

**Industria y Comercio**

SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 85878215 00000000

Folios: 74ⁿ

Fecha (AMD): 2005-07-15 17:09:37

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE**PCT****ENTRADA EN FASE NACIONAL** 16-07-05**SOLICITUD DE:**

1

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☐ Capítulo I.☒ Capítulo II.

2

SOLICITANTE
(71)Nombre: **BOEHRINGER INGELHEIM
PHARMA GMBH & CO. KG**sociedad constituida y existente bajo las
leyes de la República Federal de Alemania.Dirección: Binger Straße 173,
55216 Ingelheim,
República Federal de AlemaniaDomicilio: Ingelheim,
República Federal de Alemania**IDENTIFICACIÓN**

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

**REPRESENTANTE
O APODERADO**Nombre: **EMILIO FERRERO**

Dirección: Carrera 4ª. No. 72-35

Teléfono: 347 36 11

Fax: 211 86 50

E-mail: clientes@camyp.com.

Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número 438.019 T.P 31.929

4

INVENTOR (ES)
(72)1. **Sabine SIX**Diltheystrasse 2 A,
65203 Weisbaden,
República Federal de Alemania3. **Friedrich SCHMIDT**Feierabendweg 2,
55218 Ingelheim,
República Federal de Alemania2. **Christel SCHMELZER**Welfenstrasse 14,
55218 Ingelheim,
República Federal de Alemania

5

PCT (86)Solicitud Internacional No. PCT/EP2003/013692Fecha: 4 de Diciembre de 2003Publicación Internacional No. WO 2004/054580 A1Fecha: 1 de Julio de 2004

6

Título (54)**FORMULACIONES DE SOLUCIONES DE HFC QUE CONTIENEN TIOTROPIO**

7

Clasificación Internacional (51) A61K 31/46

8

PrioridadSI ☒ NO ☐

(33) País de Origen

EP

(32) Fecha

16 de Diciembre de 2002

(31) Número de Solicitud

02028238.0

9

Comprobante de pago No.: 05 - 46.094**Fecha:** 21 de Junio de 2005

2

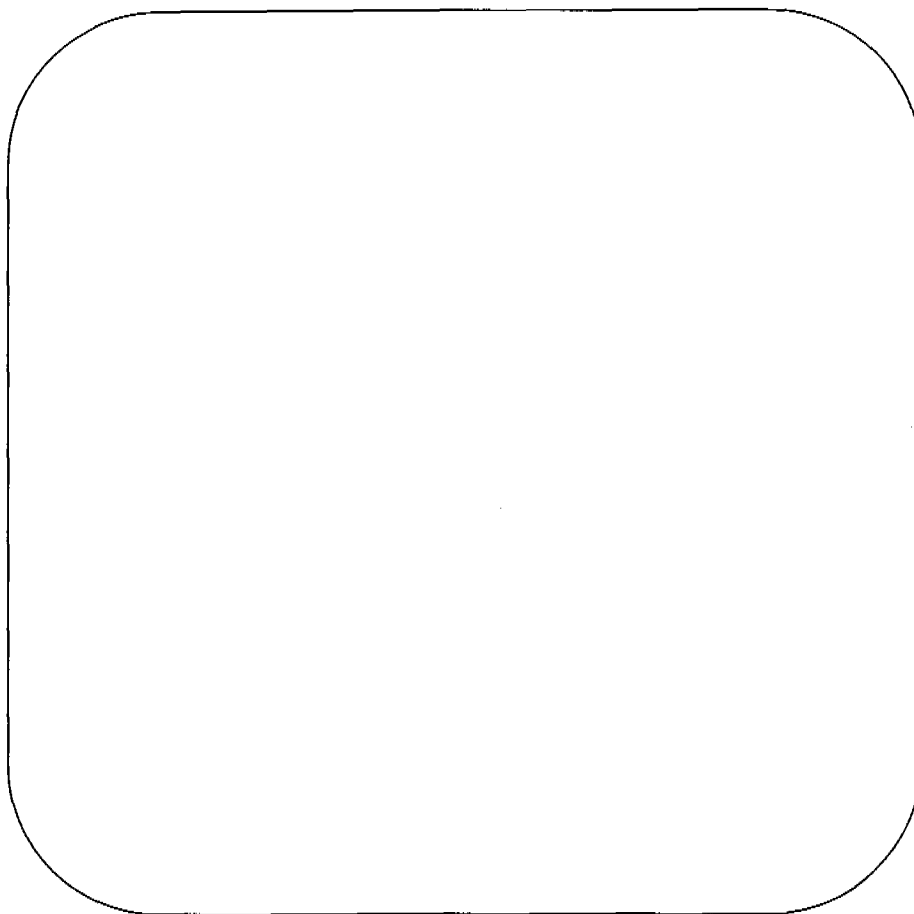
V

10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 443.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA

12

Solicito la concesión de la patente,

NOMBRE:EMILIO FERRERO**FIRMA :**

C.C. 438.019 de Usaquén T.P. 31.929

PRP

B
3**DOCUMENTOS ANEXOS**

1. ☒ **Publicación Internacional WO 2004/054580 A1**

Descripción:

Páginas 1-14 en el idioma original

Páginas 1-13 en español

Reivindicaciones: Número (s) 1-11

Figuras: Número (s) _____

2. ☒ **Forma PCT/RO/101. PCT Request**
3. ☐ **Forma PCT/RO/106. Invitation to Correct Defects.**
4. ☒ **Forma PCT/ISA/210. Informe de Búsqueda Internacional.**
5. ☐ **Forma PCT/ISA/220. Notificación De La Transmisión Del Informe De Búsqueda Internacional Y De La Opinión Escrita De La Administración Encargada De La Búsqueda Internacional, O De La Declaración.**
6. ☐ **Forma PCT/ISA/237. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.**
7. ☒ **Forma PCT/IB/304. Notification Concerning Submission Or Transmittal Of Priority Document.**
8. ☐ **Forma PCT/IB/306. Notification Of The Recoding Of A Change.**
Descripción De Modificación:

9. ☒ **Forma PCT/IB/308. Notice Informing The Applicant Of The Communication Of The International Application To The Designated Offices.**
10. ☒ **Forma PCT/IB/332. Information Concerning Elected Offices Notified Of Their Election.**
11. ☒ **Forma PCT/IPEA/401. PCT Demand**
12. ☐ **Forma PCT/IPEA/402. Notification Of Receipt Of Demand By Competent International Preliminary Examining Authority.**
13. ☐ **Forma PCT/IPEA/408. Written Opinion.**
14. ☒ **Forma PCT/IPEA/416. Notification Of Transmittal Of The International Preliminary Examination Report.**
15. ☒ **Forma PCT/IPEA/409. Informe Del Examen Preliminar Internacional.**
16. ☐ **Traducción Al Español Del Informe Del Examen Preliminar Internacional.**
17. ☐ **Traducción Al Español De Los Anexos Presentados Junto Con El Informe Del Examen Preliminar Internacional.**

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

domiciliado (s) en/of
55216 Ingelheim, Germany

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72 35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72 35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above named attorneys at law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate,

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

admit the facts of the case, desist, cancel, receive, resign and ratify done by representatives without a power of attorney.

AUTEN
El infrascrito
f. 6-2-92

Dado y firmado hoy/Given and signed this 21st day of March
en/in Ingelheim
por/by

Firma

Signature

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

ppa.

ppa.

Dr. Henz-Gerd KLÄS
Head of Patent Department

Dr. Michael KOMPTER
Principal Officer

12 JUL 2005

AUTENTICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de

1. Heinz-Gerd Kläs

2. Michael Kompter
es auténtica; que el signatario desempeña actualmente el cargo
de Representante

de la compañía Boehringer Ingelheim Pharma

GmbH & Co. KG

sociedad que actualmente existe y está organizada de acuerdo a
las leyes de Alemania

que la dirección de la compañía es 55216 Ingelheim

am Rhein Binger Straße 173

y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los
documentos respectivos y de todo da fe.

Dado y firmado en Ingelheim am Rhein

El 21 Marzo 2003

NOTARIAL AUTHENTICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature
of 1.Mr.Dr.Heinz-Gerd Kläs and
2.Mr.Dr.Michael Kompter

is authentic, that the signatory currently acts in the position of
procurists

of the company Boehringer Ingelheim Pharma
GmbH & Co. KG

a company currently existing and organized under the laws of
Germany

that the address is 55216 Ingelheim am Rhein
Binger Straße 173

and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon
examination of the corresponding documents.

Given and signed in Ingelheim am Rhein

On the 21th day of March 2003

Notary Public
(Signature-seal)

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Land Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von

Alfred Fuchs

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Dienstsiegel
des Alfred Fuchs - Notar in Ingelheim am Rhein

Bestätigt

Mainz, den 24.03.03

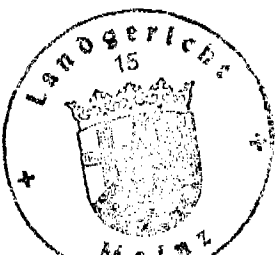
5. in Mainz 6. am 24.03.03

7. durch den Präsidenten des Landgerichts

8. unter Nr. 269/2003

9. Stempel/Siegel 10. Unterschrift

In Vertretung:



(Dr. Harald Binz)
Vizepräsident



KOSTENRECHNUNG:

Gebühr für die
Erteilung der
Legalisation
Wert: EUR 20.000,00
JVKostO v.26.7.57
i.V.m. § 45 KostO
Gebühr: EUR 18,00

Justizsekretärin

6

TRADUCCION OFICIAL No. 9468

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en Alemán que aparecen en el documento de representación y poder, escrito en español e inglés, por medio del cual la firma Boehringer Ingelheim Pharma GmbH & Co. KG, domiciliada en D-55216 Ingelheim am Rhein, Alemania, otorga poder a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia. Dado y firmado el 21 de marzo 2003 en Ingelheim am Rhein por los señores Dr. Heinz-Gerd KLÄS y Dr. Michael KOMPTER, representantes legales de la mencionada firma.

Sigue autenticación notarial en español e inglés de las firmas antecedentes por el notario de Ingelheim am Rhein, Alfred Fuchs, el 21 de marzo 2003, bajo el No. 571/2003.

COSTAS:

Derechos de legalización

Valor: EUROS 20.000,--

12 JUL 2003
Fuchs

JVKostO del 26.7.57 en combinación con Art. 45 KostO

Derechos: EUROS 18,00

Mainz, 24.03.03

Fdo.: ilegible,

Secretaria de justicia

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por el notario Alfred Fuchs

3. Actuando en calidad de notario

4. Lleva el sello oficial del notario de Ingelheim am Rhein,
Alfred Fuchs

Certificado

5. en Mainz

6. el 24.03.03

7. por el Presidente del Tribunal Regional

8. bajo el No 269/2003 /

9. Sello

10. Firma

Tribunal Regional de Mainz

Fdo.: ilegible

(Dr. Harald Binz)

Vicepresidente

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los
archivos de estas oficinas para su confrontación.

Bogotá, 7 de abril 2003

12 JUL 2003

[Handwritten signature]

MINISTERIO DE
RELACIONES

19210542
19090204

COYAFINHA
DOCUMENTO
LAS FUNCIONES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2003 APR - 8 P 1:08

JEFES DE
EL JUDIC.

COMO NOTARIO DEL CIRCULO DE SAN JUAN DE
BOGOTA HAGO CONSTAR QUE LA FIRMA DE
*Luz Arriaga de
Herber*
CON LA FIRMA REGISTRADA POR
(LOS) EN ESTA NOTARIA
SAN JUAN DE BOGOTA
09 ABR 2003

NOTA DE BOGOTA

12 JUL 2003
MORSEZ BARRONAS
BOGOTA

CAVELIER

374

ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTÁ, 8 - COLOMBIA

CESION

Yo, (nosotros) abajo firmado (s)

1. Sabine SIX
2. Christel SCHMELZER
3. Friedrich SCHMIDT

Domiciliado(s)

en

1. Diltheyst. 2A, 65203 Wiesbaden, Alemania
2. Welfenstrasse 14, 55218 Ingelheim, Alemania
3. Feierabendweg 2, 55218 Ingelheim, Alemania

Declaro(amos) bajo juramento ser único(s) y verdadero(s)
inventor(es) de la invención: *Formulaciones de soluciones de HFC que contienen tiotropio*

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

Boehringer Ingelheim Pharma GmbH & Co. KG

constituida y existente de conformidad con las leyes de

Alemania

domiciliada en **Binger Strasse 173, 55216 Ingelheim, Alemania**

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

1. Sabine SIX
2. Christel SCHMELZER
3. Friedrich SCHMIDT

of

1. Diltheyst. 2A, 65203 Wiesbaden, Germany
2. Welfenstrasse 14, 55218 Ingelheim, Germany
3. Feierabendweg 2, 55218 Ingelheim, Germany

state(s) under oath to be sole and true inventor(s) of the invention:
"TIOTROPIUM CONTAINING HFC SOLUTION FORMULATIONS"

state as well, that assign, without reservations or limitations in favour of **Boehringer Ingelheim Pharma GmbH & Co. KG**

a corporation constituted and existing in conformity with the laws of

Germany

domiciled in **Binger Strasse 173, 55216 Ingelheim, Germany**

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this

on/in

Ingelheim

13th May, 2005

Firma/Signature

Sabine SIX
Sabine SIX

Friedrich Schmidt
Friedrich SCHMIDT

Christel Schmelzer
Christel SCHMELZER

UR.Nr. 1021/2005

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200 ____ Ante mí, Notario Público de _____

compareció(eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede, y quien(es)
tiene(n) capacidad legal para _____

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this 13th day of May
200 5 before me, a Notary Public of
Ingelheim am Rhein

personally appeared Mrs.Sabine Six,
Mr.Friedrich Schmidt and Mrs.Christel
Schmelzer-----

to me known, and known to me to be the person(s) who executed
that foregoing document, and who ~~has~~(have) legal capacity to
execute it.

NOTARIO PÚBLICO-NOTARY PUBLIC

APOSTILLE

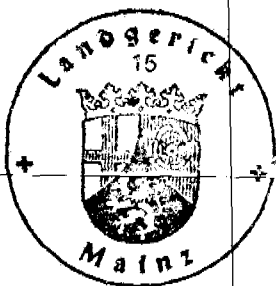
(Convention de La Haye du 5 octobre 1961)

1. Country:
This public document
2. has been signed by
3. acting in the capacity of
4. bears the seal/stamp of

Certified

5. at 6. the
7. by
8. No.
9. Seal/stamp 10. Signature

.....



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von Alfred Fuchs
3. in seiner Eigenschaft als Notar
4. sie ist versehen mit dem Dienstsiegel/stempel Alfred Fuchs - Notar in Ingelheim am Rhein

Kostenrechnung:

Gebühr für die Erteilung
der Legalisation

Wert: 20.000,00 €

JVKostO v. 26.7.1957

i.V.m. § 45 KostO

Gebühr: 18,00 €

Mainz, 17.05.05

Justizsekretärin z.A.

Bestätigt

5. in Mainz 6. am 17.05.2005
7. durch den Präsidenten des Landgerichts
8. unter Nr. 635/2005
9. Stempel/Siegel



10. Unterschrift
In Vertretung:

(Dr. Harald Binz)
Vizepräsident

10

TRADUCCION OFICIAL No. 10773

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de los sellos y autenticaciones en alemán que aparecen a continuación de un documento de Cesión, escrito en español e inglés, por medio del cual los señores

1. Sabine SIX
2. Christel SCHMELZER
3. Friedrich SCHMIDT

domiciliado(s) en

1. Diltheystr. 2A, 65203 Wiesbaden, Alemania
2. Welfenstrasse 14, 55218 Ingelheim, Alemania
3. Feierabendweg 2, 55218 Ingelheim, Alemania

declaran bajo juramento ser únicos y verdaderos inventores de la invención

“Formulaciones de soluciones de HFC que contienen tiotropio”

y declaran así mismo que ceden y transfieren sin limitación a favor de la sociedad Boehringer Ingelheim Pharma GmbH & Co. KG, constituida y existente de conformidad con las leyes de Alemania, domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. Hay dos firmas ilegibles de los mencionados señores. Dado y firmado el 11 de mayo 2005, en Ingelheim, Alemania.

Certificación en inglés de las firmas antecedentes por el notario de Ingelheim am Rhein, Alfred Fuchs, el 13 de mayo 2005 bajo UR.No. 1021/2005. Hilo y oblea notarial en relieve.

Luz Arriaga de Herber
Notario de Ingelheim am Rhein
Fuchs

11

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: República Federal de Alemania

Este documento público

2. Ha sido firmado por Alfred Fuchs

3. Actuando en calidad de notario

4. Lleva el sello oficial del notario de Ingelheim am Rhein, Alfred Fuchs

Certificado

5. en Mainz

6. el 17.05.2005

7. por el Presidente del Tribunal Regional

8. bajo el No. 635/2005

9. Sello

10. Firma

Tribunal Regional de Mainz

Fdo.: ilegible

(sello redondo No. 15)

(Dr. Rolf Höfel)

Costas

Derechos de legalización

Valor: 20.000,00 €

JVKostO del 26.7.1957 en
combinación con Art. 45 KostO

Derechos: 18.00 €

Mainz, 17.05.05

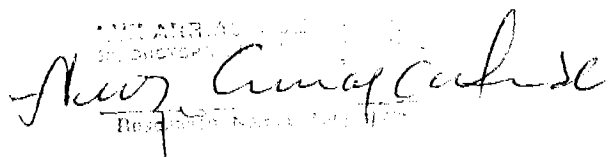
Fdo.: firma ilegible

Secretaria judicial z.A.

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas
oficinas para su confrontación.

Bogotá, 8 de junio de 2005.

C. 1842


Resolución No. 1000 de 2005

COMANDO EN JEFE DEL EJERCITO DEL CAUCASO
BOGOTÁ, D.C. 15 JUN 2005

En 2 Priaga de
Herber

COPIA REGISTRADA POR
JEFATURA NOTARIA

15 JUN 2005

NO SE ASUME
RESPONSABILIDAD DEL
2005 JUN 15 2:53
JEF. DE LEGALIZAC.
SANTAFE DE BOGOTÁ

MINISTERIO DE RELACIONES
EXTERIORES
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Jes. Priaga
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(54) Title: TIOTROPIUM CONTAINING HFC SOLUTION FORMULATIONS

(57) Abstract: This invention relates to tiotropium containing stable pharmaceutical solution formulations suitable for aerosol administration. More particularly, this invention relates to tiotropium containing stable pharmaceutical solution formulations suitable for aerosol administration wherein either an inorganic acid or an organic acid is added to the aerosol solution formulation which contains a tiotropium salt, preferably tiotropium bromide in solution with an environmentally safe hydrofluorocarbon (HFC) as a propellant, together with an organic compound as a cosolvent. The acid provides stability against degradation or decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation.

WO 2004/054580 A1

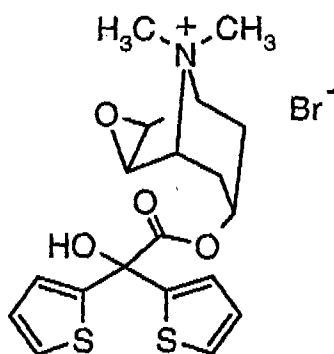
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TIOTROPIUM CONTAINING HFC SOLUTION FORMULATIONS

This invention relates to tiotropium containing stable pharmaceutical solution formulations suitable for aerosol administration. More particularly, this invention relates to tiotropium
5 containing stable pharmaceutical solution formulations suitable for aerosol administration wherein either an inorganic acid or an organic acid is added to the aerosol solution formulation which contains a tiotropium salt, preferably tiotropium bromide in solution with an environmentally safe hydrofluorocarbon (HFC) as a propellant, together with an organic compound as a cosolvent. The acid provides stability against degradation or
10 decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation.

BACKGROUND OF THE INVENTION

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and has
15 the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long-lasting activity which can be used to treat respiratory complaints, particularly COPD (chronic obstructive
20 pulmonary disease) and asthma. The term tiotropium refers to the free ammonium cation.

For treating the abovementioned complaints, it is useful to administer the active substance by inhalation. In addition to the administration of broncholytically active compounds in the form of inhalable powders containing the active substance the administration of tiotropium
25 bromide can also occur in form of hydrofluorocarbon containing aerosol solution formulations.

The administration of aerosol formulations of medicaments by means of pressurized, metered-dose inhalers (MDIs) is used widely in therapy, such as in the treatment of obstructive airway diseases and asthma. Compared with oral administration, inhalation provides more rapid onset of action while minimizing systemic side effects. Aerosol
5 formulations can be administered by inhalation through the mouth or topically by application to the nasal mucosa.

Formulations for aerosol administration via MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous in nature with the medicament and excipient completely dissolved in the propellant vehicle. Solution
10 formulations also obviate physical stability problems associated with suspension formulations and thus assure more consistent uniform dosage administration while also eliminating the need for surfactants.

The administration of aerosol solution formulations via MDIs is dependent upon the propulsive force of the propellant system used in its manufacture. Traditionally, the
15 propellant comprised a mixture of chlorofluorocarbons (CFCs) to provide the desired solubility, vapor pressure, and stability of the formulation. However, since it has been established in recent years that CFCs are environmentally harmful because they contribute to the depletion of the Earth's ozone layer, it is desirable to substitute environmentally safe hydrofluorocarbon (HFC) propellants or other non-chlorinated propellants for
20 environmentally harmful CFC propellants in aerosol inhalation formulations. For example, U.S. Patent No. 4,174,295 discloses the use of propellant systems consisting of combinations of HFCs, which may also contain a saturated hydrocarbon component, suitable for application in the fields of home products such as hair lacquers, anti-perspiration products, perfumes, deodorants, paints, insecticides and the like.

25 It is known in the art that certain HFCs have properties suitable for use as propellants for the aerosol administration of medicaments. For example, published European patent Application No. 0 372 777 (EPO89312270.5) describes the use of 1,1,1,2-tetrafluoroethane (HFC-134(a)) in combination with at least one "adjuvant" (a compound having a higher polarity than the HFC-134(a)) and a surface active agent to prepare suspension and
30 solution formulations of medicaments suitable for administration by the aerosol route. Also, PCT Published Application No. W091/11496 (PCT/EP91/00178) discloses the use of 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), optionally mixed with other propellant components, for use in preparing suspension aerosol formulations of medicaments. US-A-2 868 641 and US-A-3 282 781 disclose aerosol compositions comprising a
35 medicament (epinephrine or isoproterenol HCl), a cosolvent, a propellant and ascorbic acid

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as anti-oxidant. European Patent EP 673 240 B1 proposes the addition of acids to medicinal aerosol formulations in order to provide for the stabilization of the medicament.

DESCRIPTION OF THE INVENTION

5 The term "aerosol solution formulation" means a pharmaceutical formulation of a medicament suitable for aerosol administration wherein the medicament and excipients are completely dissolved.

The term "stabilized aerosol solution formulation" means an aerosol solution formulation which exhibits substantial chemical stability over time.

10

The present invention provides stabilized aerosol solution formulations comprising a tiotropium salt, an HFC propellant, a cosolvent, and an inorganic or an organic acid, characterized in that the concentration of the acid is in a range that corresponds with a pH range of 2.5 - 4.5 in aqueous solution.

15

In preferred aerosol solution formulations according to the invention the concentration of the acid is in a range that corresponds with a pH range of 3.0 - 4.3, more preferred 3.5 - 4.0 in aqueous solution.

20 A small amount of water (up to about 5%, preferably up to about 3 % by weight,) may also be present in the propellant/cosolvent system.

The aerosol solution formulation according to the invention preferably contains 0.00008 to 0.4 %, preferably 0.0004 to 0.16 %, more preferably 0.0008 to 0.08 % tiotropium. By
25 tiotropium is meant the free ammonium cation. In the tiotropium salt present in the formulation according to the invention the counter-ion (anion) may be chloride, bromide, iodide, methanesulphonate or para-toluenesulphonate. Of these anions, the bromide is preferred.

30 If the preferred tiotropium salt tiotropium bromide is used, the aforementioned amounts correspond to 0.000096 to 0.48 % tiotropium bromide, preferably 0.00048 to 0.192 %, more preferably 0.00096 to 0.096 % tiotropium bromide.

Tiotropium bromide is, depending on the choice of reaction conditions and solvents,
35 obtainable in different crystalline modifications. Most preferred according to the invention

are those formulations, that contain tiotropium in form of the tiotropium bromide monohydrate as disclosed in WO 02/30928. This tiotropium bromide monohydrate is characterised by an endothermic peak at $230 \pm 5^\circ\text{C}$ as determined by DSC.

- 5 Accordingly, the aerosol solution formulations according to the invention preferably contains 0.0001 to 0.5 % tiotropium bromide monohydrate, preferably 0.0005 to 0.2 %, more preferably 0.001 to 0.1 % tiotropium bromide monohydrate.

Suitable HFC propellants are those which, when mixed with the cosolvent(s), form a
10 homogeneous propellant system in which a therapeutically effective amount of the medicament can be dissolved. The HFC propellant must be toxicologically safe and must have a vapor pressure which is suitable to enable the medicament to be administered via a pressurized MDI. Additionally, the HFC propellant must be compatible with the components of the MDI device (such as containers, valves, and sealing gaskets, etc.) which
15 is employed to administer the medicament. Preferred HFC propellants are 1,1,1,2-tetrafluoroethane (HFC-134(a)) and 1,1,1,2,3,3,3,-heptafluoropropane (HFC-227). HFC-134(a) is particularly preferred. Other examples of HFC propellants are HFC-32 (difluoromethane), HFC-143(a) (1,1,1-trifluoroethane), HFC-134 (1,1,2,2-tetrafluoroethane), and HFC-152a (1,1-difluoroethane).

- 20 It will be apparent to those skilled in the art that non-halogenated hydrocarbon propellants may be used in place of the HFC propellants in the present invention. Examples of non-halogenated hydrocarbons are saturated hydrocarbons, including propane, n-butane, and isobutane, and ethers, including diethyl ether.

It will also be apparent to those skilled in the art that, although the use of a single HFC
25 propellant is preferred, a mixture of two or more HFC propellants, or a mixture of at least one HFC propellant and one or more non-CFC propellants, may be employed in the aerosol solution formulation of the present invention.

- A substantially non-aqueous HFC propellant/cosolvent system is preferred. Water may be present in small amounts as an impurity in the HFC propellant/cosolvent system, may be
30 introduced during the manufacturing process or may permeate into the system through the valve or valve/container seals or gaskets. If desired, small amounts of water may be added (up to about 5%, preferably up to about 2 % by weight) to the HFC/propellant system, for example, to aid in manufacturing.

The acid in the formulations according to the invention may be any inorganic or mineral acid, for example, hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid, or the like. From the aforementioned acids hydrochloric acid is of particular interest. The acid may also be selected from the group of acids known to those skilled in the art as organic acids, which are in most cases considered to be weak acids relative to the inorganic acids. Representative of this group and preferred in this invention are ascorbic acid, citric acid, lactic acid, malic acid, benzoic acid and tartaric acid. According to this invention, citric acid and ascorbic acid are the most preferred organic acids.

10 The formulations according to the invention can be prepared in analogy to methods known in the art.

If desired, pharmaceutically acceptable excipients can be included in the aerosol solution formulations of the present invention. For example, a soluble surface active agent can be added in order to improve the performance of valve systems employed in the MDI devices used for the aerosol administration of the formulations. Examples of preferred surface active agents are sorbitan trioleate, lecithin, and isopropylmyristate. Other suitable lubricants are well known in the art (see, for example, Published European Patent Application No. 0372777 (EPO 893122705)). Other excipients are: (a) antioxidants, for example ascorbic acid and tocopherol; (b) taste masking agents, for example, menthol, sweeteners, and artificial or natural flavors; and (c) pressure modifying agents, for example, n-pentane, iso-pentane, neo-pentane, and n-hexane.

Examples of cosolvents applicable within the formulations according to the invention are: alcohols, for example, ethyl alcohol, isopropyl alcohol, and benzyl alcohol; glycols for example, propylene glycol, polyethylene glycols, polypropylene glycols, glycol ethers, and block copolymers of oxyethylene and oxypropylene; and other substances, for example, glycerol, polyoxyethylene alcohols, polyoxetethylene fatty acid esters, and glycofurols (for example glycofurol 75).

30 Examples of cosolvents that may be inert to interaction with the medicament(s) are hydrocarbons, for example, n-propane, n-butane, isobutane, n-pentane, iso-pentane, neo-pentane, and n-hexane; and ethers, for example, diethyl ether.

A preferred cosolvent according to this invention is ethyl alcohol (ethanol).

The amount of cosolvent is preferably in the range of 5 - 50% (w/w) of the total composition. More preferably, the amount of co-solvent in the formulation according to the invention is in the range of 10 - 40 % (w/w), preferably in the range of 15 - 30 %.

- 5 As mentioned hereinbefore the formulations according to the invention may contain water a small amount of water. One preferred embodiment of the invention pertains to formulations that contain water in an amount of up to 5% (w/w), preferably of up to 3 % (w/w). Another preferred embodiment of the invention is directed to formulations that do not contain any water. In these water-free formulations the amount of cosolvent is
- 10 preferably in the range of about 20 - 50% (w/w), more preferably in the range of about 30 - 40% (w/w).

- Especially in these water-free formulations the anhydrous form of tiotropium bromide obtainable from the tiotropium bromide monohydrate mentioned hereinbefore can be used.
- 15 The anhydrous form is obtained from the crystalline tiotropium bromide monohydrate disclosed in WO 02/30928 by careful drying at more than 50°C, preferably at 60-100°C, most preferably at 70-100°C, under reduced pressure, preferably in a high vacuum over a period of 15 minutes to 24 hours, preferably 20 minutes to 12 hours, most preferably 30 minutes to 6 hours. The term "reduced pressure" most preferably refers to a pressure of up
- 20 to 5×10^{-2} bar, preferably 1×10^{-2} bar, most preferably 5×10^{-3} bar. Most preferably, the abovementioned dehydration to form the anhydrate is carried out at about 1×10^{-3} bar or less.

- Alternatively to the drying step at elevated temperature under reduced pressure described
- 25 above, the anhydrous form may also be prepared by storing the crystalline tiotropium bromide monohydrate over a drying agent, preferably over dried silica gel at ambient temperature for a period of 12 to 96 hours, preferably 18 to 72 hours, most preferably at least 24 hours. The anhydrous form thus obtained should be stored more or less dry, depending on the particle size, to preserve its anhydrous state. In the case of coarse crystals
- 30 of anhydrous tiotropium bromide, which may be prepared for example as described above, storage at < 75 % r.h. (relative humidity) is sufficient to maintain the anhydrous state. In the micronised state, i.e. when the material has a much larger surface area, water may even be absorbed at lower humidity levels. In order to maintain the anhydrous form in the micronised state, it is therefore advisable to store the anhydrous form of tiotropium
- 35 bromide over dried silica gel.

The anhydrous form of tiotropium bromide was subjected to X-ray analysis which revealed that the crystalline anhydrous tiotropium bromide is characterised by the elementary cells $a = 10.4336(2)\text{\AA}$, $b = 11.3297(3)\text{\AA}$, $c = 17.6332(4)\text{\AA}$ and $\alpha = 90^\circ$, $\beta = 105.158(2)^\circ$ and $\gamma = 90^\circ$ (cell volume = $2011.89(8)\text{\AA}^3$). The crystalline structure of the anhydrous form of tiotropium bromide can be described as a layered structure. The bromide ions are located between the layers of tiotropium. Further details concerning the determination of the crystalline structure of the said anhydrous form are outlined in the experimental part of this patent application.

10

Accordingly, a further preferred embodiment of the invention is directed to a stabilized aerosol solution formulation comprising anhydrous tiotropium bromide characterized by the aforementioned parameters, an HFC propellant, a cosolvent, and an inorganic or an organic acid, characterized in that the concentration of the acid is in a range that corresponds with a pH range of 2.5 - 4.5 in aqueous solution and further characterized in that the formulation is free of water.

15

The formulations according to the invention can be administered with inhalers known in the art (Metered dose inhalers = MDIs).

20

In another aspect the invention is directed to the use of an aerosol solution formulation as described hereinbefore for the manufacture of a medicament for the treatment of respiratory complaints, particularly COPD (chronic obstructive pulmonary disease) and asthma.

25

In yet another aspect the invention is directed to a method for treatment of respiratory complaints, such as in particular COPD (chronic obstructive pulmonary disease) or asthma, characterized by the administration of an aerosol solution formulation as described hereinbefore.

30

The following Examples serve to illustrate the present invention further without restricting its scope to the embodiments provided hereinafter by way of example.

35

I. Formulation examples

A)

Component	Concentration [% w/w]
Tiotropium bromide monohydrate	0.02
Ethanol abs. (USP)	25.0
Water (purified, USP)	1.0
Citric acid (USP)	0.003
HFC-134a	73.977

5 B)

Component	Concentration [% w/w]
Tiotropium bromide monohydrate	0.02
Ethanol abs. (USP)	20.0
Aqueous HCl 0.01 mol/l (USP)	2.0
HFC-134a	77.98

C)

Component	Concentration [% w/w]
Tiotropium bromide monohydrate	0.01
Ethanol abs. (USP)	15.0
Water (purified, USP)	2.0
Citric acid (USP)	0.004
HFC-227	82.986

D)

Component	Concentration [% w/w]
Tiotropium bromide monohydrate	0.01
Ethanol abs. (USP)	30.0
Water (purified, USP)	1.0
Ascorbic acid (USP)	0.005
HFC-134a	68.985

E)

Component	Concentration [% w/w]
Tiotropium bromide (anhydrous)	0.01
Ethanol abs. (USP)	40.0
citric acid (USP)	0.004
HFC-227	59.986

The aforementioned formulations can be prepared by conventional methods known in the state of the art.

5

II. Preparation of crystalline anhydrous tiotropium bromide:

The anhydrous form is produced from the crystalline tiotropium bromide monohydrate (obtainable as described in WO 02/30928) by careful drying at 80 – 100 °C under reduced pressure, preferably under a high vacuum (at about 1×10^{-3} bar or less) over a period of at least 30 minutes. Alternatively to the drying step at 80 – 100 °C *in vacuo* the anhydrous form may also be prepared by storing over dried silica gel at ambient temperature for a period of at least 24 hours.

15 III. Characterisation of crystalline, anhydrous tiotropium bromide

As described hereinbefore, the crystalline anhydrous tiotropium bromide according to the invention may be obtained from crystalline tiotropium bromide monohydrate.

The crystalline structure of anhydrous tiotropium bromide was determined from high-resolution X-ray powder data (synchrotron radiation) using a real space approach with a so-called simulated annealing process. A final Rietveld analysis was carried out to refine the structural parameters. Table 1 contains the experimental data obtained for crystalline, anhydrous tiotropium bromide.

22

Table 1: Experimental data relating to the crystalline structural analysis of tiotropium bromide (anhydrous)

formula	$C_{19}H_{22}NO_4S_2Br$
temperature [°C]	25
molecular weight [g/mol]	472.4
space group	$P2_1/c$
a [Å]	10.4336(2)
b [Å]	11.3297(3)
c [Å]	17.6332(4)
β [°]	105.158(2)
V [Å ³]	2011.89(8)
Z	4
calculated density [g cm ⁻³]	1.56
2Θ (range) [°]	2.0 – 20
interval [° 2Θ]	0.003
counting time / step [sec]	3
wavelength [Å]	0.7000

- 5 The crystalline structure of the anhydrous form of tiotropium bromide can be described as a layered structure. The bromide ions are located between the layers of tiotropium.

In order to clarify the structure of crystalline anhydrous tiotropium bromide a high-resolution X-ray powder diagram was taken at ambient temperature at the National
10 Synchrotron Source (Brookhaven National Laboratory, USA) at measuring station X3B1 ($\lambda = 0.700$ Å). For this experiment a sample of crystalline tiotropium bromide monohydrate was placed in a quartz glass capillary 0.7 mm in diameter. The water was eliminated by heating to 80°C in an oven under reduced pressure.

- 15 The structural resolution was obtained by a so-called simulated annealing process. The DASH program package produced by Cambridge Crystallographic Data Center (CCDC, Cambridge, United Kingdom) was used for this.

Table 2 shows the atomic coordinates obtained for crystalline anhydrous tiotropium bromide.

5 Table 2: Coordinates

Atom	x	y	z	U _{iso}
S1	1.0951(8)	0.3648(8)	0.8189(5)	0.075(9)
S1	0.9143(9)	0.1374(8)	0.9856(5)	0.075(9)
O	0.6852(13)	0.2339(6)	0.7369(6)	0.075(9)
O1	0.7389(15)	0.0898(9)	0.8234(6)	0.075(9)
O2	0.8211(10)	0.3897(17)	0.8277(7)	0.075(9)
O3	0.4975(17)	0.4816(9)	0.6011(7)	0.075(9)
N	0.4025(10)	0.2781(8)	0.5511(5)	0.075(9)
C	0.7509(8)	0.1885(6)	0.8038(5)	0.075(9)
C1	0.8593(7)	0.2788(5)	0.8495(4)	0.075(9)
C2	0.9924(9)	0.2533(6)	0.8225(6)	0.075(9)
C3	0.8884(9)	0.2664(7)	0.9382(4)	0.075(9)
C4	0.5848(12)	0.1596(8)	0.6753(8)	0.075(9)
C5	0.4544(13)	0.1929(14)	0.6809(8)	0.075(9)
C6	0.6156(13)	0.1810(13)	0.5973(9)	0.075(9)
C7	0.5493(11)	0.2881(11)	0.5578(6)	0.075(9)
C8	0.5869(12)	0.3832(11)	0.6092(7)	0.075(9)
C9	0.4947(13)	0.3902(10)	0.6575(6)	0.075(9)
C10	0.4004(10)	0.2998(11)	0.6332(6)	0.075(9)
C11	0.3220(13)	0.3670(13)	0.4935(6)	0.075(9)
C12	0.3450(19)	0.1643(26)	0.5211(11)	0.075(9)
C13	0.9184(16)	0.3808(9)	0.9920(6)	0.075(9)
C14	1.0313(16)	0.1552(15)	0.8011(15)	0.075(9)
C15	0.9515(17)	0.3374(10)	0.0501(6)	0.075(9)
C16	0.9756(18)	0.2190(11)	1.0742(5)	0.075(9)
C17	1.1483(22)	0.1762(18)	0.7718(24)	0.075(9)

24
25

C18	1.1860(16)	0.2800(15)	0.7768(19)	0.075(9)
BR	0.4597(4)	0.8200(15)	0.61902(25)	0.042(9)

In the above Table the "U_{iso}" values denote the isotropic temperature factors. For example, in single-crystal X-ray structural analysis this corresponds to the u(eq) values.

- 5 Table 3 shows the reflexes (h,k,l indices) of the powder diagram obtained for crystalline anhydrous tiotropium bromide.

Table 3: Experimental data relating to the crystalline structural analysis of anhydrous tiotropium bromide

10

No.	h	k	l	2 Θ _{obs.}	2 Θ _{calc.}	2 Θ _{obs.} - 2 Θ _{calc.}
1	1	0	0	8.762	8.769	-0.007
2	0	1	1	9.368	9.369	-0.001
3	-1	0	2	11.730	11.725	0.005
4	0	1	2	12.997	13.004	-0.007
5	-1	1	2	14.085	14.094	-0.009
6	1	0	2	15.271	15.275	-0.004
7	0	0	3	15.620	15.616	0.004
8	0	2	1	16.475	16.475	0.0
9	1	1	2	17.165	17.170	-0.005
10	2	0	0	17.588	17.591	-0.003
11	-1	2	1	18.009	18.035	-0.026
12	1	2	1	19.336	19.328	0.008
13	-2	1	2	19.596	19.600	-0.004
14	-1	0	4	20.417	20.422	-0.005
15	0	0	4	20.865	20.872	-0.007
16	2	1	1	21.150	21.145	0.005
17	-2	1	3	21.759	21.754	0.005
18	0	2	3	22.167	22.160	0.007

19	-1	2	3	22.289	22.288	0.001
20	2	0	2	22.735	22.724	0.011
21	-2	2	1	23.163	23.159	0.004
22	-2	0	4	23.567	23.575	-0.008
23	2	1	2	24.081	24.058	0.023
24	1	0	4	24.746	24.739	0.007
25	-1	3	1	25.220	25.221	-0.001
26	1	2	3	25.359	25.365	-0.006
27	0	3	2	25.790	25.783	0.007
28	1	1	4	25.978	25.975	0.003
29	0	2	4	26.183	26.179	0.004
30	-1	3	2	26.383	26.365	0.018
31	-1	1	5	26.555	26.541	0.014
32	-3	1	2	27.024	27.021	0.003
33	3	1	0	27.688	27.680	0.008
34	-3	1	3	28.221	28.215	0.006
35	3	0	1	28.377	28.376	0.001
36	-3	0	4	29.246	29.243	0.003
37	3	1	1	29.459	29.471	-0.012
38	-1	2	5	29.906	29.900	0.006
39	-3	2	1	30.171	30.165	0.006
40	0	2	5	30.626	30.626	0.0
41	1	1	5	30.871	30.856	0.015
42	0	0	6	31.504	31.532	-0.028
43	2	1	4	31.826	31.847	-0.021
44	-2	1	6	32.888	32.888	0.0
45	1	4	1	33.605	33.615	-0.010
46	3	0	3	34.379	34.377	0.002
47	1	0	6	35.021	35.018	0.003

76

48	-4	1	1	35.513	35.503	0.01
49	1	1	6	35.934	35.930	0.004
50	-1	1	7	36.544	36.543	0.001
51	-4	1	4	37.257	37.255	0.002
52	-4	2	2	37.933	37.952	-0.019
53	4	1	1	38.258	38.264	-0.006

Claims

1. Aerosol solution formulation comprising a tiotropium salt, an HFC propellant, a cosolvent, and an inorganic or an organic acid, characterized in that the concentration
5 of the acid is in a range that corresponds with a pH range of 2.5 - 4.5 in aqueous solution.
2. Aerosol solution formulation according to claim 1, characterized in that it contains 0.00008 to 0.4 % tiotropium.
- 10 3. Aerosol solution formulation according to claim 1 or 2, characterised in that the counter-ion (anion) forming together with tiotropium the tiotropium salt may be chloride, bromide, iodide, methanesulphonate or para-toluenesulphonate.
- 15 4. Aerosol solution formulation according to claim 1, 2 or 3, characterised in that the HFC propellant is selected from HFC-134(a), HFC-227, HFC-32, HFC-143(a), HFC-134, HFC-152a and mixtures thereof.
- 20 5. Aerosol solution formulation according to claim 1, 2, 3 or 4, characterised in that the acid is selected from the inorganic acids hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid.
- 25 6. Aerosol solution formulation according to claim 1, 2, 3 or 4, characterised in that the acid is selected from the organic acids ascorbic acid, citric acid, lactic acid, malic acid, benzoic acid, and tartaric acid.
7. Aerosol solution formulation according to one of claims 1 to 6, characterised in that it contains water in an amount of up to about 5%.
- 30 8. Aerosol solution formulation according to one of claims 1 to 7, characterised in that it contains as a cosolvent alcohols, glycols, glycol ethers, block copolymers of oxyethylene and oxypropylene, glycerol, polyoxyethylene alcohols, polyoxetethylene fatty acid esters or glycofurols.

9. Aerosol solution formulation according to one of claims 1 to 8, characterised in that the cosolvent is present in an amount in the range of 5 - 50% (w/w).
10. Aerosol solution formulation according to one of claims 1 to 6, 8 or 9, characterised in
5 that it contains no water.
11. Use of an aerosol solution formulation according to one of claims 1 to 10 for the manufacture of a medicament for the treatment of respiratory complaints.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/13692

29

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/46 A61K9/00

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

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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

X	WO 94 13262 A (NAGEL JURGEN H ;KONTNY MARK J (US); JAGER PAUL D (US)) 23 June 1994 (1994-06-23) page 8, line 6 - line 7; tables 1-3,5	1-11
X	WO 02 38154 A (BOEHRINGER INGELHEIM PHARMA ;NAGEL JUERGEN (DE); SCHMELZER CHRISTE) 16 May 2002 (2002-05-16) page 19, line 1 - line 4	1-11

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

3 March 2004

Date of mailing of the international search report

12/03/2004

Name and mailing address of the ISA

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

Authorized officer

Loher, F

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/13692

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9413262	A	23-06-1994	AT 177941 T	15-04-1999
			AU 680227 B2	24-07-1997
			AU 5740594 A	04-07-1994
			AU 6048694 A	04-07-1994
			BG 62382 B1	29-10-1999
			BG 99760 A	29-02-1996
			BR 9307627 A	15-06-1999
			CA 2151383 A1	23-06-1994
			CZ 9501490 A3	13-12-1995
			DE 69324161 D1	29-04-1999
			DE 69324161 T2	28-10-1999
			DK 673240 T3	11-10-1999
			EP 0673240 A1	27-09-1995
			ES 2129117 T3	01-06-1999
			FI 952842 A	09-06-1995
			GB 2288978 A ,B	08-11-1995
			GR 3030529 T3	29-10-1999
			HK 1011620 A1	20-04-2000
			HU 72985 A2	28-06-1996
			JP 3009924 B2	14-02-2000
			JP 8509459 T	08-10-1996
			LV 10911 A	20-12-1995
			LV 10911 B	20-04-1996
			NO 952269 A	08-06-1995
			NZ 259192 A	26-05-1997
			PL 309333 A1	02-10-1995
			RO 117414 B1	29-03-2002
			SG 52459 A1	28-09-1998
			SK 76095 A3	08-01-1997
			WO 9413262 A1	23-06-1994
			WO 9413263 A1	23-06-1994
			US 6045778 A	04-04-2000
			US 5676930 A	14-10-1997
			US 5955058 A	21-09-1999
			CN 1095265 A ,B	23-11-1994
			RU 2126248 C1	20-02-1999
			TW 403657 B	01-09-2000
			ZA 9309195 A	08-06-1995
WO 0238154	A	16-05-2002	DE 10056104 A1	23-05-2002
			AU 2791002 A	21-05-2002
			BR 0115226 A	07-10-2003
			CA 2429012 A1	16-05-2002
			CZ 20031444 A3	13-08-2003
			EE 200300228 A	15-10-2003
			WO 0238154 A1	16-05-2002
			EP 1335728 A1	20-08-2003
			HU 0301447 A2	28-10-2003
			NO 20032111 A	08-07-2003
			SK 7412003 A3	07-10-2003
			US 2002193392 A1	19-12-2002

PCT REQUEST

Original (for SUBMISSION) - printed on 03.12.2003 10:43:12 AM

1-1438-PCT

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	1-1438-PCT
I	Title of invention	TIOTROPIUM CONTAINING HFC SOLUTION FORMULATIONS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
II-5	Address:	Binger Strasse 173 D-55216 INGELHEIM Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	06132/77-2463
II-9	Facsimile No.	06132/77-4377
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	SIX, Sabine
III-1-5	Address:	Diltheystrasse 2 A D-65203 WIESBADEN Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

1-1438-PCT

Original (for SUBMISSION) - printed on 03.12.2003 10:43:12 AM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	SCHMELZER, Christel
III-2-5	Address:	Welfenstrasse 14 D-55218 INGELHEIM Germany
III-2-6	State of nationality	DE
III-2-7	State of residence	DE
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	SCHMIDT, Friedrich
III-3-5	Address:	Feierabendweg 2 D-55218 INGELHEIM Germany
III-3-6	State of nationality	DE
III-3-7	State of residence	DE
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
IV-1-2	Address:	Binger Strasse 173 D-55216 INGELHEIM Germany
IV-1-3	Telephone No.	06132/77-2463
IV-1-4	Facsimile No.	06132/77-4377

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier regional application	
VI-1-1	Filing date	16 December 2002 (16.12.2002)
VI-1-2	Number	02028238.0
VI-1-3	Regional Office	EP
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	14	-
IX-3	Claims	2	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	22	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	
X-1-2	Name of signatory	Dr. Kompter	
X-1-3	Capacity	ppa.	
X-2	Signature of applicant, agent or common representative		
X-2-1	Name	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	
X-2-2	Name of signatory	Dr. Weymann	
X-2-3	Capacity	i.v.	
FOR RECEIVING OFFICE USE ONLY			
10-1	Date of actual receipt of the purported international application		

50

PCT REQUEST

1-1438-PCT

Original (for SUBMISSION) - printed on 03.12.2003 10:43:12 AM

10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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36

PCT (ANNEX - FEE CALCULATION SHEET)

1-1438-PCT

Original (for **SUBMISSION**) - printed on 03.12.2003 10:43:12 AM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only		
0-1	International Application No.		
0-2	Date stamp of the receiving Office		
0-4	Form - PCT/RO/101 (Annex)		
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)	
0-9	Applicant's or agent's file reference	1-1438-PCT	
2	Applicant	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, et al.	
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (EUR)
12-1	Transmittal fee T	⇒	100
12-2-1	Search fee S	⇒	945
12-2-2	International search to be carried out by	EP	
12-3	International fee		
	Basic fee (first 30 sheets) b1	444	
12-4	Remaining sheets	0	
12-5	Additional amount (X)	10	
12-6	Total additional amount b2	0	
12-7	b1 + b2 = B	444	
12-8	Designation fees		
	Number of designations contained in international application	99	
12-9	Number of designation fees payable (maximum 5)	5	
12-10	Amount of designation fee (X)	96	
12-11	Total designation fees D	480	
12-12	PCT-EASY fee reduction R	-137	
12-13	Total International fee (B+D-R) I	⇒	787
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	1.832
12-19	Mode of payment	authorization to charge deposit account	
12-20	Deposit account instructions		
	The receiving Office:	European Patent Office (EPO) (RO/EP)	
12-20-1	Authorization to charge the total fees indicated above.	✓	
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓	
12-21	Deposit account No.	2800.0140	
12-22	Date	03 December 2003 (03.12.2003)	

37

PCT (ANNEX - FEE CALCULATION SHEET)

1-1438-PCT

Original (for SUBMISSION) - printed on 03.12.2003 10:43:12 AM

12-23	Name and signature	BOEHRINGER INGELHEIM GMBH i.V.  i.V.  Dr. Kompter Dr. Weymann
-------	--------------------	--

VALIDATION LOG AND REMARKS

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

Original (for **SUBMISSION**) - printed on 03.12.2003 10:43:12 AM**PCT-EASY INFORMATION SHEET**

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

	Contents
Green?	The international application contains no drawings. Please verify.
	Fees
Green?	Please confirm that fee schedule utilized is the latest available
	Payment
Green?	Please ensure that you have a valid deposit account with the receiving Office selected.

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
- all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION**DO NOT** modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked.

If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.



**Europäisches
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Patent Office**

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des brevets**

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02028238.0

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

Friedrich SCHMIDT, Feierabendweg 2, 55218 Ingelheim, Germany
Sabine SIX, Dilttheistr. 2A, 65203 Wiesbaden, Germany

hereby appoints (appoint) the following person as:

☐

agent

☒

common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Str. 173, 55216 Ingelheim, Germany

to represent the undersigned before

☒

all the competent International Authorities

☐

the International Searching Authority only

☐

the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention:

Applicant's or agent's file reference: Case 1/1438

International application number (if already available):

filed with the following Office European Patent Office

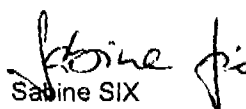
as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):



Friedrich SCHMIDT



Sabine SIX

Date:

October 21, 2003

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

Christel SCHMELZER
Welfenstrasse 14
55218 Ingelheim, Germany

hereby appoints (appoint) the following person as:

☐

agent

☒

common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Str. 173, 55216 Ingelheim, Germany

to represent the undersigned before

☒

all the competent International Authorities

☐

the International Searching Authority only

☐

the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention:

Applicant's or agent's file reference: Case 1/1438

International application number (if already available):

filed with the following Office European Patent Office as receiving Office
and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power);

Christel SCHMELZER

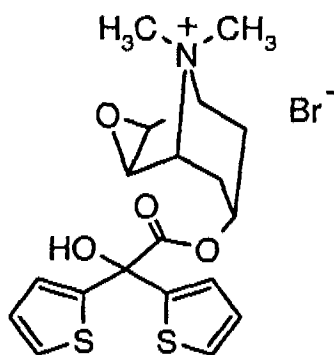
Date: October 15, 2003

TIOTROPIUM CONTAINING HFC SOLUTION FORMULATIONS

This invention relates to tiotropium containing stable pharmaceutical solution formulations suitable for aerosol administration. More particularly, this invention relates to tiotropium
5 containing stable pharmaceutical solution formulations suitable for aerosol administration wherein either an inorganic acid or an organic acid is added to the aerosol solution formulation which contains a tiotropium salt, preferably tiotropium bromide in solution with an environmentally safe hydrofluorocarbon (HFC) as a propellant, together with an organic compound as a cosolvent. The acid provides stability against degradation or
10 decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation.

BACKGROUND OF THE INVENTION

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and has
15 the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long-lasting activity which can be used to treat respiratory complaints, particularly COPD (chronic obstructive
20 pulmonary disease) and asthma. The term tiotropium refers to the free ammonium cation.

For treating the abovementioned complaints, it is useful to administer the active substance by inhalation. In addition to the administration of broncholytically active compounds in the form of inhalable powders containing the active substance the administration of tiotropium
25 bromide can also occur in form of hydrofluorocarbon containing aerosol solution formulations.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

BOEHRINGER INGELHEIM PHARMA GMBH &
CO. KG
Binger Strasse 173
55216 INGELHEIM
Germany

Eingang CD Patents

19. Jan. 2004

SB	gesehen	erledigt
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Date of mailing (day/month/year)

08 January 2004 (08.01.2004)

Applicant's or agent's file reference

1-1438-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/EP2003/013692

International filing date (day/month/year)

04 December 2003 (04.12.2003)

International publication date (day/month/year)

Not yet published

Priority date (day/month/year)

16 December 2002 (16.12.2002)

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a **priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a **priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority datePriority application No.Country or regional Office
or PCT receiving OfficeDate of receipt
of priority document

16 Dece 2002 (16.12.2002)

02028238.0

EP

23 Dece 2003 (23.12.2003)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338-7080

Authorized officer

Soumia SAADALLAH

Telephone No. (41-22) 338 8421

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

45

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

To:

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
Binger Strasse 173
55216 INGELHEIM
ALLEMAGNE

(PCT Rule 47.1(c), first sentence)

Eingang CD Patents

05 Juli 2004

ERFAST

Date of mailing (day/month/year)
01 July 2004 (01.07.2004)

SB gesehen erledigt

Applicant's or agent's file reference
1-1438-PCT

IMPORTANT NOTICE

International application No.
PCT/EP2003/013692

International filing date (day/month/year)
04 December 2003 (04.12.2003)

Priority date (day/month/year)
16 December 2002 (16.12.2002)

Applicant

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 01 July 2004 (01.07.2004) under No. WO 2004/054580

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Yolaine Cussac

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 70 80

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Eingang CD Patents

05. Juli 2004

To:

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
Binger Strasse 173
55216 INGELHEIM
ALLEMAGNE

Date of mailing (day/month/year) 01 July 2004 (01.07.2004)	SB WJ	gesehen	erledigt
Applicant's or agent's file reference 1-1438-PCT		IMPORTANT INFORMATION	
International application No. PCT/EP2003/013692	International filing date (day/month/year) 04 December 2003 (04.12.2003)		Priority date (day/month/year) 16 December 2002 (16.12.2002)
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al			

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR
National: AU, BG, BW, CA, CN, DE, EG, GB, IL, JP, KP, KR, MN, NI, NO, PG, PL, RO, RU, SK, SY, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SC, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1) (a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3) (b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yolaine Cussac
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 70 80

RW 49

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference Case 1/1438-PCT	
International application No. PCT/EP03/13692	International filing date (day/month/year) 04/12/2003
(Earliest) Priority date (day/month/year) 16/12/2002	
Title of invention Tiotropium containing HFC solution formulations	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Boehringer Ingelheim Pharma GmbH & Co. KG	
Binger Strasse 173	
55216 Ingelheim am Rhein	
DE	
Telephone No. 06132-77-2463	
Facsimile No. 06132-77-4377	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Sabine SIX	
Diltheystr. 2A	
65203 Wiesbaden	
DE	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Christel SCHMELZER	
Welfenstrasse 14	
55218 Ingelheim	
DE	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
☒ Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Friedrich SCHMIDT
Feierabendweg 2
55218 Ingelheim
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☐ agent ☒ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)*Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
DE

Telephone No.

06132-77-2463

Facsimile No.

06132-77-4377

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description

☐

as originally filed

☐

as amended under Article 34

the claims

☐

as originally filed

☐

as amended under Article 19 (together with any accompanying statement)

☐

as amended under Article 34

the drawings

☐

as originally filed

☐

as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒

which is the language in which the international application was filed.

☐

which is the language of a translation furnished for the purposes of international search.

☐

which is the language of publication of the international application.

☐

which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Boehringer Ingelheim Pharma GmbH & Co. KG

ppa.


Dr. Kompter


Dr. Weymann

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP03/13692 Applicant's or agent's file reference Case 1/1438-PCT	For International Preliminary Examining Authority use only Date stamp of the IPEA
Applicant CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee 1.530 € P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) 129 € H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box 1.659 € TOTAL MODE OF PAYMENT ☒ authorization to charge deposit account with the IPEA (see below) ☐ cheque ☐ postal money order ☐ bank draft ☐ cash ☐ revenue stamps ☐ coupons ☐ other (specify): AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all IPEAs)</i> ☒ Authorization to charge the total fees indicated above. ☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. IPEA/ <u>EP</u> Deposit Account No.: <u>2800.0140</u> Date: <u>March 17, 2004</u> Name: <u>Boehringer Ingelheim GmbH</u> Signature: <u><i>[Signature]</i></u> Dr. Kompter Signature: <u><i>[Signature]</i></u> Dr. Weymann	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

BOEHRINGER INGELHEIM
PHARMA GMBH & CO. KG Eingang CD Patents
Binger Strasse 173
D-55216 Ingelheim am Rhein 04. Feb. 2005
ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

SB	gesehen	erledigt

Date of mailing
(day/month/year)

03.02.2005

Applicant's or agent's file reference
Case 1/1438-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/13692

International filing date (day/month/year)
04.12.2003

Priority date (day/month/year)
16.12.2002

Applicant
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Sleex, C

Tel. +49 89 2399-8044



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 1/1438-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416)	
International application No. PCT/EP 03/13692	International filing date (day/month/year) 04.12.2003	Priority date (day/month/year) 16.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/46		
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 18.03.2004	Date of completion of this report 03.02.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Loher, F Telephone No. +49 89 2399-7839 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/13692**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/13692**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	5, 10
	No: Claims	1-4, 6-9, 11
Inventive step (IS)	Yes: Claims	
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 94 13262 A (NAGEL JURGEN H ;KONTNY MARK J (US); JAGER PAUL D (US)) 23 June 1994 (1994-06-23)

D2: WO 02 38154 A (BOEHRINGER INGELHEIM PHARMA ;NAGEL JUERGEN (DE); SCHMELZER CHRISTE) 16 May 2002 (2002-05-16)

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 1-4, 6-9 and 11 is not new.

D2 discloses an aerosol composition comprising tiotropium bromide, HFC 134(a), ethanol, water and citric acid in amounts as defined in the claims of the present application. Therefore, the subject-matter of claims 1-4, 6-9 and 11 is not new in the light of D2.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-11 does not seem to involve an inventive step.

D1, which is considered to represent the most relevant state of the art, discloses aerosol compositions comprising ipratropium bromide, HFC 134(a), ethanol and hydrochloric acid, ascorbic acid, citric acid or nitric acid, respectively. The acids are used in order to stabilize the composition. Tiotropium bromide as preferred active ingredient is mentioned as well.

The problem to be solved by the present invention may therefore be regarded as how to provide an stable aerosol formulation comprising a HFC propellant and a tiotropium salt.

The present application suggests to solve the problem posed by adding an organic or inorganic acid to an aerosol formulation comprising a tiotropium salt, a HFC propellant and a cosolvent.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 1-4, 6-9 and 11 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claim 5 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person as the posed problem has been solved by D1 using nitric or hydrochloric acid. The use of tiotropium instead of ipratropium is clearly contemplated by D1.

With respect to the subject-matter of the remaining claim 10 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the posed problem has been solved as the present application does not disclose a formulation containing no water, nor does it provide any data concerning the stability of such a composition that would be surprising over the teaching of D1.

It is therefore noted, that the solution proposed in claims 1-11 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

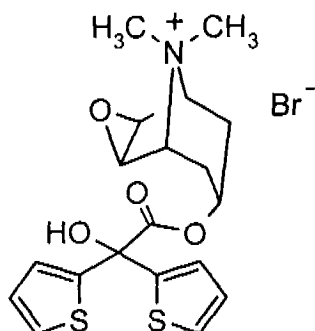
Art 33(4) The subject-matter of claims 1-11 is considered to be industrially applicable in the sense of Art 33(4) PCT.

FORMULACIONES DE SOLUCIONES DE HFC QUE CONTIENEN TIOTROPIO

Esta invención se refiere a formulaciones de soluciones farmacéuticas estables que contienen tiotropio, adecuadas para administración en aerosol. Más particularmente, esta invención se refiere a formulaciones de soluciones farmacéuticas estables que contienen tiotropio adecuadas para administración en aerosol en las que se añade un ácido inorgánico o un ácido orgánico a la formulación de la solución para aerosol que contiene una sal de tiotropio, preferiblemente bromuro de tiotropio en solución con un hidrofluorocarburo (HFC) seguro para el medio ambiente como propelente, junto con un compuesto orgánico como codisolvente. El ácido proporciona estabilidad frente a la degradación o descomposición del medicamento que se produce en gran medida a causa de la interacción del medicamento con el codisolvente y/o con el agua presente en la formulación de la solución.

ANTECEDENTES DE LA INVENCION

El bromuro de tiotropio es conocido por la solicitud de patente europea EP 418 716 A1 y tiene la siguiente estructura química:



El bromuro de tiotropio es un anticolinérgico altamente eficaz con una actividad de larga duración que se puede usar para tratar dolencias respiratorias, particularmente la COPD (enfermedad pulmonar obstructiva crónica) y el asma. El término tiotropio se refiere al catión de amonio libre.

Para tratar las dolencias mencionadas, es útil administrar la sustancia activa por inhalación. En adición a la administración de compuestos broncolíticamente activos en la forma de polvos inhalables que contienen la sustancia activa, la administración de bromuro de tiotropio se puede realizar también en forma de formulaciones de soluciones para aerosol que contienen hidrofluorocarburos.

La administración de formulaciones de medicamentos en aerosol por medio de inhaladores presurizados con medidor de dosis (los MDI) se usa ampliamente en terapéutica, tal como en el tratamiento de las enfermedades obstructivas de las vías respi-

ratorias y el asma. Comparada con la administración oral, la inhalación proporciona un comienzo de acción más rápido a la vez que minimiza los efectos secundarios sistémicos. Las formulaciones para aerosol se pueden administrar por inhalación a través de la boca o tópicamente por aplicación a la mucosa nasal.

5 Las formulaciones para administración en aerosol por medio de los MDI pueden ser soluciones o suspensiones. Las formulaciones en solución ofrecen la ventaja de ser de naturaleza homogénea con el medicamento y excipiente completamente disueltos en el vehículo propelente. Las formulaciones en solución evitan también los problemas de estabilidad física asociados con las formulaciones en suspensión y ase-
10 guran de este modo una administración de dosificación uniforme más consistente a la vez que eliminan también la necesidad de tensioactivos.

La administración de formulaciones de soluciones para aerosol por medio de los MDI depende de la fuerza propulsora del sistema propelente usado en su fabricación. Tradicionalmente, el propelente comprende una mezcla de clorofluorocarburos
15 (CFCs) para proporcionar la solubilidad, presión de vapor, y estabilidad de la formulación deseadas. Sin embargo, puesto que en los últimos años se ha establecido que los CFC son nocivos para el medio ambiente ya que contribuyen a la reducción de la capa de ozono de la tierra, es deseable reemplazar en las formulaciones para inhalación en aerosol los propelentes de CFC nocivos para el medio ambiente por los propelentes de
20 hidrofluorocarburos (HFC) u otros propelentes no clorados seguros para el medio ambiente. Por ejemplo, la Patente de Estados Unidos No. 4.174.295 describe el uso de sistemas propelentes que consisten en combinaciones de HFCs, que pueden contener también un componente hidrocarburo saturado, adecuado para aplicación en el campo de los productos del hogar, tales como lacas para el cabello, productos anti-
25 perspiración, perfumes, desodorantes, pinturas, insecticidas y similares.

Es conocido en la técnica que ciertos HFC tienen propiedades adecuadas para uso como propelentes para la administración de medicamentos en aerosol. Por ejemplo, la solicitud de patente europea publicada No. 0 372 777 (EPO89312270.5) describe el uso de 1,1,1,2-tetrafluoroetano (HFC-134(a)) en combinación con al menos un
30 "adyuvante" (un compuesto que tiene una polaridad más alta que el HFC-134(a)) y un agente tensioactivo para preparar formulaciones de medicamentos en suspensión y en solución adecuadas para la administración mediante la vía de aerosol. También, la solicitud de patente PCT publicada No. W091/11496 (PCT/EP91/00178) describe el uso de 1,1,1,2,3,3,3-heptafluoropropano (HFC-227), opcionalmente mezclado con otros
35 componentes propelentes, para uso en la preparación de formulaciones de medicamentos de suspensión para aerosol.

Los documentos US-A-2 868 641 y US-A-3 282 781 describen composiciones para aerosol que comprenden un medicamento (epinefrina o isoproterenol HCl), un codisolvente, un propelente y ácido ascórbico como anti-oxidante. La patente europea EP 673 240 B1 propone la adición de ácidos a las formulaciones medicinales para aerosol con el fin de proporcionar la estabilización del medicamento.

DESCRIPCIÓN DE LA INVENCIÓN

El término "formulación de una solución para aerosol" significa una formulación farmacéutica de un medicamento adecuada para administración en aerosol en la que el medicamento y los excipientes están completamente disueltos.

El término "formulación de una solución para aerosol estabilizada" significa una formulación de una solución para aerosol que presenta una sustancial estabilidad química a lo largo del tiempo.

La presente invención proporciona formulaciones de soluciones para aerosol estabilizadas que comprenden una sal de tiotropio, un propelente HFC, un codisolvente, y un ácido inorgánico u orgánico, caracterizadas porque la concentración del ácido está en un intervalo que se corresponde con un intervalo de pH de 2,5 - 4,5 en solución acuosa.

En las formulaciones de soluciones para aerosol preferidas según la invención la concentración del ácido está en un intervalo que se corresponde con un intervalo de pH de 3,0 - 4,3, más preferido 3,5 - 4,0, en solución acuosa.

También puede estar presente en el sistema propelente/codisolvente una pequeña cantidad de agua (hasta aproximadamente 5 %, preferiblemente hasta aproximadamente 3 % en peso).

La formulación de una solución para aerosol según la invención contiene preferiblemente de 0,00008 a 0,4 %, preferiblemente de 0,0004 a 0,16 %, más preferiblemente de 0,0008 a 0,08 % de tiotropio. Por tiotropio se entiende el catión de amonio libre. En la sal de tiotropio presente en la formulación según la invención, el contraion (anión) puede ser cloruro, bromuro, yoduro, metanosulfonato o *para*-toluenosulfonato. De estos aniones, se prefiere el bromuro.

Si se usa la sal preferida de tiotropio, bromuro de tiotropio, las cantidades mencionadas antes corresponden de 0,000096 a 0,48 % de bromuro de tiotropio, preferiblemente de 0,00048 a 0,192 %, más preferiblemente de 0,00096 a 0,096 % de bromuro de tiotropio.

El bromuro de tiotropio se puede obtener en diferentes modificaciones cristalinas, dependiendo de la elección de las condiciones de reacción y disolventes. Las más preferidas según la invención son aquellas formulaciones, que contienen tiotropio

en la forma del bromuro de tiotropio monohidratado como se describe en el documento WO 02/30928. Este bromuro de tiotropio monohidratado se caracteriza por un pico endotérmico a 230 ± 5 °C determinado por DSC.

Por consiguiente, las formulaciones de soluciones para aerosol según la invención preferiblemente contienen 0,0001 a 0,5 % de bromuro de tiotropio monohidratado, preferiblemente 0,0005 a 0,2 %, más preferiblemente 0,001 a 0,1 % de bromuro de tiotropio monohidratado.

Los propelentes HFC adecuados son aquellos que, cuando se mezclan con el codisolvente(s), forman un sistema propelente homogéneo en el que se puede disolver una cantidad terapéuticamente eficaz del medicamento. El propelente HFC debe ser toxicológicamente seguro y debe tener una presión de vapor que sea adecuada para permitir que el medicamento sea administrado por medio de un MDI presurizado. Adicionalmente, el propelente HFC debe ser compatible con los componentes del dispositivo MDI (tales como recipientes, válvulas, y juntas de sellado, etc.) que se emplea para administrar el medicamento. Los propelentes HFC preferidos son 1,1,1,2-tetrafluoroetano (HFC-134(a)) y 1,1,1,2,3,3,3-heptafluoropropano (HFC-227). El HFC-134(a) es particularmente preferido. Otros ejemplos de propelentes HFC son HFC-32 (difluorometano), HFC-143(a) (1,1,1-trifluoroetano), HFC-134 (1,1,2,2-tetrafluoroetano), y HFC-152a (1,1-difluoroetano).

Debe quedar claro para los expertos en la técnica que en la presente invención se pueden usar propelentes de hidrocarburos no halogenados en lugar de los propelentes de HFC. Ejemplos de hidrocarburos no halogenados son los hidrocarburos saturados, incluyendo propano, *n*-butano, e isobutano, y éteres, incluyendo éter dietílico.

Debe quedar claro también para los expertos en la técnica que, aunque se prefiere el uso de un único propelente HFC, se puede emplear una mezcla de dos o más propelentes HFC, o una mezcla de al menos un propelente HFC y uno o más propelentes no CFC, en la formulación de una solución para aerosol de la presente invención.

Se prefiere un sistema de propelente HFC/codisolvente, sustancialmente no acuoso. El agua puede estar presente en pequeñas cantidades como una impureza en el sistema de propelente HFC/codisolvente, se puede introducir durante el procedimiento de fabricación o se puede permear al sistema a través de la válvula o cierres o juntas de la válvula/recipientes. Si se desea, se pueden añadir pequeñas cantidades de agua (hasta aproximadamente 5 %, preferiblemente hasta aproximadamente 2 % en peso) al sistema HFC/propelente, por ejemplo, para ayudar en la fabricación.

El ácido de las formulaciones según la invención puede ser cualquier ácido inorgánico o mineral, por ejemplo, ácido clorhídrico, ácido sulfúrico, ácido nítrico, o ácido fosfórico, o similares. Entre los ácidos mencionados, el ácido clorhídrico es de particular interés. El ácido se puede seleccionar también del grupo de ácidos conocidos por los expertos en la técnica como ácidos orgánicos, que se consideran en la mayoría de los casos como ácidos débiles en relación con los ácidos inorgánicos. Representativos de este grupo y preferidos en esta invención son el ácido ascórbico, ácido cítrico, ácido láctico, ácido málico, ácido benzoico y ácido tartárico. Según esta invención, el ácido cítrico y el ácido ascórbico son los ácidos orgánicos más preferidos.

Las formulaciones según la invención se pueden preparar análogamente a los métodos conocidos en la técnica.

Si se desea, se pueden incluir excipientes farmacéuticamente aceptables en las formulaciones de soluciones para aerosol de la presente invención. Por ejemplo, se puede añadir un agente tensioactivo soluble con el fin de mejorar el funcionamiento de los sistemas de válvulas empleados en los dispositivos MDI usados para la administración en aerosol de las formulaciones. Ejemplos de agentes tensioactivos preferidos son trioleato de sorbitán, lecitina, y miristato de isopropilo. Otros lubricantes adecuados son bien conocidos en la técnica (véase, por ejemplo, la solicitud de patente europea publicada No. 0372777 (EPO 893122705)). Otros excipientes son: (a) antioxidantes, por ejemplo ácido ascórbico y tocoferol; (b) agentes enmascaradores del sabor, por ejemplo, mentol, edulcorantes, y aromas artificiales o naturales; y (c) agentes modificadores de la presión, por ejemplo, *n*-pentano, *iso*-pentano, *neo*-pentano, y *n*-hexano.

Ejemplos de codisolventes aplicables en las formulaciones según la invención son: alcoholes, por ejemplo, alcohol etílico, alcohol isopropílico, y alcohol bencílico; glicoles por ejemplo, propilenglicol, polietilenglicoles, polipropilenglicoles, éteres glicólicos, y copolímeros de bloque de oxietileno y oxipropileno; y otras sustancias, por ejemplo, glicerol, alcoholes polioxietilénicos, ésteres de ácido graso y polioxietileno, y glicofuroles (por ejemplo glicofurol 75).

Ejemplos de codisolventes que pueden ser inertes a la interacción con el medicamento(s) son los hidrocarburos, por ejemplo, *n*-propano, *n*-butano, isobutano, *n*-pentano, *iso*-pentano, *neo*-pentano, y *n*-hexano; y éteres, por ejemplo, éter dietílico.

Un codisolvente preferido según esta invención es el alcohol etílico (etanol).

La cantidad de codisolvente está preferiblemente en el intervalo de 5 - 50 % (p/p) de la composición total. Más preferiblemente, la cantidad de codisolvente en la

63
formulación según la invención está en el intervalo de 10 - 40 % (p/p), preferiblemente en el intervalo de 15 - 30 %.

Como se ha mencionado antes en esta memoria, las formulaciones según la invención pueden contener una pequeña cantidad de agua. Una realización preferida de la invención corresponde a las formulaciones que contienen agua en una cantidad de hasta 5 % (p/p), preferiblemente de hasta 3 % (p/p). Otra realización preferida de la invención se refiere a formulaciones que no contienen agua. En estas formulaciones libres de agua la cantidad de codisolvente está preferiblemente en el intervalo de aproximadamente 20 - 50 % (p/p), más preferiblemente en el intervalo de aproximadamente 30 - 40 % (p/p).

Especialmente en estas formulaciones libres de agua, se puede usar la forma anhidra de bromuro de tiotropio obtenible a partir del bromuro de tiotropio monohidratado mencionado antes en esta memoria.

La forma anhidra se obtiene a partir del bromuro de tiotropio monohidratado cristalino descrito en el documento WO 02/30928 secando cuidadosamente a más de 50 °C, preferiblemente a 60-100 °C, lo más preferiblemente a 70-100 °C, a presión reducida, preferiblemente en un alto vacío durante un periodo de 15 minutos a 24 horas, preferiblemente de 20 minutos a 12 horas, lo más preferiblemente de 30 minutos a 6 horas. El término "presión reducida" lo más preferiblemente se refiere a una presión de hasta 5×10^3 Pa, preferiblemente 1×10^3 Pa, lo más preferiblemente 5×10^2 Pa.

Lo más preferiblemente, la deshidratación mencionada antes para formar el anhidrato se realiza a aproximadamente 1×10^2 Pa o menos.

De forma alternativa a la etapa de secado a temperatura elevada a presión reducida descrita antes, se puede preparar también la forma anhidra almacenando el bromuro de tiotropio monohidratado cristalino sobre un agente desecante, preferiblemente sobre gel de sílice desecado, a temperatura ambiente durante un periodo de 12 a 96 horas, preferiblemente 18 a 72 horas, lo más preferiblemente al menos 24 horas. La forma anhidra obtenida de este modo se debe almacenar más o menos seca, dependiendo del tamaño de partícula, para conservar su estado anhidro. En el caso de cristales gruesos de bromuro de tiotropio anhidro, que se pueden preparar por ejemplo como se ha descrito antes, el almacenamiento a < 75 % h.r. (humedad relativa) es suficiente para mantener el estado anhidro. En el estado micronizado, esto es cuando el material tiene un área superficial mucho más grande, el agua puede ser absorbida incluso a niveles de humedad más bajos. Con el fin de mantener la forma anhidra en el estado micronizado, es aconsejable por tanto almacenar la forma anhidra de bromuro de tiotropio sobre gel de sílice desecado.

64

La forma anhidra de bromuro de tiotropio se sometió a análisis por rayos X que reveló que el bromuro de tiotropio anhidro cristalino se caracteriza por células elementales $a = 10,4336(2)\text{\AA}$, $b = 11,3297(3)\text{\AA}$, $c = 17,6332(4)\text{\AA}$ y $\alpha = 90^\circ$, $\beta = 105,158(2)^\circ$ y $\gamma = 90^\circ$ (volumen de la célula = $2011,89(8)\text{\AA}^3$). La estructura cristalina de la forma anhidra de bromuro de tiotropio se puede describir como una estructura en capas. Los iones bromuro están localizados entre las capas de tiotropio. En la parte experimental de esta solicitud de patente se dan detalles adicionales sobre la determinación de la estructura cristalina de dicha forma anhidra.

Por consiguiente, otra realización preferida de la invención se refiere a una formulación de una solución para aerosol estabilizada que comprende bromuro de tiotropio anhidro caracterizado por los parámetros mencionados antes, un propelente HFC, un codisolvente, y un ácido inorgánico u orgánico, caracterizada porque la concentración del ácido está en un intervalo que se corresponde con un intervalo de pH de 2,5 - 4,5 en solución acuosa y caracterizada además porque la formulación está libre de agua.

Las formulaciones según la invención se pueden administrar con inhaladores conocidos en la técnica (inhaladores con medidor de dosis = MDIs).

En otro aspecto, la invención se refiere al uso de una formulación de una solución para aerosol como se ha descrito antes en esta memoria, para la fabricación de un medicamento para el tratamiento de dolencias respiratorias, particularmente la COPD (enfermedad pulmonar obstructiva crónica) y el asma.

En otro aspecto más, la invención se refiere a un método para el tratamiento de dolencias respiratorias, tales como en particular la COPD (enfermedad pulmonar obstructiva crónica) o el asma, caracterizado por la administración de una formulación de una solución para aerosol como se ha descrito antes en esta memoria.

Los siguientes ejemplos sirven para ilustrar adicionalmente la presente invención sin restringir su alcance a las realizaciones proporcionadas a continuación a modo de ejemplo.

I. Ejemplos de formulación

A)

Componente	Concentración [% p/p]
Bromuro de tiotropio monohidratado	0,02
Etanol abs. (USP)	25,0
Agua (purificada, USP)	1,0
Ácido cítrico (USP)	0,003
HFC-134a	73,977

B)

Componente	Concentración [% p/p]
Bromuro de tiotropio monohidratado	0,02
Etanol abs. (USP)	20,0
HCl acuoso 0,01 mol/l (USP)	2,0
HFC-134a	77,98

5

C)

Componente	Concentración [% p/p]
Bromuro de tiotropio monohidratado	0,01
Etanol abs. (USP)	15,0
Agua (purificada, USP)	2,0
Ácido cítrico (USP)	0,004
HFC-227	82,986

D)

Componente	Concentración [% p/p]
Bromuro de tiotropio monohidratado	0,01
Etanol abs. (USP)	30,0
Agua (purificada, USP)	1,0
Ácido ascórbico (USP)	0,005
HFC-134a	68,985

66

E)

Componente	Concentración [% p/p]
Bromuro de tiotropio (anhidro)	0,01
Etanol abs. (USP)	40,0
Ácido cítrico (USP)	0,004
HFC-227	59,986

Las formulaciones mencionadas se pueden preparar por métodos convencionales conocidos en la técnica.

5 **II. Preparación de bromuro de tiotropio anhidro cristalino:**

Se produce la forma anhidra a partir del bromuro de tiotropio monohidratado cristalino (obtenible como se ha descrito en el documento WO 02/30928) por cuidadoso secado a 80 –100 °C bajo presión reducida, preferiblemente bajo un alto vacío (a aproximadamente 1×10^2 Pa o menos) durante un periodo de al menos 30 minutos.

10 De forma alternativa a la etapa de secado a 80 – 100 °C en vacío, se puede preparar también la forma anhidra almacenando sobre gel de sílice desecado, a temperatura ambiente durante un periodo de al menos 24 horas.

III. Caracterización del bromuro de tiotropio anhidro cristalino

15 Como se ha descrito antes en esta memoria, el bromuro de tiotropio anhidro cristalino según la invención, se puede obtener a partir de bromuro de tiotropio monohidratado cristalino.

Se determinó la estructura cristalina del bromuro de tiotropio anhidro a partir de los datos de rayos X de alta resolución en el polvo (radiación sincrotrónica) usando un método de espacio real con el llamado procedimiento de anillado simulado. Se llevó a
20 cabo un análisis final de Rietveld para refinar los parámetros estructurales. La Tabla 1 contiene los datos experimentales obtenidos para el bromuro de tiotropio anhidro cristalino.

Tabla 1: Datos experimentales que se refieren al análisis de la estructura cristalina de bromuro de tiotropio (anhidro)

67

fórmula	$C_{19}H_{22}NO_4S_2Br$
temperatura [°C]	25
peso molecular [g/mol]	472,4
grupo de espacio	$P2_1/c$
a [Å]	10,4336(2)
b [Å]	11,3297(3)
c [Å]	17,6332(4)
β [°]	105,158(2)
V [Å ³]	2011,89(8)
Z	4
densidad calculada [g cm ⁻³]	1,56
2Θ (intervalo) [°]	2,0 – 20
intervalo [° 2Θ]	0,003
tiempo de contaje / etapa [segundos]	3
longitud de onda [Å]	0,7000

La estructura cristalina de la forma anhidra de bromuro de tiotropio se puede describir como una estructura en capas. Los iones bromuro están localizados entre las capas de tiotropio.

5 Con el fin de clarificar la estructura del bromuro de tiotropio anhidro cristalino se determinó un diagrama por rayos X de alta resolución en el polvo a temperatura ambiente en el National Synchrotron Source (Brookhaven National Laboratory, USA) en la estación de medida X3B1 ($\lambda = 0,700 \text{ Å}$). Para este experimento se puso una muestra de bromuro de tiotropio monohidratado cristalino en un capilar de vidrio de cuarzo de
10 0,7 mm de diámetro. Se eliminó el agua calentando a 80 °C en una estufa a presión reducida.

La resolución estructural se obtuvo por el llamado procedimiento de anillado simulado. Para esto se usó el programa DASH producido por Cambridge Crystallographic Data Center (CCDC, Cambridge, United Kingdom).

15 La Tabla 2 muestra las coordenadas atómicas obtenidas para el bromuro de tiotropio anhidro cristalino.

Tabla 2: Coordenadas

Átomo	x	y	z	U _{iso}
S1	1,0951(8)	0,3648(8)	0,8189(5)	0,075(9)
S1	0,9143(9)	0,1374(8)	0,9856(5)	0,075(9)
O	0,6852(13)	0,2339(6)	0,7369(6)	0,075(9)
O1	0,7389(15)	0,0898(9)	0,8234(6)	0,075(9)
O2	0,8211(10)	0,3897(17)	0,8277(7)	0,075(9)
O3	0,4975(17)	0,4816(9)	0,6011(7)	0,075(9)
N	0,4025(10)	0,2781(8)	0,5511(5)	0,075(9)
C	0,7509(8)	0,1885(6)	0,8038(5)	0,075(9)
C1	0,8593(7)	0,2788(5)	0,8495(4)	0,075(9)
C2	0,9924(9)	0,2533(6)	0,8225(6)	0,075(9)
C3	0,8884(9)	0,2664(7)	0,9382(4)	0,075(9)
C4	0,5848(12)	0,1596(8)	0,6753(8)	0,075(9)
C5	0,4544(13)	0,1929(14)	0,6809(8)	0,075(9)
C6	0,6156(13)	0,1810(13)	0,5973(9)	0,075(9)
C7	0,5493(11)	0,2881(11)	0,5578(6)	0,075(9)
C8	0,5869(12)	0,3832(11)	0,6092(7)	0,075(9)
C9	0,4947(13)	0,3902(10)	0,6575(6)	0,075(9)
C10	0,4004(10)	0,2998(11)	0,6332(6)	0,075(9)
C11	0,3220(13)	0,3670(13)	0,4935(6)	0,075(9)
C12	0,3450(19)	0,1643(26)	0,5211(11)	0,075(9)
C13	0,9184(16)	0,3808(9)	0,9920(6)	0,075(9)
C14	1,0313(16)	0,1552(15)	0,8011(15)	0,075(9)
C15	0,9515(17)	0,3374(10)	0,0501(6)	0,075(9)
C16	0,9756(18)	0,2190(11)	1,0742(5)	0,075(9)
C17	1,1483(22)	0,1762(18)	0,7718(24)	0,075(9)
C18	1,1860(16)	0,2800(15)	0,7768(19)	0,075(9)
BR	0,4597(4)	0,8200(15)	0,61902(25)	0,042(9)

En la tabla anterior los valores "U_{iso}" indican los factores de temperatura isotrópicos. Por ejemplo, en el análisis estructural por rayos X en cristales individuales esto corresponde a los valores u(eq).

69
2/6

La Tabla 3 muestra los reflejos (índices h,k,l) del diagrama de polvo obtenido para el bromuro de tiotropio anhidro cristalino.

Tabla 3: Datos experimentales que se refieren al análisis de la estructura cristalina de bromuro de tiotropio anhidro

Nº	h	k	l	$2\Theta_{\text{obs.}}$	$2\Theta_{\text{calc.}}$	$2\Theta_{\text{obs.}} - 2\Theta_{\text{calc.}}$
1	1	0	0	8,762	8,769	-0,007
2	0	1	1	9,368	9,369	-0,001
3	-1	0	2	11,730	11,725	0,005
4	0	1	2	12,997	13,004	-0,007
5	-1	1	2	14,085	14,094	-0,009
6	1	0	2	15,271	15,275	-0,004
7	0	0	3	15,620	15,616	0,004
8	0	2	1	16,475	16,475	0,0
9	1	1	2	17,165	17,170	-0,005
10	2	0	0	17,588	17,591	-0,003
11	-1	2	1	18,009	18,035	-0,026
12	1	2	1	19,336	19,328	0,008
13	-2	1	2	19,596	19,600	-0,004
14	-1	0	4	20,417	20,422	-0,005
15	0	0	4	20,865	20,872	-0,007
16	2	1	1	21,150	21,145	0,005
17	-2	1	3	21,759	21,754	0,005
18	0	2	3	22,167	22,160	0,007
19	-1	2	3	22,289	22,288	0,001
20	2	0	2	22,735	22,724	0,011
21	-2	2	1	23,163	23,159	0,004
22	-2	0	4	23,567	23,575	-0,008
23	2	1	2	24,081	24,058	0,023
24	1	0	4	24,746	24,739	0,007
25	-1	3	1	25,220	25,221	-0,001

2/20

26	1	2	3	25,359	25,365	-0,006
27	0	3	2	25,790	25,783	0,007
28	1	1	4	25,978	25,975	0,003
29	0	2	4	26,183	26,179	0,004
30	-1	3	2	26,383	26,365	0,018
31	-1	1	5	26,555	26,541	0,014
32	-3	1	2	27,024	27,021	0,003
33	3	1	0	27,688	27,680	0,008
34	-3	1	3	28,221	28,215	0,006
35	3	0	1	28,377	28,376	0,001
36	-3	0	4	29,246	29,243	0,003
37	3	1	1	29,459	29,471	-0,012
38	-1	2	5	29,906	29,900	0,006
39	-3	2	1	30,171	30,165	0,006
40	0	2	5	30,626	30,626	0,0
41	1	1	5	30,871	30,856	0,015
42	0	0	6	31,504	31,532	-0,028
43	2	1	4	31,826	31,847	-0,021
44	-2	1	6	32,888	32,888	0,0
45	1	4	1	33,605	33,615	-0,010
46	3	0	3	34,379	34,377	0,002
47	1	0	6	35,021	35,018	0,003
48	-4	1	1	35,513	35,503	0,01
49	1	1	6	35,934	35,930	0,004
50	-1	1	7	36,544	36,543	0,001
51	-4	1	4	37,257	37,255	0,002
52	-4	2	2	37,933	37,952	-0,019
53	4	1	1	38,258	38,264	-0,006

21
22

REIVINDICACIONES

1. Una formulación de una solución para aerosol que comprende una sal de tiotropio, un propelente HFC, un codisolvente, y un ácido inorgánico u orgánico, caracterizada porque la concentración del ácido está en un intervalo que se corresponde con un intervalo de pH de 2,5 - 4,5 en solución acuosa.

2. La formulación de una solución para aerosol según la reivindicación 1, caracterizada porque contiene 0,00008 a 0,4 % de tiotropio.

3. La formulación de una solución para aerosol según las reivindicaciones 1 o 2, caracterizada porque el contraion (anión) que forma junto con el tiotropio la sal de tiotropio puede ser cloruro, bromuro, yoduro, metanosulfonato o *para*-toluenosulfonato.

4. La formulación de una solución para aerosol según las reivindicaciones 1, 2 o 3, caracterizada porque el propelente HFC se selecciona entre HFC-134(a), HFC-227, HFC-32, HFC-143(a), HFC-134, HFC-152a y sus mezclas.

5. La formulación de una solución para aerosol según las reivindicaciones 1, 2, 3 o 4, caracterizada porque el ácido se selecciona entre los ácidos inorgánicos, ácido clorhídrico, ácido sulfúrico, ácido nítrico, y ácido fosfórico.

6. La formulación de una solución para aerosol según las reivindicaciones 1, 2, 3 o 4, caracterizada porque el ácido se selecciona entre los ácidos orgánicos, ácido ascórbico, ácido cítrico, ácido láctico, ácido málico, ácido benzoico, y ácido tartárico.

7. La formulación de una solución para aerosol según una de las reivindicaciones 1 a 6, caracterizada porque contiene agua en una cantidad de hasta aproximadamente 5 %.

8. La formulación de una solución para aerosol según una de las reivindicaciones 1 a 7, caracterizada porque contiene como un codisolvente, alcoholes, glicoles, éteres glicólicos, copolímeros de bloque de oxietileno y oxipropileno, glicerol, alcoholes polioxietilénicos, ésteres de ácido graso y polioxietileno o glicofuroles.

9. La formulación de una solución para aerosol según una de las reivindicaciones 1 a 8, caracterizada porque el codisolvente está presente en una cantidad en el intervalo de 5 - 50 % (p/p).

10. La formulación de una solución para aerosol según una de las reivindicaciones 1 a 6, 8 o 9, caracterizada porque no contiene agua.

11. El uso de una formulación de una solución para aerosol según una de las reivindicaciones 1 a 10, para la fabricación de un medicamento para el tratamiento de dolencias respiratorias.

23/20

RESUMEN

Esta invención se refiere a formulaciones de soluciones farmacéuticas estables que contienen tiotropio, adecuadas para administración en aerosol. Más particularmente, esta invención se refiere a formulaciones de soluciones farmacéuticas estables que contienen tiotropio adecuadas para administración en aerosol en las que se añade un ácido inorgánico o un ácido orgánico a la formulación de la solución para aerosol que contiene una sal de tiotropio, preferiblemente bromuro de tiotropio en solución con un hidrofluorocarburo (HFC) seguro para el medio ambiente como propelente, junto con un compuesto orgánico como codisolvente. El ácido proporciona estabilidad frente a la degradación o descomposición del medicamento que se produce en gran medida a causa de la interacción del medicamento con el codisolvente y/o con el agua presente en la formulación de la solución.

15

COLO 13736-841-069-2

PRP/WPC13736/ID-000538

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folios: 74

Radicacion : 05070215 00000000

Fecha (AMD): 2005-07-15 17:09:37

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAR

Dependencia: 2028 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 05 - 46,094

FECHA : JUNIO 21 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	40117916	21/06/2005	62,639,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

0610 13736-841-069-2

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION	MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.		()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes.		()	()
- Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica o fotografía del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()

Firma Responsable: *PEAR*

15 de 2005

Fecha:

75

Folio ~~76~~

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a) y/o Representante
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

REFERENCIA:	Radicación No.	05 70215
	Solicitud Internacional	PCT/EP2003/013692
	Fecha límite inicio fase Nacional	16 - 07 - 2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1066
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

12/07/2005

ALIX CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Al contestar favor indique el número de
radicación consignado en el sticker

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