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No. 03-038672- -00007-0000

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011 Evento : 379 Actuación : 444

Referencia : Expediente No. 03.038.672
Asunto : Solicitud de patente para: **NUEVAS
COMPOSICIONES DE MEDICAMENTOS A BASE DE
SALES DE TIOTROPIO Y SALES DE SALMETEROL**
Solicitante : BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
Fecha de
solicitud : 8 de Mayo de 2003

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 13841 notificado por fijación en lista del 2 de Noviembre de 2007. Con memorial radicado el 30 de Enero de 2008 solicité prórroga de término para atender el Oficio No.13841.

2. Mediante el Oficio No. 13841 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

3. Claridad de la solicitud:

"Su Despacho enuncia que no se encontraron datos que demuestren la reducción de los efectos secundarios de la aplicación del salmeterol, los cuales pueden ser inquietud, excitación, asomnía, miedo, tremor de los dedos sudoraciones y dolor de cabeza, y la mayor rapidez y duración del efecto en la terapia de las enfermedades respiratorias con una aplicación al día y su comparación con los previamente divulgados en el estado de la técnica".

Con respecto al capítulo reivindicatorio su Despacho afirma lo siguiente:

"La reivindicación 11 y 20 se encuentran caracterizadas por un resultado final".

"Las reivindicaciones 31 a 34 se refieren a la utilización de las soluciones para inhalación y su uso".

4. Evaluación de la novedad:

Su Despacho establece que los documentos D1 (DE 19847970) y D2 (Trends in pharmacological science) afectan la novedad de las reivindicaciones 1 a 30 de la presente solicitud de patente, debido a lo siguiente:

"El estado de la técnica más cercano es D1, que enseña una formulación para terapia respiratoria, donde pueden ser β -miméticos, anti colinérgicos, antialérgicos, antagonistas PAF, antagonistas de leucotrienos en particular un esteroide así como sus combinaciones.

D2 enseña nuevos anticolinérgicos como el bromuro de tiotropio con la propiedad de su larga duración de la acción, sugiriendo su utilidad para uso de una sola dosis....Por lo tanto, los medicamentos caracterizados por un contenido en una o varias sales de tiotropio en combinación con una o varias sales de salmeterol,

eventualmente en su forma de enantiómeros, mezclas de los enantiómeros o en forma de los racematos, eventualmente en forma de los solvatos o hidratos así como sus formas farmacéuticas, no se consideran novedosas"...

5. Modificación a una solicitud en trámite:

Con el objeto de atender las anteriores observaciones y de conformidad con lo establecido en el artículo 34 de la Decisión 486, que permite al solicitante en cualquier momento del trámite efectuar modificaciones, sin ampliar el objeto de la invención inicialmente solicitado, me permito presentar un nuevo capítulo reivindicatorio, que comprende 8 reivindicaciones.

El nuevo capítulo reivindicatorio se modificó de tal forma que se dirige a una composición farmacéutica la cual se define como un polvo de inhalación que contiene sales de tiotropio 1 y sales de salmeterol 2 en mezcla con coadyuvantes fisiológicamente inocuos adecuados, con un tamaño de partícula medio entre 10 y 150 μm .

El nuevo capítulo reivindicatorio se adaptó al otorgado por la Oficina de Patentes Europea con número de patente EP 1 514 546. Sin embargo, se hace notar a su Despacho que las reivindicaciones 9 a 10 relacionadas con el uso de una composición se eliminaron del capítulo reivindicatorio.

Se eliminaron las reivindicaciones 11 y 20 así como las 31-34 con el fin de superar las objeciones formuladas por su Despacho.

Finalmente, atendiendo la solicitud de su Despacho se adjunta información farmacológica sobre la combinación de salmeterol y tiotropio que claramente muestra que hay un efecto sinérgico entre los componentes de la composición comparado con la aplicación individual de cada uno de ellos así como la reducción de los efectos colaterales de su aplicación.

De conformidad con lo anterior, se tiene que la presente solicitud cumple con el requisito de claridad establecido en el artículo 30 de la Decisión 486.

6. Argumentos en favor de la novedad.

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece:

"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica".

Mi representada argumenta que la nueva reivindicación 1 es novedosa frente a D1 ya que dicho documento revela composiciones líquidas para aerosoles de inhalación, mientras que la reivindicación 1 de la presente invención reclama polvos de inhalación.

Por otro lado, la nueva reivindicación 1 es novedosa frente al documento D2 ya que D2 no revela polvos de inhalación que comprenden tanto sales de tiotropio como sales de salmeterol. D2 revela en la página 416, columna derecha que el tratamiento con agonistas- β_2 inhalados de acción

prolongada puede ser una adición útil para anticolinérgicos [11] de acción prolongada.

En la referencia [11] no hay ninguna revelación de algún tratamiento de combinación de agonistas- β_2 y anticolinérgicos, y mucho menos que ambos estén presentes en uno y en el mismo polvo de inhalación. La referencia [11] solamente revela datos comparativos del salmeterol y el ipratropio con el último siendo un anticolinérgico de acción corta. Por lo tanto, la reivindicación 1 es novedosa frente a D2.

Se presenta junto con este escrito datos farmacológicos para la combinación de hemisulfato de salmeterol y el bromuro de tiotropio. Los resultados claramente indican por un lado, que hay un efecto broncoespasmolítico sinérgico comparado con sustancias aplicadas individualmente y también una reducción significativa del aumento de la frecuencia cardiaca, la cual es causada por la aplicación del hemisulfato de salmeterol, debido a la aplicación simultánea del bromuro de tiotropio.

Estos beneficios no se derivan de ninguna manera del estado del arte, y por lo tanto, las composiciones de la presente invención presentan claramente efectos sorprendentes e inesperados.

En consecuencia, el nuevo capítulo reivindicatorio es novedoso y no se derivan de manera obvia.

7. Concesión de una solicitud foránea:

Por último, aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto informamos a su Despacho que la presente invención fue otorgada por la Oficina de Patentes Europea con número de patente: EP 1 514 546. (Anexo copia de dicha patente para su información).

8. Conclusión:

Teniendo en cuenta los argumentos arriba citados así como el nuevo capítulo reivindicatorio que se presenta con este escrito, se concluye que la presente invención además de ser novedosa también cumple con el requisito de altura inventiva.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

9. Anexos:

- Nuevo pliego reivindicatorio conformado por 8 reivindicaciones.
- Formulario para modificaciones.
- Recibo por concepto de modificaciones en solicitud pendiente.
- Carátula y reivindicaciones de la patente EP 1 514 546.
- Datos farmacológicos sobre la combinación de salmeterol y tiotropio.

Bogotá,
Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Bingerstrasse 172, 55216 Ingelheim am Rhein, Alemania Domicilio: Ingelheim am Rhein, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>03.038.672</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 8 reivindicaciones para subsanar las observaciones del examen de fondo.	
6	Comprobante de pago No. <u>08-18.489</u> Fecha: <u>3 de marzo de 2008</u>	
7	Anexos ☒ Comprobante de pago de la tasa por valor de \$103.000.00 ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

REIVINDICACIONES

- 1.- Una composición farmacéutica, que contiene una o varias sales de tiotropio (1) en combinación con una o varias sales de salmeterol (2), opcionalmente en la forma de enantiómeros, mezclas de los enantiómeros o en forma de sus racematos, opcionalmente en la forma de solvatos o hidratos **caracterizada porque** es un polvo de inhalación que contiene 1 y 2 en mezcla con coadyuvantes fisiológicamente inocuos adecuados, con un tamaño de partícula medio entre 10 y 150 μm .
- 2.- La composición farmacéutica según la reivindicación 1 caracterizada porque 1 está contenido en forma del cloruro, bromuro, yoduro, metanosulfonato, paratoluenosulfonato o metilsulfato, preferiblemente en forma del bromuro.
- 3.- La composición farmacéutica según una de las reivindicaciones 1 o 2 caracterizada porque 2 se elige de las sales del ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metanosulfónico, ácido acético, ácido fumárico, ácido succínico, ácido láctico, ácido cítrico, ácido xinafónico o ácido maléico.
- 4.- La composición farmacéutica según la reivindicación 3, caracterizado porque 2 se elige de las sales de hidrocloruro, hidrobromuro, sulfato, fosfato y metanosulfonato, preferiblemente de hidrocloruro y sulfato.
- 5.- La composición farmacéutica según una de las reivindicaciones 1 a 4, caracterizado porque las relaciones en peso de tiotropio 1' a salmeterol 2' se encuentran en un intervalo de 1:300 a 30:1, preferiblemente de 1:230 a 20:1.

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6.- La composición farmacéutica según una de las reivindicaciones 1 a 5 caracterizada porque una aplicación única corresponde a una dosificación de la combinación de principios activos 1' y 2' de 0,01 a 1000 µg, preferiblemente de 0,1 a 200 µg.

7.- La composición farmacéutica según una de las reivindicaciones 1 a 6, caracterizada porque es un polvo de inhalación que contiene 1 y 2 en mezcla con coadyuvantes fisiológicamente inocuos adecuados, elegidos del grupo consistente en monosacáridos, disacáridos, oligosacáridos y polisacáridos, polialcoholes, sales o mezclas de estos coadyuvantes entre sí.

8.- Capsulas, caracterizada porque contienen polvos de inhalación según una de las reivindicaciones 1 a 7.

MGT\MGT\ID-117563\WPC13736



(11) EP 1 514 546 B1

(12) EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung: 23.05.2007 Patentblatt 2007/21 (51) Int Cl.: A61K 31/46 (2006.01) A61K 31/137 (2006.01) A61P 11/00 (2006.01) A61P 11/06 (2006.01)

(21) Anmeldenummer: 04028508.2

(22) Anmeldetag: 09.11.2001

(54) **Arzneimittelkompositionen auf der Basis von Tiotropiumsalzen und Salzen des Salmeterols**
Medicament compositions based on tiotropium salts and on salmeterol salts
Compositions de médicaments a base de sels de tiotropium et de sels de salmeterol

(84) Benannte Vertragsstaaten:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Benannte Erstreckungsstaaten:
LT LV MK RO SI

- Nagel, Hilke
55543 Bad Kreuznach (DE)
- Schmelzer, Christel, Dr.
55218 Ingelheim (DE)

(30) Priorität: 13.11.2000 DE 10056104

(56) Entgegenhaltungen:
WO-A-00/69468 DE-A- 19 847 970

(43) Veröffentlichungstag der Anmeldung:
16.03.2005 Patentblatt 2005/11

- BARNES P J: "Chronic obstructive pulmonary disease: new opportunities for drug development" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, Bd. 19, Nr. 10, Oktober 1998 (1998-10), Seiten 415-423, XP004156947 ISSN: 0165-6147
- REES P J: "BRONCHODILATORS IN THE THERAPY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE" EUROPEAN RESPIRATORY MONOGRAPH, EUROPEAN RESPIRATORY SOCIETY JOURNALS LTD., SHEFFIELD,, GB, Bd. 7, Nr. 7, 1998, Seiten 135-149, XP000937584 ISSN: 1025-448X

(60) Teilanmeldung:
07104722.9

(62) Dokumentnummer(n) der früheren Anmeldung(en) nach Art. 76 EPÜ:
01989446.8 / 1 335 728

(73) Patentinhaber: Boehringer Ingelheim Pharma GmbH & Co.KG
55216 Ingelheim am Rhein (DE)

(72) Erfinder:
• Nagel, Juergen, Dr.
deceased (DE)

EP 1 514 546 B1

Anmerkung: Innerhalb von neun Monaten nach der Bekanntmachung des Hinweises auf die Erteilung des europäischen Patents kann jedermann beim Europäischen Patentamt gegen das erteilte europäische Patent Einspruch einlegen. Der Einspruch ist schriftlich einzureichen und zu begründen. Er gilt erst als eingelegt, wenn die Einspruchsgebühr entrichtet worden ist. (Art. 99(1) Europäisches Patentübereinkommen).

der Ansprüche 1 bis 8 zur Herstellung eines Medikaments zur Behandlung von Atemwegserkrankungen.
salts, or mixtures of these excipients with one another.

- 10. Verwendung nach Anspruch 9 zur Herstellung eines Medikaments zur Behandlung von Asthma oder COPD.
8. Capsules, characterised in that they contain inhalable powders according to one of claims 1 to 7.
9. Use of a composition according to one of claims 1 to 8 for preparing a medicament for the treatment of respiratory diseases.

Claims

- 1. Pharmaceutical composition, characterised in that it contains one or more tiotropium salts (1) combined with one or more salmeterol salts (2), optionally in the form of the enantiomers, mixtures of enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with a suitable physiologically acceptable excipient which has an average particle size of between 10 and 150 µm.
- 2. Pharmaceutical composition according to claim 1, characterised in that 1 is contained in the form of the chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methylsulphate, preferably in the form of the bromide.
- 3. Pharmaceutical composition according to one of claims 1 or 2, characterised in that 2 is selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, xinafoic acid or maleic acid.
- 4. Pharmaceutical composition according to claim 3, characterised in that 2 is selected from the hydrochloride, hydrobromide, sulphate, phosphate and methanesulphonate salts, preferably from hydrochloride and sulphate.
- 5. Pharmaceutical composition according to one of claims 1 to 4, characterised in that the ratios by weight of tiotropium 1' to salmeterol 2' are in a range from 1:300 to 30:1, preferably from 1:230 to 20:1.
- 6. Pharmaceutical composition according to one of claims 1 to 5, characterised in that a single administration corresponds to a dosage of the active substance combination 1' and 2' of from 0.01 to 1000 µg, preferably from 0.1 to 200 µg.
- 7. Pharmaceutical composition according to one of claims 1 to 6, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with suitable physiologically acceptable excipients selected from among monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols,

- 10. Use according to claim 9 for preparing a medicament for the treatment of asthma or COPD.

Revendications

- 1. Médicament caractérisé par une teneur en un ou plusieurs sels de tiotropium (1) en combinaison avec un ou plusieurs sels de salmétérol (2), éventuellement sous forme de leurs énantiomères, de mélanges des énantiomères ou sous forme des racémates, éventuellement sous forme des solvates ou hydrates, caractérisé en ce qu'il s'agit d'une poudre pour inhalation qui contient 1 et 2 en mélange avec un adjuvant physiologiquement acceptable approprié, qui présente une taille particulière moyenne entre 10 et 150 µm.
- 2. Médicament selon la revendication 1 caractérisé en ce que 1 est contenu sous forme du chlorure, bromure, iodure, méthanesulfonate, paratoluènesulfonate ou méthylsulfate, de préférence sous forme du bromure.
- 3. Médicament selon l'une des revendications 1 ou 2 caractérisé en ce que 2 est choisi parmi les sels de l'acide chlorhydrique, de l'acide bromhydrique, de l'acide sulfurique, de l'acide phosphorique, de l'acide méthanesulfonique, de l'acide acétique, de l'acide fumarique, de l'acide succinique, de l'acide lactique, de l'acide citrique, de l'acide xinafoïque ou de l'acide maléïque.
- 4. Médicament selon la revendication 3 caractérisé en ce que 2 est choisi parmi les sels chlorhydrate, bromhydrate, sulfate, phosphate et méthanesulfonate, de préférence parmi chlorhydrate et sulfate.
- 5. Médicament selon l'une des revendications 1 à 4 caractérisé en ce que les rapports massiques du tiotropium 1' au salmétérol 2' sont situés dans une plage de 1 : 300 à 30 : 1, de préférence de 1 : 230 à 20 : 1.
- 6. Médicament selon l'une des revendications 1 à 5 caractérisé en ce qu'une application unique correspond à une posologie de la combinaison de principes actifs 1' et 2' de 0,01 à 1000 µg, de préférence

Anexo: datos farmacológicos

Investigaciones con perros narcotizados tratados con bromuro de tiotropio y hemisulfato de salmeterol

Durante experimentos se indujeron a perros narcotizados (barbitol) y con respiración artificial (suxametonium) con instrumentos para la medición de las funciones pulmonares y cardiovasculares a tener broncoespasmos de prueba a los 30, 15 y 0 minutos con anterioridad, así como a los 1, 5, 10, 20, 30, 60, 120 y 180 minutos posteriores a la administración inhalada de sustancias de prueba broncoespasmolíticas por inyección intravenosa de acetilcolin. A grupos de 6 perros se les suministró a través de un aplicador en aerosol (Respimat®) 3 o 6 µg de bromuro de tiotropio, 6 o 12 µg de hemisulfato de salmeterol o una combinación de 3 µg de bromuro de tiotropio y 6 µg de hemisulfato de salmeterol durante la inspiración en la tubo orotraqueal.

El efecto broncoespasmolítico del hemisulfato de salmeterol tuvo su máximo después de 1 bis 5 min y había decaído casi por completo después de 180 minutos. El efecto del bromuro de tiotropio evolucionó lentamente y alcanzó su máximo después de 60 min pero permaneció con efecto durante todo el tiempo de observación. La combinación de ambas sustancias produjo una evolución rápida con intensidad casi completa durante 180 minutos.

Los valores calculados para la inhibición broncoespásmica media más de 180 minutos después de administración de las sustancias de prueba demostraron una dependencia en la dosis para el hemisulfato de salmeterol (6 µg : $21.0 \pm 3.24\%$, 12 µg : $31.5 \pm 3.82\%$) así como para el tiotropio de bromuro (3 µg : $34.2 \pm 1.80\%$, 6 µg : $57.0 \pm 1.10\%$).

La combinación de 3 µg de bromuro de tipropio y 6 µg de hemisulfato de salmeterol produjo una inhibición media de $62.3 \pm 3.61\%$ y fue significativamente más efectiva en comparación con una de 6 o 12 de hemisulfato de salmeterol y de una de 3 µg de bromuro de tiotropio. El efecto de la combinación fue igualmente más fuerte que la suma calculada para los efectos individuales de los componentes individuales ($48.0 \pm 2.57\%$).

La frecuencia cardiaca aumentó con 6 µg de hemisulfato de salmeterol en 11.0 latidos/minuto y con 12 µg en 11.3 latidos/minuto (calculados en 60 minutos), mientras que el bromuro de tiotropio no tuvo ningún

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efecto en este sentido. El valor medio del efecto taquicárdico de 6 µg de hemisulfato de salmeterol combinado con 3 µg de bromuro de tiotropio fue inferior (3.6 latidos/minuto) que el de 6 µg de hemisulfato de salmeterol sólo; la diferencia fue estadísticamente significativa.

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Annex: pharmacologic data

COW 13736-841-007-2

Investigations of narcotised dogs being treated with tiotropium bromide and salmeterol hemisulfate

During experiments narcotized (pentobarbital) and artificially respired (suxamethonium) dogs with instrumentation for measuring of the pulmonary and cardiovascular functions were triggered to have test bronch spasms 30, 15 und 0 min before as well as 1, 5, 10, 20, 30, 60, 120 und 180 min after inhalative administration of bronchospasmolytic test substances by intravenous injection of acetylcholin. Groups of 6 dogs were provided via an aerosol applicator (Respimat®) with 3 or 6 µg tiotropium bromide, 6 or 12 µg salmeterol hemisulfate or a combination of 3 µg tiotropium bromide and 6 µg salmeterol hemisulfate during the inspiration into the orotracheal tubus.

The bronchospasmolytic effect of salmeterol hemisulfate had its maximum after 1 bis 5 min and has been decayed after 180 min nearly completely. The effect of tiotropium bromide evolved slowly and reached its maximum after 60 min, but remained in effect during the whole observation time. The combination of both substances resulted in a quickly evolving effect with nearly full strength during 180 min.

The calculated values for the mean bronchospasmic inhibition over 180 min after administration of the test substances showed a dosage dependency for salmeterol hemisulfate (6 µg : $21.0 \pm 3.24\%$, 12 µg: $31.5 \pm 3.82\%$) as well as for tiotropium bromide (3 µg : $34.2 \pm 1.80\%$, 6 µg : $57.0 \pm 1.10\%$).

The combination of 3 µg tiotropium bromide and 6 µg salmeterol hemisulfate resulted in a mean inhibition of $62.3 \pm 3.61\%$ and was significantly more effective compared to the one of 6 or 12 salmeterol hemisulfate and the one of 3 µg tiotropium bromide. The effect of the combination was as well stronger than the calculated sum of the individual effects of the individual components ($48.0 \pm 2.57\%$).

The heart frequency has been increased by 6 µg salmeterol hemisulfate by 11.0 beats/min and by 12 µg by 11.3 beats/min (calculation over 60 min), while tiotropium bromide had no effect in this regard. The mean value of the tachycardic effect of 6 µg salmeterol hemisulfate combined with 3 µg tiotropium bromide was lower (3.6 beats/min) than the one of 6 µg salmeterol hemisulfate alone; the difference was statistically significant.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2809609	03/03/2008	59.889,000.00

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12	MARCAS Y LEMAS COMERCIALES
			103,000.00
		TOTAL :	\$ 103,000.00

RESPONSABLE : 208

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Q10 13726-841-007-8
007-2



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/04319 (22) International Filing Date: 19 March 1997 (19.03.97) (30) Priority Data: 08/620,882 22 March 1996 (22.03.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/620,882 (CIP) Filed on 22 March 1996 (22.03.96) (71) Applicant (for all designated States except US): NITROMED, INC. [US/US]; 801 Albany Street, Boston, MA 02118 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GARVEY, David, S. [US/US]; 10 Grand Hill Drive, Dover, MA 02030 (US). LETTIS, L., Gordon [AU/US]; 12 Abbott Road, Dover, MA 02030 (US). RENFROE, H., Burt [US/US]; 90 Bristol Road, Wellesley, MA 02181 (US). RICHARDSON, Stewart, K. [GB/US]; 194 Southworth Drive, Ashford, CT 06278 (US).	(74) Agents: HERRON, Charles, J. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein, 6 Becker Farm Road, Roseland, NJ 07068 (US). (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>	
(54) Title: NITROSATED AND NITROSYLATED COMPOUNDS AND COMPOSITIONS AND THEIR USE FOR TREATING RESPIRATORY DISORDERS		
(57) Abstract Disclosed are (i) compounds of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase (PDE) inhibitor directly or indirectly linked to a NO or NO₂ group or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i>; (ii) compositions of steroids, β-agonists, anticholinergics, mast cell stabilizers and PDE inhibitors, which can optionally be substituted with at least one NO or NO₂ moiety or a group which stimulates endogenous production of NO or EDRF <i>in vivo</i>; and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO⁺) or nitroxyl (NO⁻), or as the neutral species, nitric oxide (NO) or that stimulates endogenous production of NO or EDRF <i>in vivo</i>; and (iii) uses for them in preventing and/or treating respiratory disorders.		

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Another group of such adducts are 2-hydroxy-2-nitrosohydrazines which donate, transfer or release nitric oxide and have a $R_{61}R_{62}-N(O-M^+)-NO$ group wherein R_{61} and R_{62} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds. M^+ is a metal cation, such as, for example, a Group I metal cation.

Another group of such adducts are thionitrates which donate, transfer or release nitric oxide and have the structure $R_{61}-S-NO_2$ wherein R_{61} is as described above.

Compounds that stimulate endogenous synthesis of NO or EDRF *in vivo* include L-arginine, the substrate for nitric oxide synthase, cytokines, adenosine, bradykinin, calreticulin, bisacodyl, phenolphthalein, and endothelin.

The compounds and compositions of the invention are useful in the treatment of a large number of disorders, particularly those related to or characterized by pulmonary dysfunction. Examples of such indications include preventing (if given prior to the onset of symptoms) or reversing the following: acute pulmonary vasoconstriction, such as may result from pneumonia, traumatic injury, aspiration of inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia), as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia.

When administered *in vivo*, the nitric oxide adduct may be administered in combination with pharmaceutical carriers and in dosages described herein.

The instant disclosure, particularly in combination with the significant body of literature, commercially available pharmaceutically acceptable liquid, solid and gaseous carriers and vehicles, volume expanders, tableting and encapsulation materials, enteric and other coatings, and inhalant and intranasal delivery devices and the ordinary skill of those practicing in the field, amply teaches the reader how to use the compounds and compositions of the invention in the methods of the invention, and particularly for oral and nasal inhalation and intranasal therapy. The following is supplementary to and exemplary thereof.

The pharmaceutical compositions utilized in this invention can be administered, preferably by inhalation (oral and/or nasal), and also by intranasal mucosal, administration, oral, enteral, topical, vaginal, sublingual, rectal, intramuscular, intravenous, or subcutaneous means.

The compounds of this invention can be employed in combination with, conventional excipients; i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or intranasal application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

Many therapeutically active ingredients have been administered or applied to the body by means of inhalation, such as in aerosol dosage form. One of the main reasons for the rapid and widespread acceptance of the inhalation dosage forms for the administration of therapeutically active agents is that it affords many and

distinct advantages to the user. These advantages have been described by various investigators and, for aerosol and metered-dose inhalers, include rapid onset of action; circumvention of the first-pass effect; avoidance of degradation in the gastrointestinal tract; lower dosage which will minimize adverse reactions; dose titration to individual needs and ideal for as-needed medication. It is an ideal alternate route when the chosen therapeutic agent may interact chemically or physically with other medicinals needed concurrently, or when the drug entity exhibits erratic pharmacokinetics upon oral or parenteral administration.

The term "aerosol" is used to denote various systems ranging from those of a colloidal nature to systems consisting of "pressurized packages." The present definition refers to those products which depend upon the power of a liquefied or compressed gas to dispense the active ingredient(s) in a finely dispersed mist, foam or semisolid. Pump systems which also dispense the active ingredient(s) in the form of a finely dispersed mist (although of greater particle size) often are classified as aerosols.

The pressure package is convenient and easy to use. Medication is dispensed in a ready-to-use form at the push of a button. Since the medication is sealed in a tamper-proof pressure container, there is no danger of contamination and the contents can be protected from air and moisture. Easily decomposed drugs especially lend themselves to this type of administration. For those products requiring regulation of dosage, a metering valve can be used. An accurately measured dose of therapeutically active drug can be administered quickly and in the proper particle-size range. In addition, when used with expensive products, such as some steroids, savings can be achieved by the user as compared to the use of other preparations such as ointments, creams or lotions. The aerosol dosage form allows for the dispensing of the product in the most desirable form; spray, foam or semisolid. Depending on the nature of the product, the characteristics of the spray or foam can be changed to insure the proper and most efficient use of the medication.

For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or a carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

The nitrosated or nitrosylated compounds of the invention are used at dose ranges and over a course of dose regimen and are administered in the same or substantially equivalent vehicles/carrier by the same or substantially equivalent oral or nasal inhalant devices as their non-nitrosated or non-nitrosylated counterparts. The nitrosated or nitrosylated compounds of the invention can also be used in lower doses and in less extensive regimens of treatment. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

~~Total daily dose administered to a host in single or divided doses may be in amounts, for example, from about 1 to about 100 mg/kg body weight daily and more usually about 3 to 30 mg/kg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.~~

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more

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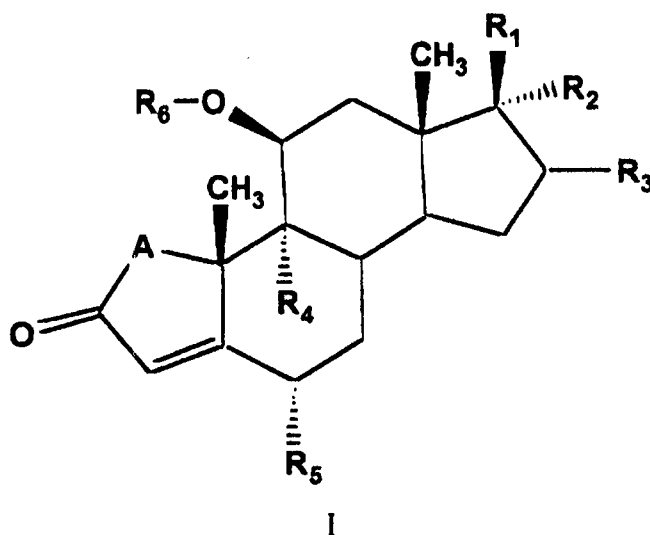
compounds which are known to be effective against the specific disease state targeted for treatment. The compositions of the invention can also be administered as described above or can be made to include one or more additional active compounds which are known to be effective against the specific disease state is targeted for treatment.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

These and other aspects of the present invention will be apparent to those skilled in the art from the teachings herein.

What is Claimed Is:

1. A compound comprising a steroid, a β -agonist, an anticholinergic, a mast cell stabilizer or a phosphodiesterase inhibitor to which is directly or indirectly linked at least one NO or NO₂ group or a group which stimulates endogenous production of NO or EDRF synthesis *in vivo*.
2. A compounds of claim 1 selected from the group consisting of:
 - (i) compounds having the structure:

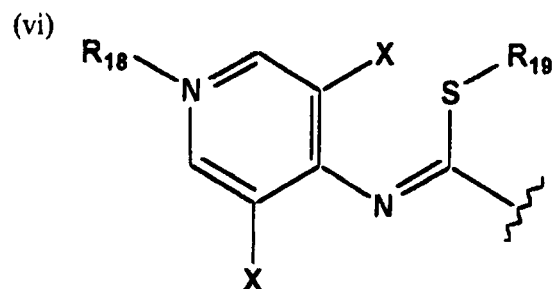
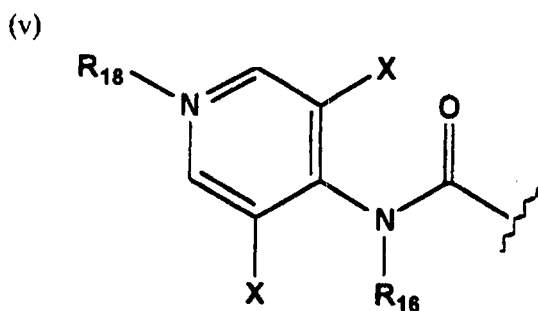


wherein

A is selected from -CH=CH- or -CH₂-CH₂-;

R₁ is selected from

- (1) -C(O)CH₂-B-D wherein B is oxygen or sulfur; D is selected from
 - (i) -NO; (ii) -NO₂; (iii) -C(R_d)-O-C(O)-Y-[C(R_e)(R_f)]_p-T-Q in which R_d is hydrogen, lower alkyl, cycloalkyl, aryl, alkylaryl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen, lower alkyl, lower haloalkyl, or heteroaryl, R_e and R_f are at each occurrence independently selected from hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, alkylamino, dialkylamino, carboxy, carboxamido, or taken together are carbonyl, cycloalkyl or bridged cycloalkyl, p is an integer from 1 to
 - 6, T is a covalent bond, oxygen, sulfur or nitrogen and Q is selected from -NO or -NO₂; (iv) -C(O)-T¹- [C(R_e)(R_f)]_p- T²-Q wherein T¹ and T² are independently selected from T and R_e, R_f, p, Q, and T are as defined above; (v) -C(O)-



wherein X is halogen and R_{26} is selected from D or M and wherein R_{16} , R_{18} , and R_{19} are defined as above.

3. A composition comprising (i) a therapeutically effective amount of a steroid, a β -agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor and (ii) a compound that donates, transfers or releases nitric oxide or stimulates endogenous production of NO or EDRF *in vivo*;

4. The composition of claim 3 wherein

(i) the steroid is selected from the group consisting of beclomethasone, fluticasone, flunisolide, triamcinolone, butixocort, dexamethasone, fluocortin, budesonide, tixocortol, tipredane and mometasone;

(ii) the β -agonist is selected from the group consisting of salmeterol, albuterol, metaproterenol, terbutaline, pirbuterol, rimiterol, clenbuterol, bitolterol and reproterol;

(iii) the anticholinergic is selected from the group consisting of ipratropium, flutropium, tiotropium and rispenzepine;

(iv) the mast cell stabilizer is selected from the group consisting of cromolyn and nedocromil; and

(v) the PDE inhibitor is selected from the group consisting of tolafentrine, piclamilast, rolipram, filaminast, denbufylline, and zardaverine.

5. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

6. The composition of claim 5 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

(i) $\text{CH}_3[\text{C}(\text{R}_e)(\text{R}_f)]_x\text{SNO}$;

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(54) Title: COMBINATIONS OF FORMOTEROL AND A TIOTROPIUM SALT			
(57) Abstract A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.			

Combinations of Formoterol and a Tiotropium Salt

This invention relates to combinations of formoterol and a tiotropium salt and their use for the treatment of inflammatory or obstructive airways diseases.

Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)-ethyl)phenyl]formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases. Use of tiotropium bromide, (1 α ,2 β ,5 α ,7 β)-7-((hydroxydi-2-thienylacetyl)oxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo(3.3.1.0^{2,4})-nonane bromide, in the treatment of chronic obstructive bronchitis is described in US5610163. It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by combination therapy using formoterol, or a salt or solvate thereof, and a tiotropium salt. For instance, it is possible using this combination therapy to reduce the dosages required for a given therapeutic effect considerably compared with those required using treatment with formoterol or a tiotropium salt alone, thereby minimising possibly undesirable side effects.

In a further aspect, this combination therapy exhibits both a fast onset of action and a long duration of action, so that patients feel a rapid improvement in their condition and, in view of the long duration of action, a reduced need for short-acting rescue medicaments, such as salbutamol or terbutaline. Surprisingly this effect is exhibited even when the two drugs are administered at the same time, i.e. in a composition containing both drugs or sequentially, so that medicaments of the invention facilitate the treatment of inflammatory or obstructive airways diseases with a medicament which need be administered only once a day. Where necessary, medicaments of the invention can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, so that they facilitate treatment of such diseases with a single medicament.

In one aspect, the present invention provides a medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined.

In a further aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with a pharmaceutically acceptable carrier.

The present invention also provides (A) and (B) as hereinbefore defined for use in combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

The invention further provides the use of (A) as hereinbefore defined or (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

The present invention still further provides the use of (A) and (B) as hereinbefore defined for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

Pharmaceutically acceptable salts of formoterol include, for example, salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acids.

Component (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. It may be in the form of a solvate, for example a hydrate, thereof, for example as described in US3994974 or US5684199, and may be present in a particular crystalline form, for example as described in WO95/05805. Preferably, component (A) is formoterol fumarate, especially in the form of the dihydrate.

The tiotropium salt (B) is preferably tiotropium methanesulfonate or, especially, tiotropium bromide, $(1\alpha, 2\beta, 4\beta, 5\alpha, 7\beta)$ -7-((hydroxydi-2-thienylacetyl)oxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo(3.3.1.0^{2,4})-nonane bromide, the preparation of which is described in US5610163.

Administration of the medicament or pharmaceutical composition as hereinbefore described, i.e. with (A) and (B) in admixture or separate, is preferably by inhalation, i.e. (A) and (B) or the mixture thereof are in inhalable form. The inhalable form of the medicament i.e. of (A) and/or (B) may be, for example, an atomizable composition such as an aerosol comprising the active ingredient, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the medicament may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant. In another example, the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium, or a combination of a dispersion of (A) in such a medium with a dispersion of (B) in such a medium.

An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in suspension in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by

weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of 1 µg to 140 µg of the active ingredient. Alternatively, the dry powder may be contained as a reservoir in a multi-dose dry powder inhalation device.

In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average particle diameter of up to about 10 µm, for example 0.1 to 5 µm, preferably 1 to 5 µm. The finely divided carrier, where present, generally has a maximum particle diameter up to 300µm, preferably up to 212 µm and conveniently has a mean particle diameter of 40 to 100µm, preferably 50 to 75 µm. The particle size of the active ingredient, and that of the carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device, or a pack of two or more inhalation devices, containing a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described.

Where the inhalable form of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100 μ l, e.g. 25 to 50 μ l, of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, for example an electronically controlled device such as an AERx (ex Aradigm, US) or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100 μ l, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing dry powder comprising a dosage unit of (A) and/or (B), or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 5-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US3991761, while a suitable MDPI device is that described in WO97/20589.

The medicament of the invention is preferably a pharmaceutical composition comprising a mixture of (A) as hereinbefore defined and (B) as hereinbefore defined, preferably together with a pharmaceutically acceptable carrier as hereinbefore described.

The weight ratio of formoterol, or salt or solvate thereof, to tiotropium salt may be, in general, from 72:1 to 1:160, for example from 72:1 to 1:120, from 72:1 to 1:80, from 60:1 to 1:80, from 60:1 to 1:70, from 50:1 to 1:60, from 60:1 to 1:50, from 50:1 to 1:50, from 60:1 to 1:40, from 50:1 to 1:40, from 50:1 to 1:30, from 50:1 to 1:20, from 50:1 to 1:30, from 50:1 to 1:20, from 50:1 to 1:10, from 40:1 to 1:20, from 40:1 to 1:10, from 30:1 to 1:20, from 30:1 to 1:10, from 20:1 to 1:20, from 20:1 to 1:10, from 20:1 to 1:5, from 16:1 to 1:4, from 10:1 to 1:5, from 6:1 to 1:4, or from 4:1 to 1:3. More usually, this ratio is from 3:1 to 1:3, for example from 2.5:1 to 1:2, from 2:1 to 1:2, from 1.5:1 to 1:1.5, or from 1.5:1 to 1:1.2. The two drugs may be administered separately in the same

ratio. Specific examples of this ratio include 3:1, 2.9:1, 2.8:1, 2.7:1, 2.6:1, 2.5:1, 2.4:1, 2.3:1, 2.2:1, 2.1:1, 2:1, 1.9:1, 1.8:1, 1.7:1, 1.6:1, 1.5:1, 1.4:1, 1.3:1, 1.2:1, 1.1:1, 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9 and 1:2. The above weight ratios apply particularly where (A) is formoterol fumarate dihydrate and (B) is tiotropium bromide. Thus, since the molecular weights of formoterol fumarate dihydrate and tiotropium bromide are 840.9 and 472.4 respectively, the corresponding molar ratios, which apply to any forms of (A) and (B), can be readily calculated. For instance, the above weight ratios of 60:1 and 1:80 correspond to molar ratios of 33.7:1 and 1:142.3 respectively.

A suitable daily dose of formoterol, or salt or solvate thereof, particularly as formoterol fumarate dihydrate, for inhalation may be from 1 to 72 μg , for example from 1 to 60 μg , generally from 3 to 50 μg , preferably from 6 to 48 μg , for instance from 6 to 24 μg . A suitable daily dose of tiotropium salt, particularly as tiotropium bromide, for inhalation may be from 1 to 160 μg , for example from 1 to 120 μg , from 1 to 80 μg , from 1 to 70 μg , from 1 to 60 μg , from 1 to 50 μg , from 1 to 40 μg , from 1 to 25 μg , preferably from 3 to 36 μg , for instance from 9 to 36 μg . The precise dose used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device. The unit doses of (A) and (B) and their frequency of administration may be chosen accordingly. A suitable unit dose of formoterol component (A), particularly as formoterol fumarate dihydrate, may be from 1 to 72 μg , for example from 1 to 60 μg , generally from 3 to 48 μg , preferably from 6 to 36 μg , especially from 12 to 24 μg . A suitable unit dose of tiotropium salt (B), particularly as tiotropium bromide, may be from 1 μg to 80 μg , for example from 1 μg to 50 μg , preferably from 3 μg to 36 μg , especially from 9 to 36 μg . These unit doses may suitably be administered once or twice daily in accordance with the suitable daily dose mentioned hereinbefore. For on demand usage, unit doses of 6 μg to 12 μg of (A) and 3 μg to 36 μg of (B) are preferred.

In one preferred embodiment of the invention, when the medicament of the invention is a pharmaceutical composition which is a dry powder in capsules containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsules may suitably contain, where (A) is formoterol fumarate dihydrate, and (B) is tiotropium bromide, from 3 μg to 36 μg of (A), preferably from 6 μg to 24 μg of (A), especially from 12 μg to 24 μg of (A), and from 3 μg to 80 μg of (B), preferably from 5 μg to 50 μg of (B), especially from 9 to 36 μg of (B), together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to

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between 5 mg and 50mg, for example 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg, preferably 20 to 25 mg, especially 25 mg.

In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver 3mg to 25mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is formoterol fumarate dihydrate, and (B) is tiotropium bromide, a powder comprising, by weight, 3 to 36 parts, preferably 6 to 24 parts, especially 12 to 24 parts of (A); 3 to 80 parts, preferably 5 to 50 parts, especially 9 to 36 parts of (B); and 2884 to 24994 parts, preferably 4884 to 14994 parts, especially 4884 to 9994 parts of a pharmaceutically acceptable carrier as hereinbefore described.

In accordance with the above, the invention also provides a pharmaceutical kit comprising (A) and (B) as hereinbefore defined in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and (B). For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of (B). In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (B). In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising (A) in a propellant and a metered dose inhaler containing an aerosol comprising (B) in a propellant.

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Example 2 - Dry Powder

Ingredient	% by weight
Formoterol fumarate dihydrate	0.05
Tiotropium bromide	0.05
Lactose monohydrate	99.90

Example 3

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 12 parts of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1.5 μ m in an air-jet mill, 18 parts of tiotropium bromide which has been similarly ground to a mean particle diameter of 1.5 μ m and 4970 parts of lactose monohydrate having a particle diameter below 212 μ m.

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Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Tiotropium Bromide (Parts)	Lactose Monohydrate (Parts)
4	12	3	4985
5	12	9	4979
6	12	36	4952
7	12	80	4908
8	6	3	4991
9	6	9	4985
10	6	18	4976
11	6	36	4958
12	6	80	4914
13	18	3	4979
14	18	9	4973
15	18	18	4964

16	18	36	4946
17	18	80	4902
18	24	3	4973
19	24	9	4967
20	24	18	4958
21	24	36	4940
22	24	80	4896
23	30	3	4967
24	30	9	4961
25	30	18	4952
26	30	36	4934
27	30	80	4890
28	36	3	4961
29	36	9	4955
30	36	18	4946
31	36	36	4928
32	36	80	4884
33	6	3	9991
34	6	9	9985
35	6	18	9976
36	6	36	9958
37	6	80	9914
38	12	3	9985
39	12	9	9979
40	12	18	9970
41	12	36	9952
42	12	80	9908
43	18	3	9979
44	18	9	9973
45	18	18	9964
46	18	36	9946
47	18	80	9902
48	24	3	9973
49	24	9	9967
50	24	18	9958

Claims

1. A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) a tiotropium salt of a pharmaceutically acceptable acid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.
2. A medicament according to claim 1 which is a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier.
3. A medicament according to claim 1 or 2, in which (A) is formoterol fumarate.
4. A medicament according to claim 3, in which formoterol fumarate is in the form of the dihydrate thereof.
5. A medicament according to any one of claims 1 to 4, in which (B) is tiotropium bromide.
6. A medicament according any one of claims 1 to 5, which is in inhalable form.
7. A medicament according to claim 6, in which (A) and/or (B) are present in an atomizable composition.
8. A medicament according to claim 7, in which the inhalable form is an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant.
9. A medicament according to claim 7, in which the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium or a combination of a dispersion of (A) in said medium with a dispersion of (B) in said medium.

10. A medicament according to claim 6, in which (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a pharmaceutically acceptable carrier in finely divided form.
11. A medicament according to claim 10, in which the carrier is present and is a saccharide.
12. A medicament according to claim 11, in which the carrier is lactose.
13. A medicament according to any one of claims 10 to 12, in which (A) and/or (B) has an average particle diameter up to 10 μm .
14. A medicament according to any one of the preceding claims, in which the weight ratio of (A) to (B) is from 72:1 to 1:160.
15. A medicament according to claim 14, in which said ratio is from 60:1 to 1:80.
16. A medicament according to claim 15, in which said ratio is from 3:1 to 1:3.
17. A medicament according to claim 2, which is a dry powder in a capsule, the capsule containing from 3 to 36 μg of (A) as formoterol fumarate dihydrate, from 3 to 80 μg of (B) as tiotropium bromide and a pharmaceutically acceptable carrier in an amount to bring the total weight of dry powder per capsule to between 5mg and 50 mg.
18. A medicament according to claim 2, which is a dry powder comprising, by weight, 3 to 36 parts of (A) as formoterol fumarate dihydrate, 3 to 80 parts of (B) as tiotropium bromide and 2884 to 24994 parts of a pharmaceutically acceptable carrier.
19. The use of (A) as defined in any one of claims 1, 3 and 4 or (B) as defined in claim 1 or 5 in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.
20. The use of (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 or 5 for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.