solutions, ointments, gels, sustained release formulations or devices, suspensions or formulations, tablets, or capsules of this invention. The kits can be designed to facilitate one or more aspects of shipping, use, and storage.

[0097] The kits may optionally include instructional materials containing directions (i.e., protocols) disclosing means of use of the formulations provided therein. While the instructional materials typically comprise written or printed materials they are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated by this invention. Such media include, but are not limited to electronic storage media (e.g., magnetic discs, tapes, cartridges, chips), optical media (e.g., CD ROM), and the like. Such media may include addresses to internet sites that provide such instructional materials.

[0098] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each

individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EXAMPLES

[0099] The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

Example 1

Formulation of Acular (Ketorolac Tromethamine) with a Carboxymethyl Cellulose (CMC)-Based Artificial Tear

[0100] The following study compared the efficacy of ketorolac tromethamine 0.5% ophthalmic solution

(Acular®), Acular® combined with a CMC-based artificial tear (Refresh®) (1:1 dilution, final concentration ketorolac tromethamine 0.25%), and Refresh® alone, in reducing ocular discomfort.

[0101] A specially developed chamber called the controlled adverse environment (CAE) was used as a model for evaluating ocular discomfort caused by irritation. The CAE is a chamber in which humidity is controlled at a low level, and temperature, wind flow, lighting and visual tasking are all controlled. Patients who enter the CAE will develop ocular discomfort over time. This model allows for the precise evaluation of agents which can act to treat dry eye and/or ocular irritation.

[0102] Baseline ocular exams were performed by an ophthalmologist on eighteen subjects. Subjects then entered the CAE and remained for 60 minutes. Every 5 minutes the ocular discomfort of each eye was assessed by the subject on a standardized 0-4 ocular discomfort scale, and was recorded by study staff. When an eye manifested a score of at least 3 at two consecutive assessments, 1-2 drops of either ketorolac tromethamine 0.5% ophthalmic solution, combined ketorolac tromethamine 0.25%/Refresh® formulation, or placebo (Refresh® artificial tear alone), was instilled into the eye. Subjects recorded comfort of the drop immediately following instillation of the drop on a 0-9 comfort scale (0=extremely comfortable and 9=extremely uncomfortable) and remained in the CAE 90 more minutes, with ocular discomfort assessments.

[0103] Each eye was dosed and assessed separately when it reached a score of at least 3 at two consecutive measurements during the initial CAE exposure.

[0104] An exit ocular exam was performed following the 90 minute follow-up CAE exposure by an ophthalmologist.

[0105] Ketorolac tromethamine 0.5% ophthalmic solution (N=8 eyes) showed a reduction in ocular discomfort scores compared with placebo (N=7 eyes) following dosing when subjects were exposed to the CAE. The reduction was evident starting at 15 minutes of exposure in the CAE postdosing. The ketorolac 0.25%/Refresh® combined formulation (N=5) also showed a reduction in ocular discomfort.

fort scores compared with placebo (N=5) following dosing when subjects were exposed to the CAE. The reduction with the combined ketorolac 0.25%/Refresh® formulation was evident at 40 minutes post-instillation of treatment. While the effect of the combined ketorolac 0.25%/Refresh® formulation was less than that of ketorolac 0.5%, there was still evidence that the combined ketorolac 0.25%/Refresh® formulation reduced discomfort.

[0106] The comfort of the drop immediately following instillation in the eye was superior in the placebo and the combined ketorolac 0.25%/Refresh® formulation treated eyes than the ketorolac 0.5% ophthalmic solution treated eyes. There was no difference between the comfort of the combined ketorolac 0.25%/Refresh® formulation and placebo drops. Thus, a drop consisting of a concentration less than currently available Acular® (0.5% ketorolac ophthalmic solution) was more comfortable when placed in the eye but still acted to treat ocular discomfort due to irritation. It can be expected that further dose range testing can identify a concentration higher than 0.25% but less than 0.5% which is more comfortable than 0.5% but is more efficacious than 0.25%. Other concentrations with these characteristics are also intended to be encompassed in this invention.

[0107] The data (FIG. 1) shows that a concentration of a topical NSAID can be identified which is able to reduce ocular discomfort.

Example 2

Formulation of Acular® (Ketorolac Tromethamine
0.5% Ophthalmic Solution) with a
Hydroxypropylmethyl Cellulose (HPMC)-Based
Artificial Tear

[0108] The following study compares the efficacy of an HPMC-based artificial tear with a combined formulation of Acular® and an HPMC-based artificial tear (1:1 dilution, final concentration ketorolac 0.25%), in reducing ocular discomfort.

[0109] Baseline ocular exams were performed by an ophthalmologist on eight subjects. Subjects then entered the CAE (described in Example 1) and remained for up to 90 minutes. Every 5 minutes the ocular discomfort of each eye was assessed by the subject on a standardized 0-4 ocular discomfort scale, and was recorded by study staff. When an eye manifested a score of at least 3 at two consecutive assessments, 1-2 drops of the HPMC-based tear was instilled in one eye and 1-2 drops of the combined Acular®/HPMC-based tear formulation in the contralateral eye. Subjects recorded comfort of the drop immediately following instillation of the drop on a 0-9 comfort scale (0=extremely comfortable and 9=extremely uncomfortable) and remained in the CAE 60 more minutes, with ocular discomfort assessments every 5 minutes.

[0110] Each eye was dosed and assessed separately when it reached a score of at least 3 at two consecutive measurements during the initial CAE exposure.

[0111] An exit ocular exam was performed following the 60 minute follow-up CAE exposure by an ophthalmologist.

[0112] FIG. 2 depicts the results of this study. The combined Acular®/HPMC-based tear formulation (final concentration ketorolac 0.25%) significantly improved ocular discomfort during CAE challenge. The HPMC-based tear reduced the ocular stinging typically associated with ketorolac upon instillation.

Example 3

Tear Film Break-Up Time (TFBUT)

[0113] The "tear film break-up time" or "TFBUT" test, an index of the severity of dry eye syndrome, can be used to measure the efficacy of a solution in maintaining the tear film. It is correlated with the degree of ocular discomfort a subject may feel. In a study involving hundreds of subjects, over 70% reported ocular discomfort within 1 second of tear film break-up. On average, the tear film in a normal eye breaks up in 7.1 seconds. In contrast, the tear film in a "dry eye" breaks up in an average of 3.2 seconds. Thus, agents having the ability to increase the TFBUT could be used in treating and preventing dry eye.

[0114] For example, the TFBUT may be assessed as follows. A patient's eye is first instilled with 2% sodium fluorescein. After the fluorescein instillation, the patient places his or her head in a slit lamp, and the investigator views the eye under cobalt blue illumination. The patient is instructed to blink three times and hold the eyes open at normal aperture after the third blink.

[0115] A stop watch is started when the eye is opened following the third blink, and is stopped when the investigator identifies a region of tear film break-up that has started to expand. The region of tear film break-up is identifiable by black voids in the otherwise confluent appearing tear film. The eye is video taped during the test.

[0116] The efficacy of the ophthalmic solutions described in Examples 1 and 2 on the TFBUT in dry-eye patients may be tested as follows. First, a TFBUT baseline for each patient is established. One or two drops of the ophthalmic formulation is then applied into one eye of each patient and the TFBUT is measured at 5, 10, 15, 30, 45, and 60 minutes after the application.

[0117] The TFBUT may be used to derive an ocular protection index (OPI) (Nally L, Ousler G W, Abelson M B. Ocular discomfort and tear film break-up time in dry eye 25 patients: a correlation. IOVS 2000 41; 4 (ARVO Abstract): 1436.), which is obtained by dividing the TFBUT by the time in seconds between blinks (the inter-blink interval, or "IBI"). An OPI of 1 or more than 1 (that is, the TFBUT is greater than or equal to the IBI) indicates a tear-protected ocular surface, with minimized signs or symptoms of dry eye. An OPI of less than 1 (that is, the TFBUT is less than the IBI) indicates an unprotected ocular surface, with exacerbated signs or symptoms of dry eye.

Example 4

Formulation of Various NSAIDs with an
HPMC-Based Artificial Tear

[0118] The following study compares the efficacy of an HPMC-based artificial tear with various 1:1 tear:NSAID combined formulations. The following commercially available ophthalmic NSAIDs were diluted 1:1 with an HPMC-based artificial tear: ketorolac tromethamine 0.4% (Acular-LS®), yielding an effective concentration of ketorolac tromethamine 0.2%; diclofenac 0.1% (Voltaren®) yielding an effective concentration of diclofenac 0.05%; bromfenac 0.09% (Xibrom®) yielding an effective concentration of 0.045%; and nepafenac 0.1% (Nevanac®), yielding an effective concentration of nepafenac 0.05%.

[0119] The HPMC-based tear used in this study was comprised of 0.8% sodium chloride, 0.7% HPMC K4M, and had a pH of 7.4±0.1, and a viscosity of 50 centipoise (cpi).

[0120] The CAE chamber described in Example 1 was used as a model for evaluating ocular discomfort caused by irritation. Subjects entered the CAE and remained for up to 30 minutes. Every 5 minutes the ocular discomfort of each eye was assessed by the subject on a standardized 0-4 ocular discomfort scale (0=no discomfort, 4=worst discomfort), and was recorded by study staff. When an eye manifested a score of greater than or equal to 3 at two consecutive assessments, 1-2 drops of the HPMC-based tear was instilled in one eye, and 1-2 drops of the combined NSAID/HPMC-based tear formulation in the contralateral eye, in a randomized fashion. Subjects recorded comfort of the drop immediately following instillation of the drop on a 0-9 comfort scale (0=extremely comfortable and 9=extremely uncomfortable) and remained in the CAE 60 more minutes, with ocular discomfort assessments every 5 minutes.

[0121] FIGS. 3-6 depict the results of this study. It was observed that 3 of the 4 combined NSAID/HPMC-based tear formulations reduced ocular discomfort during the CAE challenge (see FIGS. 3-5). The combined Acular LS®/HPMC-based tear formulation (final concentration ketorolac 0.2%) yielded the maximal reduction in ocular discomfort compared to the other NSAIDs tested at the given concentrations. While the combined Voltaren®/HPMC-based tear formulation, at the concentration tested, was not more effective than the HPMC-based tear formulation alone (see FIG. 6), the formulation was still effective in reducing ocular discomfort. Additional studies will be designed to test a concentration range of Voltaren® combined with a variety of artificial tears (including but not limited to CMC and HPMC-based artificial tears), ranging in viscosity, to determine the appropriate formulation whereby Voltaren combined with a tear substitute is more efficacious in reducing ocular discomfort in subjects exposed to the CAE challenge.

Example 5

Formulation of 0.25%, 0.125%, and 0.06% Ketorolac with an HPMC-Based Artificial Tear

[0122] The following study compares the efficacy of various concentrations of ketorolac tromethamine in formulation with an HPMC tear component. The HPMC-based tear used in this study was comprised of 0.8% sodium chloride, 0.72% HPMC K4M, and had a pH of 7.4±0.1, and a viscosity of 70 centipoise (cpi).

[0123] Ketorolac tromethamine was formulated at a final concentration of 0.25%, 0.125%, and 0.06% in the HPMC-based artificial tear solution as follows:

	0.25% Ketorolac tromethamine	0.125% Ketorolac tromethamine	0.06% Ketorolac tromethamine
HPMC K4M	0.72%	0.72%	0.72%
Sodium Chloride	0.8%	0.8%	0.8%
NaOH/HCl	pH 7.4 ± 0.1	pH 7.4 ± 0.1	pH 7.4 ± 0.1

[0124] Note that in the formulations described in the above table, all percentages are percent weight per volume.

[0125] The CAE chamber described in Example 1 was used as a model for evaluating ocular discomfort caused by irritation. Subjects entered the CAE and remained for up to 30 minutes. Every 5 minutes the ocular discomfort of each eye was assessed by the subject on a standardized 0-4 ocular discomfort scale (0=no discomfort, 4=worst discomfort), and was recorded by study staff. When an eye manifested a score of greater than or equal to 3 at two consecutive assessments, 1-2 drops of HPMC-based vehicle was instilled in one eye, and 1-2 drops of the ketorolac/HPMC formulation in the contralateral eye, in a randomized fashion. Subjects recorded comfort of the drop immediately following instillation of the drop on a 0-9 comfort scale (0=extremely comfortable and 9=extremely uncomfortable) and remained in the CAE 60 more minutes, with ocular discomfort assessments every 5 minutes.

[0126] FIGS. 7-9 depicts the results of this study. It was observed that the combined ketorolac 0.25%/HPMC-based tear formulation was efficacious in reducing ocular discomfort while the combined ketorolac 0.125%/tear and ketorolac 0.06%/tear formulations were not. While not intending to be bound by any theory, these results suggest a loss of pharmacologic activity at a point between ketorolac 0.125% and ketorolac 0.25%.

Example 6

TFBUT Testing Using Various NSAID/Artificial Tear Formulations

[0127] The following study evaluates the efficacy of 3 formulations of artificial tear components (approximately 50-80 cpi) with ketorolac on increasing TFBUT and the Ocular Protection Index (OPI). Two of the tear components were HPMC based (depicted as formulation C-2 and D-2 in the table below, and in FIGS. 10 and 11), and one was CMC based (depicted as Liquigel in the table below and in FIGS. 10 and 11). The formulations used in this study are given in the table below.

	C-2	D-2	Liquigel ¹
Sodium chloride		0.8%	X
Sodium phosphate, dibasic•7H ₂ O	0.34%		
Potassium phosphate, monobasic	0.17%		
Glycerin	1.8%		
Magnesium chloride•6H ₂ O			X ^a
HPMC K4M	0.7%	0.7%	
Ketorolac tromethamine	0.25%	0.25%	0.25% (1:1 dilution with Acular®-ketorolac 0.5%)
Glycine	0.0075%		
NaOH/HCl	pH 7.4 ± 0.1	pH 7.4 ± 0.1	
Carboxymethyl-cellulose sodium			1.0
Boric acid			X
Calcium chloride			X
Potassium chloride			X
Sodium borate			X

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-continued			
	C-2	D-2	Liqagel ¹
PURITE [®] (stabilized oxychloro complex)			X
Purified Water	q.s. 100	q.s. 100	X

¹PDR for Ophthalmic Medicines, 35th Edition, 2007
²"X" denotes inactive ingredient of unknown percentage
³does not clarify 6H2O

[0128] 1-2 drops of the formulation was instilled in each eye and TFBUT was assessed, as well as blink rate to calculate OPI, as described in Example 3 above. TFBUT was assessed at baseline, and 5, 10, 15, 20, 30, 45, 60 minutes post-dosing. A comparison of each formulation on TFBUT and OPI are shown in FIGS. 10 and 11, respectively.

Example 7

Formulation of an NSAID with a Different Artificial Tear

[0129] The following study compares the efficacy of an NSAID combined with an artificial tear solution containing the demulcents polyethylene glycol 400 and propylene glycol with HP-Guar (Systane[®]), in reducing ocular discomfort, with the artificial tear solution alone. The NSAID used in this study was Nevanac[®]. Systane[®] was formulated in a 1:1 ratio with the NSAID Nevanac[®] (nepafenac 0.1%) to yield an effective concentration of 0.5% nepafenac.

[0130] The CAE chamber described in Example 1 was used as a model for evaluating ocular discomfort caused by irritation. Subjects entered the CAE and remained for up to 30 minutes. Every 5 minutes the ocular discomfort of each eye was assessed by the subject on a standardized 0-4 ocular discomfort scale (0=no discomfort, 4=worst discomfort), and was recorded by study staff. When an eye manifested a score of greater than or equal to 3 at two consecutive assessments, 1-2 drops of the artificial tear was instilled in one eye, and 1-2 drops of the NSAID/artificial tear formulation in the contralateral eye, in a randomized fashion. Subjects recorded comfort of the drop immediately following instillation of the drop on a 0-9 comfort scale (0=extremely comfortable and 9=extremely uncomfortable) and remained in the CAE 60 more minutes, with ocular discomfort assessments every 5 minutes.

[0131] FIG. 12 depicts the results of this study. It was observed that the combined nepafenac/artificial tear formulation reduced ocular discomfort during the CAE challenge.

REFERENCES

[0132] All publications and patents mentioned herein are hereby incorporated by reference in their entireties as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0133] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described herein. While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. An ophthalmic formulation comprising a combination of:

- 1) a tear substitute component; and
- 2) a low-dose amount of an NSAID selected from the group consisting of ketorolac tromethamine, nepafenac, and bromfenac,

wherein the combination is effective to treat or prevent the signs and symptoms dry eye.

2. An ophthalmic formulation comprising a combination of:

- 1) a tear substitute component; and
- 2) a low dose amount of an NSAID selected from the group consisting of ketorolac tromethamine, nepafenac, and bromfenac,

wherein the low dose is an amount effective to reduce ocular surface discomfort without producing an anesthetic effect.

3. The ophthalmic formulation of claim 3, comprising about 0.15% to about 0.26% ketorolac tromethamine.

4. The ophthalmic formulation of claim 1, comprising about 0.03% to about 0.08% nepafenac.

5. The ophthalmic formulation of claim 5, comprising about 0.05% to about 0.065% nepafenac.

6. The ophthalmic formulation of claim 1, comprising about 0.027% to about 0.072% bromfenac.

7. The ophthalmic formulation of claim 7, comprising about 0.036% to about 0.059% bromfenac.

8. The ophthalmic formulation of claim 1, wherein the tear substitute component has a viscosity ranging from about 50-120 cpi.

9. The ophthalmic formulation of claim 8, wherein the tear substitute component has a viscosity ranging from about 70-120 cpi.

10. The ophthalmic formulation of claim 1, wherein the tear substitute component comprises an ingredient selected from the group consisting of: a polyol, a dextran, a water soluble protein, a carbomer, a gum, and a cellulose derivative.

11. The ophthalmic formulation of claim 10, wherein the cellulose derivative is selected from the group consisting of: hydroxypropylmethyl cellulose, carboxymethyl cellulose sodium, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, and one or more combinations thereof.

12. The ophthalmic formulation of claim 11, wherein the cellulose derivative is hydroxypropylmethyl cellulose (HPMC).

13. The ophthalmic formulation of claim 11, wherein the cellulose derivative is carboxymethyl cellulose sodium (CMC).

14. The ophthalmic formulation of claim 11, wherein cellulose derivative is a combination of CMC and HPMC.

15. An ophthalmic formulation comprising a combination of:

- 1) an HPMC-based tear substitute having a viscosity of about 50 centipoise, and
- 2) 0.2% ketorolac tromethamine,

wherein the combination is effective to treat or prevent the signs and symptoms dry eye.

16. An ophthalmic formulation comprising a combination of:

- 1) an HPMC-based tear substitute having a viscosity of about 50 centipoise, and
- 2) 0.05% nepafenac,

wherein the combination is effective to treat or prevent the signs and symptoms dry eye.

17. An ophthalmic formulation comprising a combination of:

- 1) an HPMC-based tear substitute having a viscosity of about 50 centipoise, and
- 2) 0.045% bromfenac,

wherein the combination is effective to treat or prevent the signs and symptoms dry eye.

18. An ophthalmic formulation comprising a combination of:

- 1) an HPMC-based tear substitute having a viscosity of about 70 centipoise, and
- 2) 0.25% ketorolac tromethamine,

wherein the combination is effective to treat or prevent the signs and symptoms dry eye.

19. A method of treating, and evaluating the treatment of, a subject having dry eye and/or eye irritation, comprising:

- (a) determining a first measurement of the tear film break-up time (TFBUT) or ocular protection index (OPI) or non-invasive tear film break-up time in a subject and evaluating the patient's ocular discomfort;
- (b) administering an ophthalmic formulation according to claim 1;
- (c) determining a second measurement of the TFBUT or OPI or non-invasive tear film break up time in the subject;

wherein and an increase in the second measurement of TFBUT or OPI or non-invasive tear film break up time as compared to the first measurement indicates that the ophthalmic formulation is efficacious in treating the subject.

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