Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-088171- -00003-0000

Fecha: 2011-01-18 11:55:53 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 68

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [X] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificacion.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: 09 088171
Solicitante: ALMIRALL, S.A.
Apoderado: LUZ CLEMENCIA SUAREZ DE PAEZ
Título de la nueva creación o denominación del signo: "NUEVOS METODOS"
Gaceta: 621

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: LABORATORIOS SYNTHESIS S.A.S.
Dirección: CARRERA 44 N° 20C 73
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BOGOTA
Teléfono: 3 69 22 22 Fax:
E-mail:

IDENTIFICACION
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual
Número 860,000,760-1

REPRESENTANTE O APODERADO

Nombre: ELIANA ISAURA MORENO BOHORQUEZ
Dirección: CARRERA 13 No. 119-95
Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 51'975.664 TP 83823

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

⑤ **Comprobante de pago No.** _____ **Fecha** _____

⑥ **ANEXOS**

- [x] Comprobante de pago de la tasa.
- [x] Poderes, si fuere el caso.
- [x] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [x] 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 **T.P.** 83823

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 09 088171
Asunto	: Oposición a la solicitud de patente de Invención titulada "NUEVOS METODOS"
Solicitante	: ALMIRALL, S.A.
Opositora	: LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 621 del 20 de octubre de 2010

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 Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "NUEVOS METODOS", cuyos titulares son ALMIRALL, S.A., 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 ACLIDINIO. 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 21 de agosto de 2009 reivindicando prioridad bajo la solicitud US20070902843 del 2007-02-21; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 621 del 20 de octubre de 2010**, cuya publicación internacional corresponde a la WO2008101591 del 2008-08-28.

2.2. La solicitud colombiana 09 088171 objeto de la presente oposición se refiere a métodos para el tratamiento por inhalación de una enfermedad o estado respiratorio en un paciente que necesite dicho tratamiento sin producir en dicho paciente efectos anti muscárnicos sistémicos, comprendiendo administrar a dicho paciente una cantidad eficaz de aclidinio.

2.3.En primera instancia, se debe advertir que en el capítulo reivindicatorio de la solicitud objeto de la presente oposición, se hace referencia a métodos terapéuticos, no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*", los usos no están contemplados como patentables; y, Artículo 20.- "*No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente a métodos terapéuticos no sería patentable.

2.4.Con base en el articulo 14 de la Decisión 486 de la CAN que consagra: "*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*", tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: MOLFINO NESTOR A: "DRUGS IN CLINICAL DEVELOPMENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE" RESPIRATION, KARGER, BASEL, CH, vol. 72, no. 1, 2005, páginas 105-112.
- D2: WO2005115462 publicada el 08 de diciembre de 2005.

2.5. Ahora bien, el documento D1, está centrado en los compuestos existentes mejorados y los compuestos descubiertos que se encuentran en ensayos clínicos, pero no son comercializados todavía. Los compuestos mejorados existentes incluyen: isómeros de los broncodilatadores de acción prolongada, los agonistas beta2 adrenérgicos una vez al día, anticolinérgicos y corticosteroides. Para el mismo documento D1 la gama de nuevos compuestos se encuentra en constante fluctuación y cuenta con medicamentos antiinflamatorios, antioxidantes, modificadores de leucotrienos y una serie de compuestos que tienden a tratar diferentes aspectos de la EPOC (COPD), como la hipertensión pulmonar y la hipofosfatemia. Dicho documento D1 revela de forma particular el uso del agonista selectivo de los receptores muscárnicos M3, bromuro de aclidinio en el tratamiento de la enfermedad pulmonar obstructiva crónica (EPOC) y el asma; la solicitud objeto de la presente oposición no es novedosa pues lo reclamado ya era parte del arte anterior.

2.6. El documento D2 por su parte se refiere a una combinación que comprende (a) un agonista Beta2 y (b) un antagonista de los receptores muscarínicos M3 que es 3(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1- azoniabiciclo[2,2,2]octano, en forma de una sal que tiene un anión X, que es un anión farmacéuticamente aceptable de un ácido mono o polivalente para el tratamiento de trastornos respiratorios. Dicho documento D2 describe el uso combinado del agonista selectivo de los receptores muscárnicos M3, bromuro de aclidinio e inhibidores específicos de POE4 y beta2-miméticos o coriticosteroides en el tratamiento del enfisema, COPD y el asma, también revela composiciones inhalables en polvo que comprenden el bromuro de aclidinio y la lactosa.

2.7. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1 por sí solo, o en combinación con D2 que revela composiciones inhalables en polvo que comprenden el bromuro de aclidinio, concebir métodos para el tratamiento por inhalación de una enfermedad o estado respiratorio en un paciente que necesite dicho tratamiento sin producir en dicho paciente efectos antimuscárnicos sistémicos, comprendiendo administrar a dicho paciente una cantidad eficaz de aclidinio. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 088171 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

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

2.9.1. CARENCIA DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*. A la fecha de prioridad, 21 de febrero de 2007 ya era conocido, pues como se demostró, eran parte del arte anterior con base en los documentos D1 y D2, métodos para el tratamiento por inhalación de una enfermedad o estado respiratorio en un paciente que necesite dicho tratamiento, comprendiendo administrar a dicho paciente una

cantidad eficaz de aclidinio; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9.2. 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, 21 de febrero de 2007, a partir del documento D1 por sí solo, que revela de forma particular el uso del agonista selectivo de los receptores muscárnicos M3, bromuro de aclidinio en el tratamiento de la enfermedad pulmonar obstructiva crónica (EPOC) y el asma, o en combinación con D2 que revela composiciones inhalables en polvo que comprenden el bromuro de aclidinio para enfermedades como el asma, un experto en la materia puede llegar de manera evidente a métodos para el tratamiento por inhalación de una enfermedad o estado respiratorio en un paciente que necesite dicho tratamiento sin producir en dicho paciente efectos antimuscárnicos sistémicos, comprendiendo administrar a dicho paciente una cantidad eficaz de aclidinio; sobre lo cual busca protección en el capítulo reivindicatorio.

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

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

2.11. **Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada "NUEVOS METODOS", cuyos titulares son ALMIRALL, S.A., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010.**

3. PRUEBAS

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

- D1: MOLFINO NESTOR A: "DRUGS IN CLINICAL DEVELOPMENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE" RESPIRATION, KARGER, BASEL, CH, vol. 72, no. 1, 2005, páginas 105-112.
- D2: WO2005115462 publicada el 08 de diciembre de 2005.

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: MOLFINO NESTOR A: "DRUGS IN CLINICAL DEVELOPMENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE" RESPIRATION, KARGER, BASEL, CH, vol. 72, no. 1, 2005, páginas 105-112.
- D2: **WO2005115462** publicada el 08 de diciembre de 2005.

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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 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.

12

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 004765

Bogotá D.C., 18 de 2011 - 11:28:31

RECIBIDO DE : LABORATORIOS SYNTHESIS LTDA & CIA S.C.A. NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	396966916	17/01/2011	1.216.000.00

*** 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. 09-088171- -00003-0000
Fecha: 2011-01-18 11:55:53 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 68

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN,** 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 Gerente 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. **09 088.171,** titulada "**COMPOSICIÓN PARA INHALACIÓN",** cuyo titular es ALMIRALL, S.A, publicada en la gaceta No. 621 del 20 de Octubre de 2010.

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 ____ días del mes de ____ de 2011.

LABORATORIOS SYNTHESIS S.A.S.

_____

Cédula de Extranjería: No. 319788.
NIT: 860.000.760-1
Gerente

Acepto:

_____

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

REPÚBLICA DE COLOMBIA

DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Círculo de Bogotá, LUIS ALBERTO DARGAS

quien exhibió la C.C. E 3197788

Expedida en [illegible] y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

BOGOTA, D.C. 17 ENE 2011

FIRMA

HUELLA INDICE DERECHO

EL NOTARIO

NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTA D.C.
LA HUELLA SE AUTENTICA POR SOLICITUD DEL INTERESADO

REPÚBLICA DE COLOMBIA
ALBERTO VARGAS FIALLO
NOTARIO 18 (E) DEL CIRCULO DE BOGOTÁ

01

9991867

CAMARA DE COMERCIO DE BOGOTA

SEDE CENTRO

14 DE ENERO DE 2011 HORA 10:58:20

R030239466 PAGINA: 1 de 5

* *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S
N.I.T. : 860000760-1
DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73
MUNICIPIO : BOGOTA D.C.
EMAIL DE NOTIFICACION JUDICIAL : synthe@synthesis.com.co
DIRECCION COMERCIAL : CRA 44 NO 20C 73
MUNICIPIO : BOGOTA D.C.
EMAIL COMERCIAL : synthe@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LA-BORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE CO MERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LI-- BRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE:"LABORATORIOS --- BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS RE-- FORMAS.

CERTIFICA :_

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LI-BRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

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

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CAMARA DE COMERCIO DE BOGOTA

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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

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 CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR : $20,000,000,000.00
NO. DE ACCIONES : 20,000,000.00
VALOR NOMINAL : $1,000.00

** CAPITAL SUSCRITO **

VALOR : $17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : $1,000.00

** CAPITAL PAGADO **

VALOR : $17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : $1,000.00

CERTIFICA:

REPRESENTACION LEGAL: GERENCIA LA CUAL SERÁ ASUMIDA POR UN GERENTE Y UN SUBGERENTE QUIENES TENDRÁN REPRESENTACIÓN LEGAL DE LA SOCIEDAD.

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

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 ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA

DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 654 DE LA NOTARIA 01 DE BOGOTA D.C., DEL 20 DE FEBRERO DE 2009, INSCRITA EL 02 DE MARZO DE 2009 BAJO EL NO. 15209 DEL LIBRO V, COMPARECIO ORLANDO MUÑOZ MARTINEZ IDENTIFICADO CON CEDULA DE CIUDADANIA NO. 8.317.044 EN SU CALIDAD DE DELEGADO GENERAL SUPLENTE DEL SOCIO GESTOR LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL SEÑOR ANDRES FERNANDO MOLLAJOLI CENTURION, IDENTIFICADO CON CÉDULA DE EXTRANJERÍA NO. 351.283 QUE EN NOMBRE DE LA SOCIEDAD QUE REPRESENTO, ACTUÉ CON LAS MÁS AMPLIAS FACULTADES EN LA REPÚBLICA DE COLOMBIA, EN LOS SIGUIENTES ASUNTOS 1. PARTICIPAR EN CALIDAD DE SOCIO, ACCIONISTA O EMPRESARIO EN PERSONAS JURÍDICAS COLOMBIANAS, CONSTITUIDAS O POR CONSTITUIRSE, EN EL PORCENTAJE QUE LA APODERADA AQUÍ NOMBRADA ESTIME CONVENIENTE A NUESTROS INTERESES, CON FACULTAD PARA ENTREGAR LAS SUMAS CORRESPONDIENTES AL PAGO DEL MISMO; 2. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS; 3. REPRESENTAR A LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., EN LAS REUNIONES ASAMBLEA GENERAL O JUNTAS EN LAS CUALES TENGA INTERÉS; 4. EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRÉSTAMOS DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS, OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, Y NEGOCIAR EN GENERAL TÍTULOS VALORES Y RECIBIRLOS EN PAGO; 5. CELEBRAR ASÍ MISMO OPERACIONES RELACIONADAS CON LA PROTECCIÓN DE SUS BIENES, NEGOCIOS Y PERSONAS A SU SERVICIO; 6. CELEBRAR CONTRATOS DE CUENTAS EN

PARTICIPACIÓN, SEA COMO PARTÍCIPE ACTIVA O COMO PARTÍCIPE INACTIVA; 7. TRANSIGIR, DESISTIR Y APELAR DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIÓNES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES; 8. 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. 9. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEA CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES; 10. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. 11. NOTIFICARSE VÁLIDAMENTE DE AQUELLOS ACTOS DEL ORDEN ADMINISTRATIVO O JUDICIAL QUE SE FORMULEN CONTRA LA SOCIEDAD, ASÍ CÓMO ABSOLVER INTERROGATORIOS CON CAPACIDAD PARA CONFESAR; 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SYNTHEIS LTDA & CIA S.C.A. 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SÍNTESIS LTDA. & CIA S.C.A., RECAUDAR O RECIBIR POR SUS FRUTOS Y CELEBRAR TODA CLASE DE CONTRATOS RELACIONADOS CON LA ADMINISTRACIÓN. 13. ENAJENAR, ADQUIRIR, PERMUTAR, GRAVAR, ARRENDAR BIENES MUEBLES, PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTIIESIS LTDA & CIA S.C.A, SIN LÍMITE DE CUANTIA. 14. ENAJENAR, PERMUTAR, ADQUIRIR, GRAVAR, ARRENDAR BIENES MUEBLES E INMUEBLES PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MAS ALTO EN LA FECHA DE CELEBRACIÓN Y TENGA RELACIÓN DIRECTA CON EL DESARROLLO SOCIAL, ASÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DE LA SOCIEDAD GESTORA. 15. TOMAR DINERO EN MUTUO, CON FACULTAD PARA ESTIPULAR TODO TIPO DE INTERESES, PLAZOS Y DEMÁS CONDICIONES Y CELEBRAR CONTRATOS DE CUENTA CORRIENTE; 16. GIRAR, ORDENAR GIRAR, ENDOSAR, PROTESTAR, OTORGAR, ACEPTAR ORDENAR AVALÚOS Y HACER TODA CLASE DE NEGOCIOS RELACIONADOS CON TÍTULOS VALORES CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MÁS ALTO EN LA FECHA DE SU CELEBRACIÓN, SÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DEL REPRESENTANTE LEGAL DE LA SOCIEDAD GESTORA. 17. PRESENTAR DECLARACIÓN DE RENTA, PATRIMONIO, IMPUESTOS A LAS VENTAS EN ADMINISTRACIÓN DE IMPUESTOS NACIONES Y MUNICIPALES E INTERPONER LOS RECURSOS Y DECLARACIONES PERTINENTES CONTRA ACTOS DE DICHA ADMINISTRACIÓN CON FACULTAD PARA DEFENDER LOS INTERESES DE LA SOCIEDAD EN ÉSTA MATERIA. 18. DESIGNAR APODERADO ESPECIAL PARA CADA PROCESO JUDICIAL O ADMINISTRATIVO. 19. PRÉSENTAR RECURSOS POR VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR 20. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES 21. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES 22. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA

CERTIFICA:

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

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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. 52.780.308 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. ADELANTAR 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. I. 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 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 PRINCIPAL	
AGUILLON ROJAS SANDRA MILENA	C.C. 000000047436442
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

CERTIFICA:

PERMISO DE FUNCIONAMIENTO:QUE POR RESOLUCION NO.05952 DEL 11 DE - JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA - DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA SOCIEDAD.

CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERIN-TENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR SETENTA Y CUATRO MIL ($74.000) ACCIONES DE LAS QUE TIENE EN RE-SERVA, A SU VALOR NOMINAL DE CIEN PESOS ($100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM
MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010
ULTIMO AÑO RENOVADO : 2010

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NOMBRE : GENERICS
MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010
ULTIMO AÑO RENOVADO : 2010

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NOMBRE : MASCOTT
MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010
ULTIMO AÑO RENOVADO : 2010

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NOMBRE : ONCOPHARM
MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010
ULTIMO AÑO RENOVADO : 2010

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NOMBRE : GASTROPHARM
MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010

ULTIMO AÑO RENOVADO : 2010
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NOMBRE : GYNECOPHARM
MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994
RENOVACION DE LA MATRICULA : EL 29 DE MARZO DE 2010
ULTIMO AÑO RENOVADO : 2010
****
NOMBRE : ENTEROPHARM
MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994
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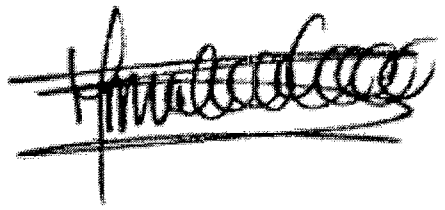

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Drugs in Clinical Development for Chronic Obstructive Pulmonary Disease

Néstor A. Molfino

Otsuka Maryland Research Institute, Rockville, Md., USA

Key Words
Therapy · Chronic bronchitis · Emphysema · Drugs · Asthma · Treatments · Bronchodilators · Antimuscarinic · Anti-inflammatories

Abstract
Many drugs may be potentially useful in the treatment of chronic obstructive pulmonary disease (COPD), but relatively few become available for human use due to lack of safety, lack of efficacy, or both. This is an inherent risk in the drug development process, which coupled with the limited understanding of the molecular pathogenesis of COPD, has produced a trend toward improving existing compounds rather than to develop new compounds. This review focuses on improved existing compounds and newly discovered compounds that are in clinical trials, but not yet marketed. The improved existing compounds include: isomers of the long-acting bronchodilators, once-daily β_2-adrenoceptor agonists, anticholinergics and corticosteroids. The pool of novel compounds is in constant fluctuation and comprises anti-inflammatory drugs, antioxidants, leukotriene modifiers and a number of compounds aimed at treating different aspects of COPD such as pulmonary hypertension and hypophosphatemia.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) are treated with inhaled short-acting bronchodilators during mild stages of the disease or acute exacerbations, whereas inhaled long-acting bronchodilators and inhaled corticosteroids are used when COPD is stable, but the patient exhibits moderate to severe airflow limitation [1]. In the near future, phosphodiesterase-4 (PDE4) inhibitors could be added to this armamentarium [2]. Some existing therapies may be able to deter the progression of the chronic airflow limitation that determines the prognosis of COPD patients. Smoking cessation and long-term oxygen therapy are the only interventions known to alter disease progression and improve prognosis in some patients [3–5]. Inhaled steroids in combination with long-acting β_2-adrenoceptor agonists seem to reduce the number of exacerbations in severe COPD [1] and the rate of decline of the lung function as measured by forced expiratory volume in 1 s (FEV_1) [6].

The challenges in the development of novel therapies for the treatment of COPD include not only the limited understanding of the molecular pathogenesis of COPD, but also the lack of integration between the new findings (i.e. inflammation), the physiological responses (i.e. improvement in lung function) and the clinical implications (i.e. symptoms, morbidity and mortality). Despite these uncertainties, a number of improved compounds and newly discovered compounds are in clinical development. Of the many compounds stemming from discovery [7], few will go beyond the proof-of-concept stage and ad-

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Néstor A. Molfino, MD, MSc, FCCP
Otsuka Maryland Research Institute
2440 Research Boulevard, 3rd Floor
Rockville, MD 20850 (USA)
Tel. +1 240 683 3143, Fax +1 301 721 7143, E-Mail nestorm@otsuka.com

vance into further clinical development. These clinical candidates are reviewed here. Other products that are also in clinical development for COPD (such as vaccines, antibiotics, mucolytics and products that appear to inhibit or reduce bacterial colonization in the airways) are not covered in this review.

Improved Compounds

Improved Long-Acting β_2-Adrenoceptor Agonists

Formoterol and salmeterol were the first members of a new generation of long-acting β_2-adrenoceptor agonists for inhalation. There are two alternative models that offer an explanation of the long duration of effect: the exosite binding model (salmeterol) and the more general diffusion microkinetic model (formoterol and salmeterol) [8, 9]. Once the principle of a long duration of effect was established, a number of novel long-acting β_2-adrenoceptor agonists of various chemical structures have emerged. Like all other β_2-adrenoceptor agonists currently in clinical use, formoterol and salmeterol are racemic mixtures. The marketed form of formoterol is a racemic mixture composed of a 50:50 mixture of *R*- and *S*-isomers. Only the *R,R*- and *R*-enantiomers are pharmacologically active. The *S,S*-form is essentially inactive; accordingly, pure *(R,R)*-formoterol provides bronchodilatation at lower doses than the racemate, resulting in fewer β_2-adrenergic-mediated side effects. In addition, variations in metabolism may produce progressive accumulation of *(S,S)*-formoterol [10]. Moreover, in horses with reactive airways, *(S,S)*-formoterol facilitates acetylcholine release even in the absence of atropine [11, 12]. Thus, if this observed effect were to have a clinical meaning, *(R,R)*-formoterol would be preferable to the racemic form for the treatment of COPD, particularly in patients using inhaled anticholinergics [13].

Once-daily β_2-adrenoceptor agonists are in development for the treatment of asthma and COPD. Once-daily dosing would allow better compliance and management of patients if desensitization and accumulation do not occur. The once-daily approach has been combined with the enantiomer hypothesis, and as a result, the experimental long-lasting β_2-adrenoceptor agonists TA-2005 and picumeterol have been developed as pure *R,R*- and *R*-enantiomers, respectively. In cats, TA-2005 inhibits 5-HT-induced bronchoconstriction by up to 72% and is more potent than procaterol, formoterol, isoprenaline, salbutamol and salmeterol. Similar results were obtained for histamine-induced bronchoconstriction in anesthetized guinea pigs. In radioligand binding studies using guinea pig lung and cardiac ventricles, TA-2005 had a high affinity for β_2-receptors. In U937-derived macrophages, TA-2005 inhibited the lipopolysaccharide-induced release of tumor necrosis factor-α (TNF-α) and increased the release of the anti-inflammatory interleukin (IL)-10 [14]. Picumeterol has been shown to produce long-lasting relaxation of the airway smooth muscle, both in vitro and in vivo. However, in atopic asthmatics, the bronchodilatation was not long-lasting. In addition, it did not improve PC_{20}, when compared with placebo. In vitro, picumeterol showed lower intrinsic activity than the other β_2-adrenoceptor agonists, isoprenaline and salbutamol, and this may explain the poor results in humans [15].

Improved Anticholinergics

The treatment of obstructive airway diseases may be improved by antimuscarinic agents which selectively block M_1 and M_3 receptors, but do not inhibit the prejunctional M_2 cholinergic autoreceptors which limit the release of acetylcholine. The finest example of this is tiotropium [16, 17] which has a slow dissociation from M_1 and M_3 muscarinic receptors and is currently marketed in many countries.

There are other anticholinergics in development. LAS-34273 is an M_3 antimuscarinic in development for the treatment of asthma and chronic bronchitis. In a double-blind, placebo-controlled phase I trial in 16 male COPD patients, inhaled LAS-34273 at doses of 50, 300 and 600 µg caused rapid, significant bronchodilatation in all patients, with a duration of action of up to 24 h. It showed a good safety and tolerability profile in healthy subjects and COPD patients [18, 19]. Revatropate is a novel antimuscarinic agent that shows some 50-fold selectivity for M_1 and M_3 receptors in guinea pig trachea and, in contrast to the nonselective agent ipratropium, it did not potentiate bronchoconstrictor responses induced by vagal nerve stimulation, indicating that inhibitory auto-receptors were still functional. Early clinical studies in COPD patients showed that inhaled revatropate was an effective well-tolerated bronchodilator [20] (table 1).

Improved Inhaled Steroids

The development of inhaled steroids for the treatment of COPD is based on the premise that the inflammation found in the lung compartment of COPD patients [21–28] is important enough to have an impact on the prognosis of the disease, and that the inflammation is steroid responsive. Clearly, many trials with steroids have not

Table 1. Improved compounds potentially useful in COPD

Compounds	Mechanism of action	Indications and regimen	Development phase
(*R,R*)-Formoterol	β_2-adrenoceptor agonist	COPD, asthma, b.i.d.	phase III
TD-3327 (GSK-159797)	β_2-adrenoceptor agonist	COPD, asthma q.d.	phase I
THRX-502038 (GSK-597901)	β_2-adrenoceptor agonist	COPD, asthma q.d.	phase I
QAB-149	β_2-adrenoceptor agonist	COPD, asthma q.d.	phase II
TA-2005 and picumeterol	β_2-adrenoceptor agonist	asthma, COPD, q.d.	phase II
LAS-34273	muscarinic M3 antagonist	asthma, chronic bronchitis	phase I
Revatropate	M1 and M3 antagonist	COPD	phase I
Enantiomers of structurally related chiral antagonists	M3 antagonist	COPD	preclinical
Inhaled steroids (ciclesonide)	prodrug, selective therapeutic ratio	asthma	phase III
Anti-elastases	A_1AT gene in plasmid vector	A_1AT deficiency, COPD, CF	phase I

See text for explanations on each compound.

shown positive results in terms of improvement of FEV_1 and better prognosis [29], except when inhaled steroids are combined with long-acting bronchodilators. With the combination, fewer exacerbations occurred, but no change in the rate of decline of FEV_1 was noted [30, 31]. More recently, a meta-analysis of 8 trials has shown that inhaled steroids can indeed slow the decline of FEV_1 [6].

Ciclesonide is a non-halogenated inhaled corticosteroid that is converted into a ciclesonide-active principle (CIC-AP) in the lung. It has a selective therapeutic ratio (local systemic activity) that is 10 times higher than that of reference compounds and it is in development for the treatment of bronchial asthma. Yet, it is unclear at this point if it is also being developed for COPD [32]. Pooled data from 9 phase I studies show that ciclesonide or CIC-AP causes negligible cortisol suppression [33].

Improved Anti-Elastases

α_1-Antitrypsin (A_1AT) deficiency is a proven genetic factor in COPD [34]. It is found in a small number of COPD patients who can be treated with intravenous augmentation therapy, and new routes of delivery are currently being sought [35]. Alphagen is an A_1AT gene in a plasmid vector formulated with a cationic lipid that is in development for the treatment of A_1AT deficiency, COPD and cystic fibrosis (CF). In a phase I study of intranasal alphagen in A_1AT-deficient patients, the formulation expressed the A_1AT gene in respiratory epithelium for >1 week and had anti-inflammatory activity. No information has yet been published.

Table 2. PDE4 inhibitors in clinical development

Compound	Indication	Development stage
Cilomilast (Ariflo)	COPD	phase III
	asthma	phase II
Roflumilast	asthma, COPD	phase III
Pumafentrine	asthma	phase II
BAY 19-8004	COPD	phase III
	asthma	phase II
V-11294A	asthma	phase II
SCH 351591	asthma	phase I
YM-976	asthma	phase I
Arofylline	COPD	phase III
ONO-6126	COPD, asthma	phase II
IC-485	COPD, RA	phase II
AWD-12-281	asthma, COPD	phase II
CT-2820	asthma, COPD	phase I
L-826141	asthma, COPD	phase I

See text for explanations on each compound. Modified from Giembycz [2].

New Compounds

For the purpose of this review, the new compounds are classified as follows: anti-inflammatory drugs, anti-oxidants, leukotriene modifiers and miscellaneous drugs.

Anti-Inflammatory Drugs

Inflammation has been described in COPD [21–28] and new anti-inflammatory drugs are in clinical develop-

ment. These include PDE4 inhibitors, immunomodulators, and neurogenic-peptide receptor antagonists.

There are a number of PDE4 inhibitors in development (table 2). The current hypothesis is that an increase of cyclic AMP (cAMP) would lead to better control of the inflammation present in COPD. PDE4 is the predominant PDE type expressed in neutrophils, CD8+ cells and macrophages, all of which seem to be associated with COPD [21–28]. Inhibition of PDE4 increases cAMP in the cytosol. One of these selective PDE4 inhibitors, cilomilast, has shown mixed results in 4 large phase III clinical trials and has been granted an approvable letter by the FDA. It is likely that FDA approval is awaiting the results of ongoing trials or the conduct of studies longer than 6 months, with more end points in addition to FEV_1. Cilomilast improved FEV_1 by 30 ml and reduced exacerbations in 2 of the 4 large trials conducted [36]. Roflumilast, another PDE4 inhibitor, is also in phase III clinical trials and has shown benefits not only in COPD, but also in asthma. It is given once a day and appears to exhibit a better safety profile than cilomilast. Roflumilast elicited a difference of 97 ml in FEV_1 versus placebo in COPD, which is comparable to the improvements in trough FEV_1 conferred by bronchodilators [37].

A number of other PDE4 inhibitors are in clinical development, yet no scientific publications are available. ONO-6126 is an inhibitor of PDE4, in development as an oral tablet formulation for the treatment of asthma and COPD. It has a dual mode of action, inhibiting airway inflammation and inducing bronchodilatation. It is in phase II trials in Europe for bronchial asthma and is being studied in the US for COPD. IC-485 is the lead compound in a series of oral selective PDE4 inhibitors, in development for the treatment of COPD and rheumatoid arthritis. Arofylline is a PDE4 inhibitor that had an ED_{50} of 0.023 times that of theophylline in the anesthetized guinea pig model of bronchoconstriction. On the bronchomotor tone of isolated human bronchus, arofylline had an EC_{25} of 0.1 times that of theophylline. In a double-blind, placebo-controlled phase III trial in 141 patients with moderate to severe COPD, inhaled arofylline 90 mg for 3 months improved FEV_1 and reduced the incidence of exacerbations to 15.3%, compared with 35.4% in the placebo group. The most common adverse events were transient gastrointestinal effects. A slow-release oral formulation is in phase III trials. AWD-12-281 is a selective PDE4 inhibitor in development for rhinitis, asthma and COPD. It is in phase II trials for allergic rhinitis (intranasal formulation) and for asthma and COPD (inhaled formulation). In sensitized mice, 5 × 60 mg/kg intraperitoneal doses inhibited antigen-induced eosinophil recruitment to levels seen in naive mice, and also reduced bronchial hyperreactivity. The emetic dose was 710 mg/kg given intravenously. In vitro, it was selective for PDE4 with an IC50 of 7 nmol/l, and in cell assays it inhibited the release of pro-inflammatory cytokines (GM-CSF and TNF-α) and histamine [38–41]. CT-2820 and L-826141 are other PDE4 inhibitors under investigation for the treatment of asthma and COPD. Phase II trials of a previous once-daily oral PDE4 inhibitor in asthma and COPD were stopped after a patient developed hemorrhagic colitis. Phase I testing of back-up compounds is ongoing.

Immunomodulators of potential therapeutic relevance include: NF-κB inhibitors, chemokine inhibitors, p38 mitogen-activated protein (MAP) inhibitors, PI-3K inhibitors, adhesion molecule inhibitors, IL-10 and monoclonal antibodies against TNF-α (table 3). Of all these, monoclonal antibodies against IL-8 and TNF-α seem to be the farthest along in clinical development [41].

RDP-58 is an orally active, rationally designed decapeptide inhibitor of TNF-α mRNA translation that may have potential as an inhaled treatment for respiratory conditions such as asthma, COPD and pulmonary fibrosis. It prevents translation of the TNF protein rather than binding to the protein to inhibit function. RDP-58 reduces inflammation by targeting TRAFYK, a TRAF6/MyD88/IRAK protein complex implicated in several inflammatory diseases [42].

AZD 8309 is a chemokine receptor antagonist that is being developed as an anti-inflammatory agent. It is in phase I clinical development for the treatment of rheumatoid arthritis. Preclinical development is underway in COPD. No clinical trials have been reported.

CGH 2466 is an anti-inflammatory agent with multiple mechanisms of action. It is an inhibitor of PDE4 and p38 mitogen-activated protein kinase and is an antagonist at adenosine receptors. The compound is administered as an intranasal preparation in preclinical studies for asthma and COPD. In vitro, CGH 2466 inhibited the enzymes PDE4 and p38 MAP kinase, and functioned as an antagonist at adenosine A2b receptors, with IC_{50} values of 40, 95 and 63 nmol/l, respectively. In vivo, intranasal CGP 2466 inhibited both neutrophilic (induced by lipopolysaccharide) and eosinophilic (induced by ovalbumin) lung inflammation in mice, with ED_{50} values in the range of 1–5 mg/kg [43].

GSK-681323 is a p38 MAP kinase inhibitor, under development for the treatment of atherosclerosis. COPD

Table 3. Immunomodulators potentially useful in COPD

Compound	Mechanism of action	Comments	References
Hypocstoxide	selective inhibitor of NF-κB kinase	increased sepsis in animal models	72
Anti-IL8 mAb	reduction of neutrophilic inflammation	efficacy shown in animal model	73
CXCR2 inhibitors	reduction of neutrophilic chemotaxis	more useful than CxCR1 antagonists	74
CCR2 antagonists	reduction of monocyte recruitment		75
IL-10	anti-inflammatory	in development for inflammatory bowel disease, psoriasis and rheumatoid arthritis	76

See text for explanations on each compound.

and rheumatoid arthritis. No clinical trials have been reported.

A number of studies indicated that selectin-mediated rolling of immune cells along vascular endothelium is implicated in acute inflammation. OC 229648, an imidazole, is a selectin inhibitor in development in asthma and chronic obstructive pulmonary disease [44]. The tachykinins substance P and neurokinin (NK) A are found within airway nerves and immune cells. Both tachykinin NK-1 and NK-2 receptors are involved in the bronchoconstriction and the pro-inflammatory changes induced by substance P and NKA. Tachykinin NK-1 and NK-2 receptor antagonists are active in various animal models of allergic asthma and chronic bronchitis. It is possible that dual NK-1/NK-2 and triple NK-1/NK-2/NK-3 tachykinin receptor antagonists have potential in the treatment of obstructive airway diseases [45, 46]. CS-003 is a tachykinin receptor antagonist in development for the oral treatment of COPD. It is an antagonist of NK-1, 2 and 3, and is currently in phase II trials. DNK-333 is an orally active dual antagonist of NK-1 and NK-2 receptors in development for the treatment of rhinitis, asthma and COPD. In a 3-center, randomized, placebo-controlled cross-over study in 19 mild asthmatics, single doses of 100 mg administered orally at 1 and 10 h post-NKA challenge resulted in a significant shift of the dose-response curve for NKA at the 1-hour time point. DNK-333 was well tolerated, with no significant adverse events. Talnetant (SB-223412) is another orally active selective NK-3 antagonist in development for the treatment of COPD.

Antioxidants

Oxidative stress is increased in patients with COPD [47, 48]. N-acetyl cysteine provides cysteine for the enhanced production of glutathione and has antioxidant effects in vitro and in vivo. Studies with oral N-acetyl cysteine in COPD suggest small but significant reductions in the incidence of exacerbations [49–51]. More effective antioxidants, including stable glutathione compounds, are now in development for clinical use. For example, BXT-51072 is the lead compound in a series of small-molecule glutathione peroxidase mimics that accelerate the metabolism of peroxides and is a potent inhibitor of NF-kB. It prevents oxidative damage and downregulates the inflammatory response [35].

In addition to oxidative stress, increased nitric oxide release via inducible nitric oxide synthetase is present in the airways of COPD patients [52–54]. *L*-N-(1-imminoethyl) lysine is one selective inhibitor of inducible nitric oxide synthetase that causes a profound and long-lasting reduction in exhaled nitric oxide [55].

Leukotriene Modifiers

A number of leukotriene modifiers are being tried in COPD. Yet, few publications are available. CJ-13610 is a 5-lipoxygenase inhibitor in development for the treatment of asthma and COPD, and a multicenter, randomized, double-blind phase II trial has been conducted in patients with COPD. Orally active amelubant (BIIL-284) is an unusually potent and long-acting new leukotriene B_4 (LTB_4) receptor antagonist that is in clinical development as a novel anti-inflammatory drug for CF, COPD and asthma [56]. BIIL-284 is a prodrug and has negligible binding to the LTB_4 receptor. However, ubiquitous esterases metabolize BIIL-284 into two active metabolites: BIIL-260 and BIIL-315, the glucuronidated form of BIIL-260. BIIL-284 inhibited LTB_4-induced mouse ear inflammation (ED_{50} = 0.008 mg/kg p.o.), LTB_4-induced transdermal chemotaxis in guinea pigs (ED_{50} = 0.03 mg/kg p.o.), LTB_4-induced neutropenia in various species (monkey: ED_{50} = 0.004 mg/kg p.o.), and LTB_4-induced Mac1 expression in monkeys (ED_{50} = 0.05 mg/kg p.o.). Full blockade of LTB_4 receptors over 24 h was achieved after a single oral dose of 0.3 mg/kg BIIL-284, as measured by

LTB_4-induced neutropenia and Mac1 expression in the monkey model.

In a double-blind, randomized cross-over trial in 24 COPD patients, LTB 019 – another LTB_4 receptor antagonist – did not produce statistically significant differences regarding percentage of sputum neutrophils, total cell count in sputum, sputum levels of myeloperoxidase, IL-8 and TNF-α, FEV_1 or use of rescue medication. The plasma concentrations of LTB 019 achieved in the study were similar to the levels that have been shown to prevent ex vivo LTB_4-induced upregulation of neutrophil CD11b/18. Yet these results question the role of LTB_4 as a relevant neutrophil chemo-attractant in vivo in COPD and the approach of LTB_4 receptor blockade as an effective treatment option [57].

Miscellaneous Drugs

DX-890 is a recombinant protein derived from the human protein inter-α-trypsin inhibitor. It is in development for CF, bronchitis, emphysema, asthma and acute respiratory distress syndrome. It is an inhibitor of human neutrophil elastase and is 50 times more potent than previously developed elastase inhibitors [58]. In phase Ia and Ib trials in 50 volunteers, DX-890 in doses of 3.75–15 mg by inhalation was well tolerated, and the active inhibitor was present in bronchoalveolar lavage fluid, indicating therapeutic activity in the lungs of dosed individuals. Phase II trials in CF were ongoing in 2002, and this drug could be launched in 2005 [59].

Midesteine is an elastase inhibitor in development for emphysema. In a double-blind, randomized, placebo-controlled phase III trial in 60 patients with COPD, oral midesteine 500 mg b.i.d. for 4 weeks was well tolerated. There were no signs of modification of biochemical markers of lung destruction, but a subset of treated patients did show a post-treatment reduction of urine desmosine levels [60].

Previous work has shown that all-*trans*-retinoic acid reverses elastase-induced emphysema in rats [61]. Retinoic acid is the bioactive metabolite of vitamin A, and considerable evidence implicates retinoic acid as important signaling molecule during normal lung development, and retinoid signaling elements such as receptors and binding proteins have been described in the developing lung. However, the exact mechanism governing this regeneration is still unknown [62].

The effect of retinoic acid has been further investigated in other adult species such as an elastase-induced emphysema model for acute alveolar destruction and a TNF-α transgenic mouse which exhibits chronic air space enlargement, loss of elastic recoil, increased lung volume and pulmonary hypertension comparable to human pulmonary emphysema. All-*trans*-retinoic acid (2 mg/kg) was injected for 12 successive days after the establishment of emphysema. The effects of treatment were evaluated using physiological and morphometric analyses. In contrast to the rat, administration of all-*trans*-retinoic acid in these murine models did not improve the emphysema. Moreover, worsening of emphysema was observed in TNF-α transgenic mice treated with all-*trans*-retinoic acid. The level of keratinocyte chemoattractant, a CXC chemokine, in bronchoalveolar lavage fluid was increased in TNF-α transgenic mice following retinoic acid treatment. These data raise the possibility that retinoic acid causes deterioration of emphysema by promoting inflammation in this model. In these models, retinoic acid did not show positive effects on emphysema. The effect of retinoic acid in the treatment of pulmonary emphysema remains controversial [63].

Endothelin-1 (ET-1) has been implicated in the pathogenesis of asthma and COPD. During exacerbations of asthma and COPD, ET-1 levels are elevated in bronchoalveolar lavage, serum, sputum and urine [64], and the levels fall with treatment of the exacerbation. Hypoxemia stimulates ET-1 secretion [65]. Nonapneic oxyhemoglobin desaturation associated with sleep has been described in patients with COPD. Once released, ET-1 can act locally to elicit sustained pulmonary artery vasoconstriction, bronchoconstriction and activation of alveolar macrophages [66]. CI-1034 is a highly selective ET-1A antagonist in development for the treatment of COPD [67, 68].

Hypophosphatemia is present in many patients with COPD [69, 70]. Fructose-1,6-diphosphate (FDP) has been developed for the prevention and treatment of respiratory failure resulting from hypophosphatemia and phosphate depletion in patients receiving artificial nutrition after surgery, trauma or severe burns, in the refeeding phase of malnutrition or chronic alcoholism, and in cardiac indications. FDP is a naturally occurring metabolite of the yeast glycolytic pathway and facilitates intracellular build-up of high energy phosphates required for efficient muscular contractility. As such, it may also have potential in the treatment of patients with moderate to severe COPD and in weaning patients from mechanical ventilation. Administration of FDP to 45 malnourished COPD patients produced a significant increase in PImax (43.0 ± 18.3 cm H_2O before treatment vs. 49.8 ± 14.9 cm H_2O after treatment; $p < 0.005$) [71]. In patients with respiratory failure due to COPD or malnutrition, intravenous FDP in doses

of 100–150 mg/kg/day over 5–6 days significantly improved inspiratory power and respiratory endurance, with good systemic and local tolerance [71].

Conclusions

The current therapies for COPD are suboptimal since they are unable to deter the downward trend in pulmonary function [77]. Many new compounds are being discovered, and a subset of these is tested in humans. Until major findings occur to further our understanding of COPD and surrogate markers become available, the hopes reside on the new long-acting bronchodilators and anti-inflammatory medications either inhaled or oral. PDE4 inhibitors appear to be the first candidates to be added to the COPD therapies in the near future.

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(71) Applicant *(for all designated States except US)*: **ALMIRALL PRODESFARMA S.A.** [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GRAS ESCARDO, Jordi** [ES/ES]; c/ Roger de flor 3, Atico, E-08018 Barcelona (ES). **LLENAS CALVO, Jesus** [ES/ES]; Ganduxer 39, 5° 2ª, E-08021 Barcelona (ES). **RYDER, Hamish** [GB/ES]; Pasaje Barnadas, 18, E-08190 La Floresta Sant Cugat del Vallés (Barcelo, na) (ES). **ORVIZ DIAZ, Pio** [ES/ES]; Avda. Piscina 37, E-08198 Saint Cugat del Vallès (Barcelona) (ES).

(74) Agent: **R C SRINIVASAN**; J. A. Kemp & Co, 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

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(54) Title: COMBINATIONS COMPRISING ANTIMUSCARINIC AGENTS AND PDE4 INHIBITORS

(57) Abstract: A combination which comprises (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid.

COMBINATIONS COMPRISING ANTIMUSCARINIC AGENTS AND PDE4 INHIBITORS

This application claims priority from Spanish patent application number P200401312 filed 31 May 2004, which is incorporated by reference.

The present invention relates to new combinations of certain antimuscarinic agents with PDE4 inhibitors and their use in the treatment of respiratory disorders.

BACKGROUND OF THE INVENTION

PDE4 inhibitors and antimuscarinic agents, in particular antagonists of M3 muscarinic receptors, are two classes of drugs useful in the treatment of respiratory disorders such as, asthma or Chronic Obstructive Pulmonary Diseases (COPD).

Although PDE4 inhibitors and antimuscarinic agents may be effective therapies, there exists a clinical need for asthma and COPD therapies having potent and selective action and having an advantageous profile of action.

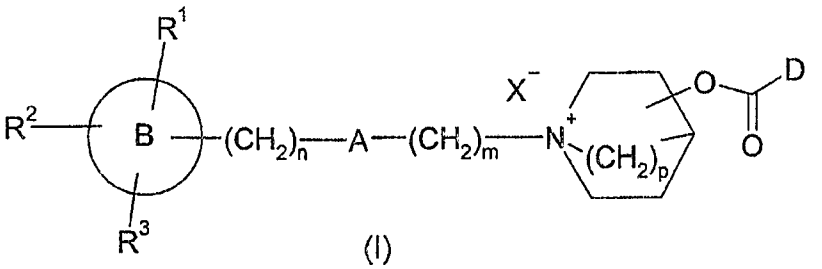
It is known that both classes of drugs can be used in combination

Combinations of drugs in which the active ingredients operate via different physiological pathways are known to be therapeutically useful. Frequently, the therapeutic advantage arises because the combination can achieve a therapeutically useful effect using lower concentrations of each active component. This enables the side-effects of the medication to be minimised. Thus, the combination can be formulated so that each active ingredient is present at a concentration which is subclinical in cells other than the target disease cells. The combination is nevertheless therapeutically effective in target cells which respond to both ingredients.

DESCRIPTION OF THE INVENTION

Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory or obstructive diseases of the respiratory tract if an antimuscarinic of formula (I) used with one or more PDE4 inhibitors. In view of this effect the pharmaceutical combinations according to the invention can be used in smaller doses than would be the case with the individual compounds used in monotherapy in the usual way. This reduces unwanted side effects such as may occur when PDE4 inhibitors or antimuscarinics of formula (I) are administered alone.

The present invention accordingly provides a combination which comprises (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors of formula (I)



(I)

wherein:

B is a phenyl ring, a 5 to 10 membered heteroaromatic group containing one or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3] dioxolyl or biphenyl group;

R^1, R^2 and R^3 each independently represent a hydrogen atom or halogen atom, or a hydroxy group, or a phenyl, $-OR^4$, $-SR^4$, $-NR^4R^5$, $-NHCOR^4$, $-CONR^4R^5$, -CN, $-NO_2$, $-COOR^4$ or $-CF_3$ group, or a straight or branched lower alkyl group which may optionally be substituted, for example, with a hydroxy or alkoxy group, wherein R^4 and R^5 each independently represent a hydrogen atom, straight or branched lower alkyl group or together form an alicyclic ring ; or R^1 and R^2 together form an aromatic, alicyclic or heterocyclic ring,

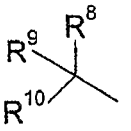
n is an integer from 0 to 4;

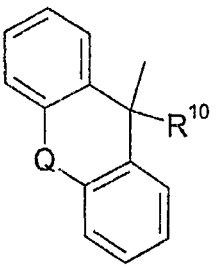
A represents a $-CH_2-$,$-CH=CR^6-$, $-CR^6=CH-$, $-CR^6R^7-$, -CO-, -O-, -S-, -S(O)-, $-SO_2-$ or $-NR^6-$ group, wherein R^6 and R^7 each independently represent a hydrogen atom, straight or branched lower alkyl group or R^6 and R^7 together form an alicyclic ring;

m is an integer from 0 to 8 provided that when m = 0, A is not $-CH_2-$;

p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons ;

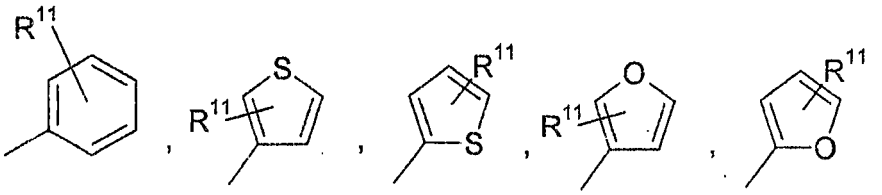
D represents a group of formula i) or ii):

i) 

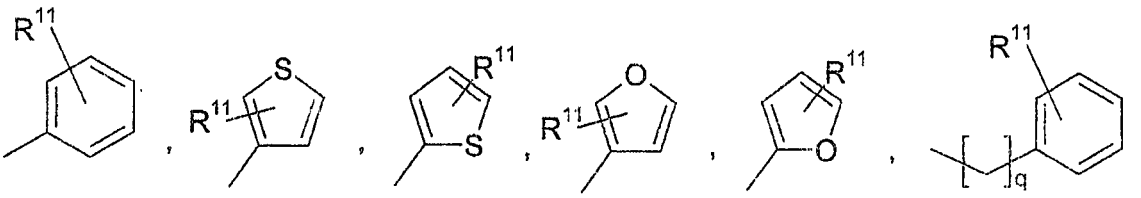
ii) 

wherein R^{10} represents a hydrogen atom, a hydroxy or methyl group or a $-CH_2OH$ group;

R^8 represents



R^9 represents an alkyl group of 1 to 7 carbon atoms, an alkenyl group containing 2 to 7 carbon atoms, an alkynyl group containing 2 to 7 carbon atoms, a cycloalkyl group of 3 to 7 carbon atoms, or a group selected from:



wherein R^{11} represents a hydrogen or halogen atom, a straight or branched substituted or unsubstituted lower alkyl group, a hydroxy group, an alkoxy group, a nitro group, a cyano group, $-CO_2R^{12}$, $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are identical or different and are selected from hydrogen and straight or branched lower alkyl groups

and Q represents a single bond, $-CH_2-$, $-CH_2-CH_2-$, $-O-$, $-O-CH_2-$, $-S-$, $-S-CH_2-$ or $-CH=CH-$; and

X represents a pharmaceutically acceptable anion of a mono or polyvalent acid optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof.

The compounds of the present invention represented by the formula (I) described above, which may have one or more asymmetric carbons, include all the possible stereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

As used herein, an alkyl group is typically a lower alkyl group. A lower alkyl group preferably contains 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms. In particular it is preferred that such an alkyl group is represented by a methyl, ethyl, propyl, including i-propyl, or butyl including a n-butyl, sec-butyl and tert-butyl group. An alkyl group containing 1 to 7 carbon atoms as mentioned herein may be a C_{1-4} alkyl group as mentioned above or a straight or branched pentyl, hexyl or heptyl group.

Alkenyl groups having 2 to 7 carbon atoms mentioned herein are straight or branched groups such as ethenyl, or straight or branched propenyl, butenyl, pentenyl, hexenyl or heptenyl. The double bond may be in any position in the alkenyl group, such as on the terminal bond.

Alkynyl groups having 2 to 7 carbon atoms mentioned herein are straight or branched groups such as ethynyl, propynyl or straight or branched butynyl, pentynyl, hexynyl or heptynyl. The triple bond may be in any position in the alkynyl group, such as on the terminal bond.

Alkoxy groups mentioned herein are typically lower alkoxy groups, that is groups containing from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight. Preferred alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy and t-butoxy.

Alicyclic groups or rings as mentioned herein, unless otherwise specified, typically contain from 3 to 8 carbon atoms, preferably from 3 to 6 carbon atoms. Alicyclic rings of 3 to 6 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

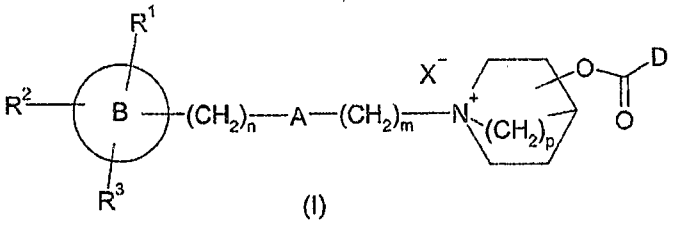
The aromatic ring as mentioned herein typically contains from 5 to 14, preferably 5 to 10 carbon atoms. Examples of aromatic groups include cyclopentadienyl, phenyl and naphthalenyl.

A heterocyclic or heteroaromatic group mentioned herein is typically a 5 to 10 membered group, such as a 5, 6 or 7 membered group, containing one or more heteroatoms selected from N, S and O. Typically, 1, 2, 3 or 4 heteroatoms are present, preferably 1 or 2 heteroatoms. A heterocyclic or heteroaromatic group may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. Examples of heterocyclic groups include piperidyl, pyrrolidyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl and thienyl. Examples of heteroaromatic groups include pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, benzothiazolyl, pyridinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, triazolyl and pyrazolyl.

As used herein a halogen atom includes a fluorine, chlorine, bromine or iodine atom, typically a fluorine, chlorine or bromine atom.

Examples of pharmaceutically acceptable anions of mono or polyvalent acids are the anions derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or organic acids such as methanosulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid or maleic acid. Furthermore, mixtures of the aforementioned acids can be used.

Preferably, the M3 antagonists according to the present invention are those having formula (I)

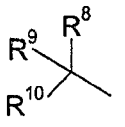


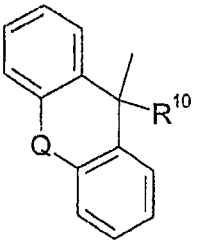
(I)

wherein:

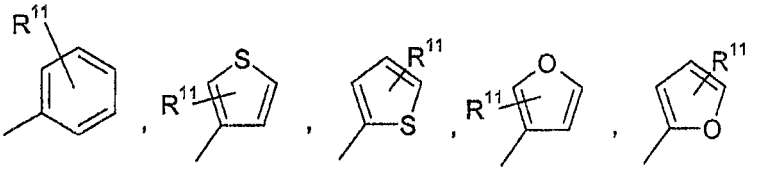
- B is a phenyl ring, a C_4 to C_8 heteroaromatic group containing one or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;
- R^1, R^2 and R^3 each independently represent a hydrogen atom or halogen atom, or a hydroxy group, or a phenyl, $-OR^4$, $-SR^4$, $-NR^4R^5$, $-NHCOR^4$, $-CONR^4R^5$, -CN, $-NO_2$, $-COOR^4$ or $-CF_3$ group, or a straight or branched lower alkyl group which may optionally be substituted, for example, with a hydroxy or alkoxy group, wherein R^4 and R^5 each independently represent a hydrogen atom, straight or branched lower alkyl group or together form an alicyclic ring ; or R^1 and R^2 together form an aromatic, alicyclic or heterocyclic ring,
- n is an integer from 0 to 4;
- A represents a $-CH_2-$, $-CH=CR^6-$, $-CR^6=CH-$, $-CR^6R^7-$, -CO-, -O-, -S-, -S(O)-, $-SO_2-$ or $-NR^6-$ group, wherein R^6 and R^7 each independently represent a hydrogen atom, straight or branched lower alkyl group or R^6 and R^7 together form an alicyclic ring;
- m is an integer from 0 to 8 provided that when m = 0, A is not $-CH_2-$;

- p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons ;
- D represents a group of formula i) or ii):

i) 

ii) 

wherein R^{10} represents a hydrogen atom, a hydroxy or methyl group; and R^8 and R^9 each independently represent

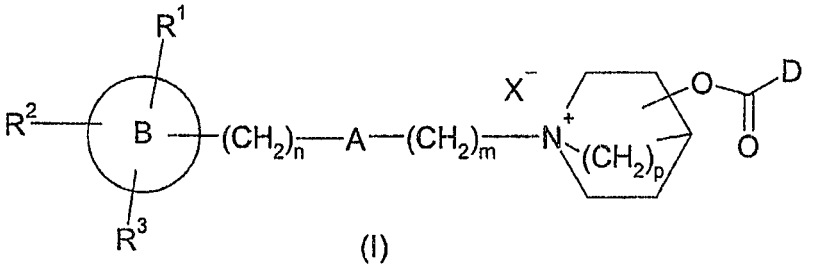


wherein R^{11} represents a hydrogen or halogen atom or a straight or branched lower alkyl group and Q represents a single bond, $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ or -CH=CH-; and

- X represents a pharmaceutically acceptable anion of a mono or polyvalent acid

optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof.

It is a preferred embodiment of the present invention a combination which comprises (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors of formula (I)



(I)

wherein:

B represents a phenyl group;

R^1, R^2 and R^3 represent a hydrogen atom

m is an integer from 1 to 3;

n is zero;

A is a group selected from –O- and -CH_2-;

p is an integer from 1 to 2; the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons ;

-OC(O)D is selected from 2-hydroxy-2,2-dithien-2-ylacetoxy, 9H-xanthene-9-carbonyloxy and (2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy; and

X represents a pharmaceutically acceptable anion of a mono or polyvalent acid optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof.

The M3 antagonists of the present invention represented by the formula (I) described above, which may have one or more asymmetric carbons, include all the possible stereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

Those M3 antagonists in which the ester group, -OC(O)D, is attached to the ring comprising the quaternary nitrogen atom at the 3 position are especially preferred.

The M3 antagonists described can optionally be used in the form of their pure enantiomers, mixtures thereof or their racemates. Typically the carbon atom carrying the –OC(O)D group has the (R) configuration.

It is especially preferred that one of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide, (3R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane bromide and (3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide is used as an M3 antagonist of the invention.

The present invention accordingly provides a combination which comprises (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid. Typically the antagonist of M3 muscarinic receptors is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide.

Typically the combination contains the active ingredients (a) and (b) forming part of a single pharmaceutical composition.

For the avoidance of doubt, the formula depicted above and the term 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane is meant to embrace the salts in dissociated, partially dissociated or undissociated form, for example in aqueous solution. The different salts of the compound may exist in the form of solvates, i.e. in the form of hydrates and all these forms are also within the scope of the present invention. Furthermore the different salts and solvates of the compound may exist in amorphous form or in the form of different polymorphs within the scope of the present invention.

Also provided is a product comprising (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) as a combined preparation for simultaneous, separate or sequential use in the treatment of a human or animal patient. Typically the product is for simultaneous, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient.

The present invention further provides the use of (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide), for the preparation of a medicament for simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient.

Also provided is the use of (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) for the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in combination with (a) a PDE4 inhibitor for the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient.

Also provided is the use of (a) a PDE4 inhibitor for the preparation of a medicament for use in the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient by simultaneous, concurrent, separate or sequential co-administration with (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide).

The invention also provides the use of (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide), for the preparation of a medicament for use in the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient by simultaneous, concurrent, separate or sequential co-administration with (a) a PDE4 inhibitor.

The present invention further provides a method of treating a human or animal patient suffering from or susceptible to a respiratory disease which responds to M3 antagonism which method comprises simultaneously, concurrently, separately or sequentially administering to said patient an effective amount of (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and (a) a PDE4 inhibitor.

Typically said respiratory disease is asthma, acute or chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), bronchial hyperreactivity or rhinitis, in particular asthma or chronic obstructive pulmonary disease (COPD).

Preferably said patient is human.

Also provided is a pharmaceutical composition comprising (a) a PDE4 inhibitor; and (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono

or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide), in association with (c) a pharmaceutically acceptable carrier or diluent.

The invention also provides a kit of parts comprising (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) together with instructions for simultaneous, concurrent, separate or sequential use in combination with (a) a PDE4 inhibitor for the treatment of a human or animal patient suffering from or susceptible to a respiratory disease which responds to M3 antagonism.

Further provided is a package comprising (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and (a) a PDE4 inhibitor for the simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism.

Further provided is a combination, product, kit of parts or package as hereinabove described wherein such combination, product, kit of parts or package further comprises (c) another active compound selected from: (a) β2 agonist, (b) cortiocosteroids, (c) leukotriene D4 antagonists, (d) inhibitors of egfr-kinase, (e) p38 kinase inhibitors and (f) NK1 receptor agonists for simultaneous, separate or sequential use. Typically the additional active compound (c) is selected from the group consisting of (a) β2 agonists and (b) cortiocosteroids.

It is a embodiment of the present invention that the combination, product, kit of parts or package comprise (b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and (a) a PDE4 inhibitor as the sole active compounds.

It is also an embodiment of the present invention the use of b) an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and (a) a PDE4 inhibitor without any other active compound for the preparation of a medicament for simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism in a human or animal patient.

Examples of PDE4 inhibitors to be used in the combinations of the present invention are selected from the group comprising Theophylline, Drotaverine hydrochloride, Cilomilast, Roflumilast, Denbufylline, Rolipram, Tetomilast, Enprofylline, Arofylline, Cipamfylline, Tofimilast, Filaminast, Piclamilast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, Mesopram, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide, CDC-801 (ex. Celgene), CC-1088 (ex. Celgene), Lirimilast, ONO-6126 (ex. Ono), CC-10004 (ex. Celgene), MN-001 (ex. Kyorin), KW-4490 (ex. Kyowa Hakko), Benafentrine dimaleate, Zardaverine, Tolafentrine, 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride, N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide, 4-(3-Chlorophenyl)-1,7-diethylpyrido[2,3-d]pyrimidin-2(1H)-one, N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-

yl]pyridine-4-carboxamide, 3,5-Dichloro-4-[8-methoxy-2-(trifluoromethyl)quinolin-5-ylcarboxamido]pyridine-1-oxide, NIK-616 (ex. Nikken Chemicals), CDC-998 (ex. Celgene), Project PDE 4 (ex. Celltech), EHT-0202 (ex. ExonHit Therapeutics), 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one, ND-1251 (ex. Neuro3d), GRC-3886 (ex. Glenmark Pharmaceuticals), Atizoram, Pumafentrine, 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one, 2-[4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]pyridin-2-yl]-4-(3-pyridyl)phthalazin-1(2H)-one hydrochloride, 1-Ethyl-8-methoxy-3-methyl-5-propylimidazo[1,5-a]pyrido[3,2-e]pyrazin-4(5H)-one, 4-(3-Bromophenyl)-1-ethyl-7-methyl-1,8-naphthyridin-2(1H)-one, N-[9-Amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin- 3(R)-yl]pyridine-3-carboxamide, hydroxypumafentrine and the compounds exemplified in PCT patent applications number WO 03/097613, WO, 2004/058729 and WO 2005/

Preferred PDE4 inhibitors under the present invemtion are: Theophylline, Drotaverine hydrochloride, Cilomilast, Roflumilast, Denbufylline, Rolipram, Tetomilast, Enprofylline, Arofylline, Cipamfylline, Tofimilast, Filaminast, Piclamilast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, Mesopram, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide, CDC-801 (ex. Celgene), CC-1088 (ex. Celgene), Lirimilast, ONO-6126 (ex. Ono), CC-10004 (ex. Celgene), MN-001 (ex. Kyorin) and the compounds exemplified in PCT patent applications number WO 03/097613, WO, 2004/058729 and WO 2005/.

Still more preferred PDE4 inhibitors under the present invention are : Theophylline, Drotaverine hydrochloride, Cilomilast, Roflumilast, Denbufylline, Rolipram, Tetomilast, N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide, Enprofylline, Arofylline and the compounds exemplified in PCT patent applications number WO 03/097613, WO, 2004/058729 and WO 2005/. The most preferred PDE4 inhibitors are Cilomilast, Roflumilast, Denbufylline, Tetomilast and the compounds exemplified in PCT patent applications number WO 03/097613, WO,

2004/058729 and WO 2005/, in special Cilomilast, Roflumilast, Denbufylline, and Tetomilast most preferably Roflumilast and Cilomilast.

Pharmaceutically acceptable salt forms of the combinations of compounds of the present invention are prepared for the most part by conventional means. Where the component compound contains a carboxylic acid group, a suitable salt thereof may be formed by reacting the compound with an appropriate base to provide the corresponding base addition salt. Examples of such bases are alkali metal hydroxides including potassium hydroxide, sodium hydroxide, and lithium hydroxide; alkaline earth metal hydroxides such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, e.g., potassium ethanolate and sodium propanolate, and various organic bases such as piperidine, diethanolamine, and N-methylglutamine. Also included are the aluminum salts of the component compounds of the present invention.

For certain component compounds, acid addition salts may be formed by treating said compounds with pharmaceutically acceptable organic and inorganic acids, e.g., hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, etc.; and alkyl- and monoarylsulfonates such as ethanesulfonate, toluenesulfonate, and benzenesulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate, etc.

Accordingly, the pharmaceutically acceptable acid addition salts of the component compounds of the present invention include, but are not limited to: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, *iso*-

butyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, and phthalate.

Particularly preferred examples of pharmacologically acceptable acid addition salts of the PDE4 inhibitors are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts of the PDE4 inhibitors.

In the pharmaceutical compositions according to the invention, the PDE4 inhibitors may be present in the form of their racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g., by chromatography on chiral phases, etc.).

A preferred embodiment of the present invention is a combination of an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) with a PDE4 inhibitor selected from Cilomilast, Roflumilast, Denbufylline, and Tetomilast. Even more preferred is the combination 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) with cilomilast and the combination of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-

azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) with roflumilast.

A particularly preferred embodiment of the present invention is a combination of an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) with a PDE4 inhibitor selected from cilomilast, roflumilast, denbufylline, and tetomilast.

Another embodiment of the present invention is a combination of an M3 antagonist selected from the group consisting of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide, (3R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane bromide, and (3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide with a PDE4 inhibitor selected from cilomilast, roflumilast, denbufylline, and tetomilast.

According to one embodiment of the invention the antagonist of M3 muscarinic receptors is a compound of formula (I) and in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and the PDE4 inhibitor is roflumilast.

According to another embodiment of the invention the antagonist of M3 muscarinic receptors is a compound of formula (I) and in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a

pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and the PDE4 inhibitor is cilomilast.

The combinations of the invention can optionally comprise one or more additional active substances which are known to be useful in the treatment of respiratory disorders, such as β2-agonists, corticosteroids or glucocorticoids, leukotriene D4 inhibitors, inhibitors of egfr-kinase, p38 kinase inhibitors and/or NK1-receptor antagonists.

The preferred β2-agonists to be used in the combinations of the invention are: arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaprotenerol, nolomirole, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, rimoterol, salbutamol, salmefamol, salmeterol, sibenadet, sotenerot, sulfonterol, terbutaline, tiaramide, tulobuterol, GSK-597901, GSK-159797, GSK-678007, GSK-642444, GSK-159802, HOKU-81, (-)-2-[7(S)-[2(R)-Hydroxy-2-(4-hydroxyphenyl)ethylamino]-5,6,7,8-tetrahydro-2-naphthyloxy]-N,N-dimethylacetamide hydrochloride monohydrate, carmoterol, QAB-149 and 5-[2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulfonyl} ethyl]amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzylamino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N -dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert-butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol optionally in the form of their

racemates, their enantiomers, their diastereomers, and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts.

Examples of suitable corticosteroids and glucocorticoids that can be combined with M3-antagonists and PDE4 inhibitors are prednisolone, methylprednisolone, dexamethasone, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, deprodone propionate, fluticasone propionate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate and hydrocortisone probutate.

Examples of suitable LTD4 antagonists that can be combined with M3 antagonists and PDE4 inhibitors are tomelukast, Ibudilast, pobilukast, pranlukast hydrate, zafirlukast, ritolukast, verlukast, sulukast, cinalukast, iralukast sodium, montelukast sodium, 4-[4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propylsulfonyl]phenyl]-4-oxobutyric acid, [[5-[[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio]-1,3,4-thiadiazol-2-yl]thio]acetic acid, 9-[(4-Acetyl-3-hydroxy-2-n-propylphenoxy)methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one, 5-[3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl]-8-(N,N-dimethylcarbamoyl)-4,6-dithiaoctanoic acid sodium salt; 3-[1-[3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl]-1-[3-(dimethylamino)-3-oxopropylsulfanyl]methylsulfanyl]propionic acid sodium salt, 6-(2-Cyclohexylethyl)-[1,3,4]thiadiazolo[3,2-a]-1,2,3-triazolo[4,5-d]pyrimidin-9(1H)-one, 4-[6-Acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid, (R)-3-Methoxy-4-[1-methyl-5-[N-(2-methyl-4,4,4-trifluorobutyl)carbamoyl]indol-3-ylmethyl]-N-(2-methylphenylsulfonyl)benzamide, (R)-3-[2-Methoxy-4-[N-(2-methylphenylsulfonyl)carbamoyl]benzyl]-1-methyl-N-

(4,4,4-trifluoro-2-methylbutyl)indole-5-carboxamide, (+)-4(S)-(4-Carboxyphenylthio)-7-[4-(4-phenoxybutoxy)phenyl]-5(Z)-heptenoic acid and the compounds claimed in the PCT patent application number PCT/EP03/12581.

Examples of suitable inhibitors of egfr-kinase that can be combined with M3 antagonists and PDE4 inhibitors are palifermin, cetuximab, gefitinib, repifermin, erlotinib hydrochloride, canertinib dihydrochloride, lapatinib, and N-[4-(3-Chloro-4-fluorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)-2(E)-butenamide.

Examples of suitable p38 kinase inhibitors that can be combined with M3 antagonists and PDE4 inhibitors are chlormethiazole edisylate, doramapimod, 5-(2,6-Dichlorophenyl)-2-(2,4-difluorophenylsulfanyl)-6H-pyrimido[3,4-b]pyridazin-6-one, 4-Acetamido-N-(tert-butyl)benzamide, SCIO-469 (described in Clin Pharmacol Ther 2004, 75(2): Abst PII-7 and VX-702 described in Circulation 2003, 108(17, Suppl. 4): Abst 882.

Examples of suitable NK1-receptor antagonists that can be combined with M3 antagonists and PDE4 inhibitors are nolpitantium besilate, dapitant, lanepitant, vofopitant hydrochloride, aprepitant, ezlopitant, N-[3-(2-Pentylphenyl)propionyl]-threonyl-N-methyl-2,3-dehydrotyrosyl-leucyl-D-phenylalanyl-allo-threonyl-asparaginyl-serine C-1.7-O-3.1 lactone, 1-Methylindol-3-ylcarbonyl-[4(R)-hydroxy]-L-prolyl-[3-(2-naphthyl)]-L-alanine N-benzyl-N-methylamide, (+)-(2S,3S)-3-[2-Methoxy-5-(trifluoromethoxy)benzylamino]-2-phenylpiperidine, (2R,4S)-N-[1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperidin-4-yl]quinoline-4-carboxamide, 3-[2(R)-[1(R)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3(S)-(4-fluorophenyl)morpholin-4-ylmethyl]-5-oxo-4,5-dihydro-1H-1,2,4-triazole-1-phosphinic acid bis(N-methyl-D-glucamine) salt; [3-[2(R)-[1(R)-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3(S)-(4-fluorophenyl)-4-morpholinylmethyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonic acid 1-deoxy-1-(methylamino)-D-glucitol (1:2) salt, 1'-[2-[2(R)-(3,4-Dichlorophenyl)-4-(3,4,5-trimethoxybenzoyl)morpholin-2-yl]ethyl]spiro[benzo[c]thiophen-1(3H)-4'-piperidine] 2(S)-oxide hydrochloride and the compound CS-003 described in Eur Respir J 2003, 22(Suppl. 45): Abst P2664.

The combinations of the invention may be used in the treatment of any disorder which is susceptible to amelioration by simultaneous, concomitant or sequential antagonism of M3 muscarinic receptors and inhibition of phosphodiesterase 4. Thus, the present application encompasses methods of treatment of these disorders, as well as the use of the combinations of the invention in the manufacture of a medicament for the treatment of these disorders.

Preferred examples of such disorders are those respiratory diseases, wherein the use of bronchodilating agents is expected to have a beneficial effect, for example asthma, acute or chronic bronchitis, emphysema, or Chronic Obstructive Pulmonary Disease (COPD).

The active compounds in the combination, i.e. the M3 antagonist of the invention, the PDE4 inhibitors and any other optional active compounds may be administered together in the same pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

In one embodiment the present invention provides a kit of parts comprising an antagonist of M3 muscarinic receptors of formula (I) together with instructions for simultaneous, concurrent, separate or sequential use in combination with a PDE4 inhibitor for the treatment of a respiratory disease which responds to M3 antagonism.

In a preferred embodiment the present invention provides a kit of parts comprising an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) together with instructions for simultaneous, concurrent, separate or sequential use in combination with a PDE4 inhibitor for the treatment of a respiratory disease which responds to M3 antagonism.

In another embodiment the present invention provides a package comprising an antagonist of M3 muscarinic receptors of formula (I) and a PDE4 inhibitor for the simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism.

In another embodiment the present invention consists of a package comprising an antagonist of M3 muscarinic receptors of formula (I) and in particular an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid (in particular 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide) and a PDE4 inhibitor for the simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism.

In a preferred embodiment of the invention the active compounds in the combination are administered by inhalation through a common delivery device, wherein they can be formulated in the same or in different pharmaceutical compositions.

In the most preferred embodiment the M3 antagonist of the invention and the PDE4 inhibitor are both present in the same pharmaceutical composition and are administered by inhalation through a common delivery device.

In one aspect the invention provides a combination as herein defined characterised in that the active ingredients (a) and (b) form part of a single pharmaceutical composition.

In another aspect the invention provides a process for the production of a pharmaceutical composition as herein defined characterised in that an antagonist of M3 muscarinic receptors, a PDE4 inhibitor and optionally other additives and/or carriers are mixed and processed by methods known per se.

The active compounds in the combination, i.e. the M3 antagonist of the invention, the PDE4 inhibitor and any other optional active compounds may be administered by any suitable route, depending on the nature of the disorder to be treated, e.g. orally (as syrups, tablets, capsules, lozenges, controlled-release preparations, fast-dissolving preparations, lozenges, etc); topically (as creams, ointments, lotions, nasal sprays or aerosols, etc); by injection (subcutaneous, intradermic, intramuscular, intravenous, etc.) or by inhalation (as a dry powder, a solution, a dispersion, etc).

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil- in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, natural, synthetic or semisynthetic oils such as peanut oil and olive oil, glycerine or water with flavouring, sweetener and/or colouring agent.

Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include celluloses, stearates such as magnesium stearate or stearic acid, talc, gelatine, acacia, starches, lactose and sucrose.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, lubricants, inert diluents, lubricating, surface active or dispersing agents. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered blend comprising the active compounds moistened with an inert liquid diluent and optionally dried and sieved. The tablets may optionally be coated or scored and may be formulated so as to provide modified (i.e. slow or controlled) release of the active ingredient therein.

Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatine capsule. Where the composition is in the form of a soft gelatine capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatine capsule.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in different primary packaging systems (such as capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil), for use in an inhaler or insufflator.

Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi- dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

Formulations generally contain a powder mix for inhalation of the compounds of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 2μg and 400 μg of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

For single dose inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients. Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported (e. g. Nielsen et al, 1997).

Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e. g. EP0069715) or disks (e. g. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (e. g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e. g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring slides (e. g.US 5201308 and WO 97/00703) or measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit e. g. EP 0505321, WO 92/04068 and WO 92/04928.

Reproducible dose measuring is one of the major concerns for multi dose inhaler devices.

The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity.

For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high

number of doses in multi- dose devices, powder adhesion onto the inner walls of the air conduits and the de- agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (e. g. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even stricter.

Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers, via which solutions of pharmacologically-active substances can be sprayed under high pressure so that a mist of inhalable particles results. The advantage of these atomisers is that the use of propellant gases can be completely dispensed with.

Such atomisers are described, for example, in PCT Patent Application No. W0 91/14468 and International Patent Application No. WO 97/12687, reference here being made to the contents thereof.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the active ingredient (s) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1, 1, 2-tetrafluoroethane, 1,1, 1,2, 3,3, 3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be free from excipients other than the propellant or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvens eg ethanol. Pressurised formulations will generally be

retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μ, preferably 2-5μ. Particles having a size above 20μ are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation or supercritical fluid techniques. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

Achieving a high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient such as lactose, manitol or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, preferably crystalline alpha lactose monohydrate.

Pressurized aerosol compositions will generally be filled into canisters fitted with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e. g. a fluorocarbon polymer as described in W096/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

Typical compositions for nasal delivery include those mentioned above for inhalation and further include non-pressurized compositions in the form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, mucoadhesive agents, tonicity modifying agents and viscosity modifying agents which may be administered by nasal pump.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

The proportions in which (a) the PDE4 inhibitor and (b) the antagonist of M3 muscarinic receptors may be used according to the invention are variable. Active substances (a) and (b) may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds (a) and (b), the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various salt forms. The pharmaceutical combinations according to the invention may contain (a) and (b) generally in a ratio by weight (b):(a) ranging from 1: 5 to 500: 1, preferably from 1: 10 to 400: 1.

The weight ratios specified below are based on the compound (b) expressed as 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and the PDE4 inhibitors roflumilast and cilomilast which are particularly preferred according to the invention.

The pharmaceutical combinations according to the invention may contain (a) and (b) in the case of roflumilast, for example, in a ratio by weight (b):(a) ranging from 1: 10 to 300: 1, preferably from 1: 5 to 200: 1, preferably 1: 3 to 150: 1, more preferably from 1: 2 to 100: 1.

The pharmaceutical compositions according to the invention containing the combinations of (a) and (b) are normally administered so that 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and roflumilast are present together in doses of 0,5 to 5000 μg, preferably from 1 to 2000 μg, more preferably from 5 to 1000 μg, better still from 10 to 800 μg per single dose.

For example, without restricting the scope of the invention thereto, combinations in which 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-

azoniabicyclo[2.2.2]octane bromide is used as (b) and roflumilast is used as (a), the compositions according to the invention may contain for instance from 20 to 1000 μg of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and from 5 to 500 μg of roflumilast.

For example, the active substance combinations according to the invention may contain 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and (a) in the case of cilomilast, in a ratio by weight (b):(a) in the range from about 1: 30 to 400: 1, preferably 1: 25 to 200: 1, preferably 1: 20 to 100: 1, more preferably from 1: 15 to 50: 1.

The pharmaceutical compositions according to the invention containing the combinations of (a) and (b) are usually administered so that 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and cilomilast are present together in dosages of 1 to 10000 μg, preferably from 5 to 5000μg, more preferably from 10 to 2000μg, even more preferably from 20 to 800μg per single dose.

For example, without restricting the scope of the invention thereto, combinations in which 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide is used as (b) and cilomilast is used as (a), the compositions according to the invention may contain for instance from 5 to 5000 μg of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide and from 15 to 300 μg of cilomilast.

The aforementioned examples of possible doses applicable for the combinations according to the invention are to be understood as referring to doses per single application. However, these examples are not be understood as excluding the possibility of administering the combinations according to the invention multiple times. Depending on the medical need patients may receive also multiple inhalative applications. As an example patients may receive the combinations according to the invention for instance two or three times (e. g. two or three puffs with a powder inhaler, an MDI etc) in the morning of each

treatment day. As the aforementioned dose examples are only to be understood as dose examples per single application (i. e. per puff) multiple application of the combinations according to the invention leads to multiple doses of the aforementioned examples. The application of the compositions according to the invention can be for instance once a day, or depending on the duration of action of the anticholinergic agent twice a day, or once every 2 or 3 days.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit contains suitably from 20 μg to 1000 μg and preferably from 50 μg to 300 μg of an M3 antagonist according to the invention or a pharmaceutical acceptable salt thereof and 1 μg to 300 μg, and preferably from 5 μg to 100 μg of a PDE4 inhibitor according to the invention.

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

The active ingredients may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity. Preferably, the active ingredients are administered once or twice a day.

It is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one or two actives could be taken in the morning and the other (s) later in the day. Or in another scenario, one or two actives could be taken twice daily and the other (s) once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably at least two, and more preferably all, of the actives would be taken together at the same time. Preferably, at least two, and more preferably all actives would be administered as an admixture.

The active substance compositions according to the invention are preferably administered in the form of compositions for inhalation delivered with the help of inhalers, especially dry powder inhalers, however, any other form or parenteral or oral application is possible. Here, the application of inhaled compositions embodies the preferred application form, especially in the therapy of obstructive lung diseases or for the treatment of asthma.

The following preparations forms are cited as formulation examples:

Example 1

Ingredient	Amount in µg
3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide	100
Roflumilast	5
Lactose	2.500

Example 2

Ingredient	Amount in µg
3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide	100
Cilomilast	100
Lactose	2.500

Example 3

Ingredient	Amount in µg
(3R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane bromide	100
Roflumilast	5
Lactose	2.500

Example 4

Ingredient	Amount in µg
(3R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane bromide	100
Cilomilast	100
Lactose	2.500

Example 5

Ingredient	Amount in µg
(3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide	100
Roflumilast	5
Lactose	2.500

Example 7

Ingredient	Amount in µg
(3R)-3-[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide	100
Cilomilast	100
Lactose	2.500

Pharmacological activity

Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory or obstructive diseases of the respiratory tract if an antimuscarinic of formula (I) used with one or more PDE4 inhibitors. In view of this effect the pharmaceutical combinations according to the invention can be used in smaller doses than would be the case with the individual compounds

used in monotherapy in the usual way. This reduces unwanted side effects such as may occur when PDE4 inhibitorsare administered, for example.

Consequently, the combinations of the invention possess therapeutically advantageous properties, which make them particularly suitable for the treatment of respiratory diseases in all kind of patients.

CLAIMS

1. A combination which comprises (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors which is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, in the form of a salt having an anion X, which is a pharmaceutically acceptable anion of a mono or polyvalent acid.

2. A combination according to claim 1 wherein the antagonist of M3 muscarinic receptor (b) is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide.

3. A combination according to claim 1 or 2 characterised in that the active ingredients (a) and (b) form part of a single pharmaceutical composition.

4. A product comprising (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2, as a combined preparation for simultaneous, concurrent, separate or sequential use in the treatment of a patient suffering from or susceptible to a respiratory disease which responds to M3 antagonism.

5. A kit of parts comprising (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2 together with instructions for simultaneous, concurrent, separate or sequential use in combination with (a) a PDE4 inhibitor for the treatment of a patient suffering from or susceptible to a respiratory disease which responds to M3 antagonism.

6. A package comprising (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2 and (a) a PDE4 inhibitor for the simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism.

7. Use of (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2 for the preparation of a medicament, for simultaneous, concurrent,

separate or sequential use in combination with (a) a PDE4 inhibitor for the treatment of a respiratory disease which responds to M3 antagonism in a patient.

8. Use of (a) a PDE4 inhibitor for the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in combination with (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2 for the treatment of a respiratory disease which responds to M3 antagonism in a patient.

9. Use of (a) a PDE4 inhibitor and (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2, for the preparation of a medicament for simultaneous, concurrent, separate or sequential use in the treatment of a respiratory disease which responds to M3 antagonism in a patient.

10. A method of treating a patient suffering from or susceptible to a respiratory disease or condition which responds to M3 antagonism which method comprises simultaneously, concurrently, separately or sequentially administering to said patient an effective amount of (b) an antagonist of M3 muscarinic receptors as defined in claim 1 or 2 and (a) a PDE4 inhibitor.

11. The product according to claim 4, kit of parts according to claim 5, use according to claims 7 to 9 or method according to claim 10 wherein the respiratory disease is asthma or chronic obstructive pulmonary disease (COPD).

12. The combination, product, kit of parts, package, use or method according to anyone of claims 1 to 11 wherein the PDE4 inhibitor is selected from the group comprising : theophylline, drotaverine hydrochloride, cilomilast, roflumilast, denbufylline, rolipram, tetomilast, enprofylline, arofylline, cipamfylline, tofimilast, filaminast, piclamilast, (R)-(+)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, mesopram, N-(3,5-dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-

oxoacetamide, CDC-801 (ex. Celgene), CC-1088 (ex. Celgene), Lirimilast, ONO-6126 (ex. Ono), CC-10004 (ex. Celgene) and MN-001 (ex. Kyorin), optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts.

13. The combination, product, kit of parts, package, use or method according to anyone of claims 1 to 12 wherein the PDE4 inhibitor is selected from the group comprising cilomilast, roflumilast, denbufylline and tetomilast optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts.

14. The combination, product, kit of parts, package, use or method according to anyone of claims 1 to 13 wherein the PDE4 inhibitor is roflumilast.

15. The combination, kit of parts, package, use or method according to anyone of claims 1 to 13 wherein the PDE4 inhibitor is cilomilast.

16. The combination according to claims 1 to 3, product according to claim 4, kit of parts according to claim 5 or package according to claim 6 wherein such combination, product, kit of parts or package further comprises (c) another active compound selected from: (a) β2-agonists, (b) cortiocosteroids, (c) leukotriene D4 antagonists, (d) inhibitors of egfr-kinase, (e) p38 kinase inhibitors and (f) NK1 receptor agonists for simultaneous, separate or sequential use.

17. The combination, product, kit of parts or package according to claim 16 wherein the active compound (c) is selected from the group consisting of (a) β2-agonists and (b) cortiocosteroids.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005836

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/00 A61K31/439 A61K31/167 A61K31/137 A61P11/00
A61P11/06 A61P11/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/04118 A (ALMIRALL PRODESFARMA SA ; BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ FO) 18 January 2001 (2001-01-18)	1-12
Y	page 1, lines 1-21; claims 1,20,33-35; example 44	1-17
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Y	page 1, lines 18-34; claims 1,33-36	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2005	10/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Internat[illegible] Application No
PCT/EP2005/005836

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/005836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004084896 A	07-10-2004	WO 2004084896 A1	07-10-2004
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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09-88171

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **621** DE

FECHA **20 DE OCTUBRE DE 2010** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **18 DE ENERO DE 2011**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ___X___ NO _____

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctora:
Luz Clemencia De Páez.
Apoderada

Oficio N°: 0 1 0 8 6 7

ASUNTO:

Radicación PCT Nº	09-088171
Trámite	011
Evento	378
Actuación	440
Folios	010

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

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

CARLOS DANIEL LEMUS GIRALDO
Profesional Universitario 2044-09 (P)
Con asignación de funciones de la
Dirección de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 14 JUL. 2011.

2020103

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Av. Carrera 50 No. 27-55, Int. 2.
Conmutadores: 5870000 y 5880234
Fax: 5870284 Línea 018000-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia