



Industria y Comercio
SUPERINTENDENCIA

PCT

SOLICITUD
PATENTE DE INVENCION

03-28806

21 EXPEDIENTE N°

54 TÍTULO

NUEVAS COMPOSICIONES FARMACEUTICAS QUE CONTIENEN
EPINASTINA Y PSEUDOEFEEDRINA

51 CLASIFICACIÓN INTERNACIONAL

A61K 9/20

71 SOLICITANTE

BOEHRINGER INGELHEIM INTERNATIONAL GmbH

DOMICILIO

Ingelheim am Rhein, República Federal de Alemania.

74 APODERADO

EMILIO FERRERO

Código No. 1092

22 BOGOTÁ, D C

04 - 04 - 2003


Industria y Comercio
SUPERINTENDENCIA

33 028806 00

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Folios: 35

Radicación: 43028806 00000000

Fecha (AMB): 2003-04-04 17 10 52

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**

1

SOLICITUD DE

Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

**SOLICITANTE
(71)****Nombre BOEHRINGER INGELHEIM
INTERNATIONAL GmbH**sociedad constituida y existente bajo las
leyes de la Republica Federal de
AlemaniaDirección D-55216 Ingelheim am Rhein
Republica Federal de AlemaniaDomicilio Ingelheim am Rhein
Republica Federal de Alemania**IDENTIFICACION**

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 217 92 11

E-mail clientes@camvo.com

Domicilio Bogotá Colombia

IDENTIFICACION

C C



NIT



C E



Otro



Cual

Numero 438 019 T P. 31 929

4

**INVENTOR (ES)
(72)****1- Sara ABELAIRA**

Salazar 1483

1686 Hurlingham Buenos Aires

Argentina

3- Francisco GEL

Vicente Damonte 1520

(1824) Lanus Este Buenos Aires

Argentina

5- Mabel FERNÁNDEZ

Marconi 4848

1605 Munro Buenos Aires

Argentina

2- Daniel BIANCHI

Bulnes 2736

(P 15 Dpto 05) 1425 Buenos Aires

Argentina

4- Victor DENKER

Mendoza 2295

1428 Buenos Aires

Argentina

6- Marta Cicconi de VIDAL

Ituzaingo 4156

1754 San Justo Buenos Aires

Argentina

5

PCT (86)

Solicitud Internacional No PCT/EP01/11229

Publicación Internacional No WO 02/28373 A1

Fecha 28 de septiembre de 2001

Fecha 11 de abril de 2002

6

**Título (54) NUEVAS COMPOSICIONES FARMACEUTICAS QUE CONTIENEN
EPINASTINA Y PSEUDOEFEEDRINA**

7

Clasificación Internacional (51) A61K 9/20

8

PrioridadSI ☒NO ☐**(33) País de Origen**

EP

(32) Fecha

6 de octubre de 2000

(31) Numero de Solicitud

00121828 8

10

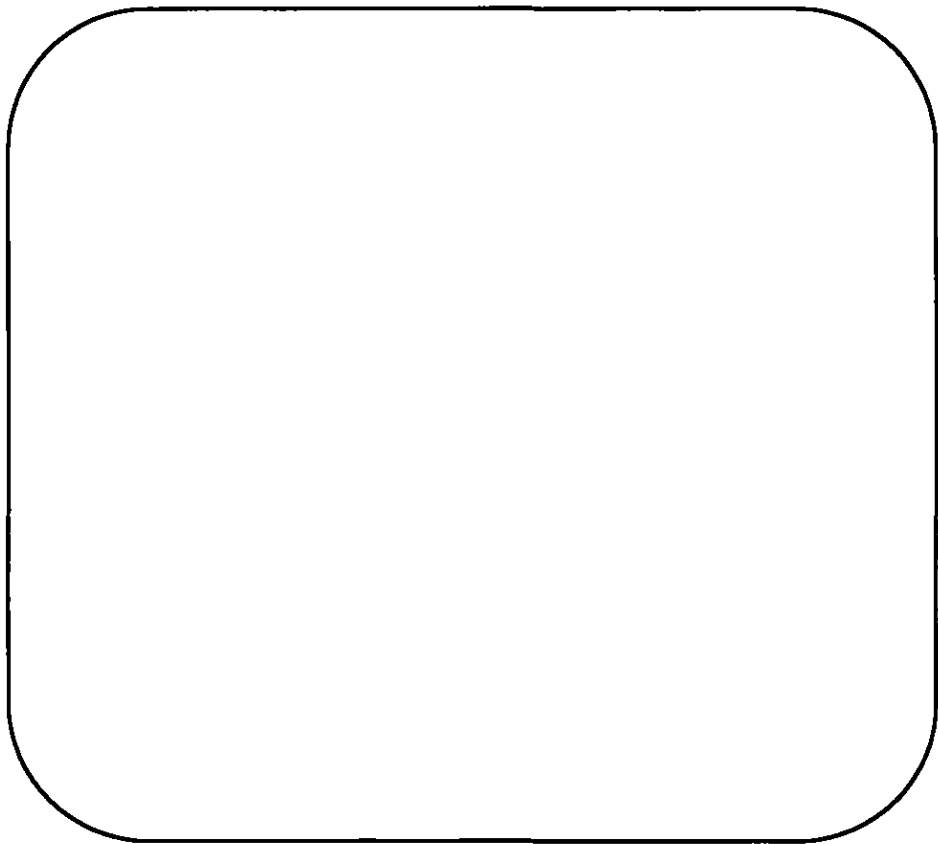
Anexos

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 400 000 oo
- ☐ 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

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

3

NOMBRE EMILIO FERRERO

FIRMA 

C C 438 019 de Usaquén T P 31 929

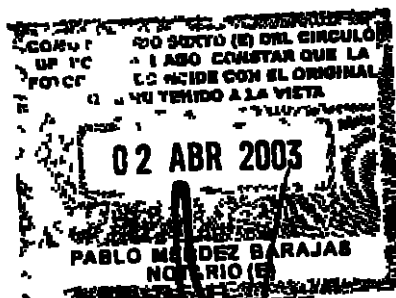
 MRE/mrm-Id-201

LEGALIZACION

El Seno Consul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que esta ejerce su objeto social, y (3) que las personas que otorgan el poder estan autorizadas para dñrlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3)

LEGALIZATION

The Colombia Consul must issue a *consular certificate* on (1) the legal existence of the company which grants a Power-of Attorney (2) that it is in actual exercise of company purposes and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect please show the Consul the evidence to prove the above facts (1), (2) and (3)



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA Según los artículos 65 del C de P C y 480 del C de Co , si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales

REPRESENTACION Y PODER

REPRESENTATION AND
POWER OF ATTORNEY

9255
0569

I (we), the undersigned / Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of / domiciliado (s) en **D-55216 Ingelheim am Rhein,
GERMANY**

por el presente nombramos a GERMAN CAVELIER, tpa. 832, GONZALO PERDOMO tpa. 831, EMILIO FERRERO, tpa. 31929 y LUZ CLEMENCIA DE PAEZ, tpa. 23555 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 aquel. 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 solo 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 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 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 oficiales.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832, GONZALO PERDOMO, tpa. 831 EMILIO FERRERO, tpa. 31929 and LUZ CLEMENCIA DE PAEZ, tpa. 23555 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 of 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) Obtaining of patents utility models and industrial designs the registration of trademarks, collective defensive and service marks, slogans, commercial names, trade emblems, 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, admit the facts of the case desist, cancel, transact, conciliate, admit the facts of the case done by representatives, without a power of attorney.

Given and signed this / Dado y firmado hoy

**BOEHRINGER INGELHEIM
INTERNATIONAL GMBH**

in/en

ppc

ppc

Dr Dieter Laudien

Dr Gerhard Huber

Signature

Firma

Vorseitige vor mir gefertigte Namensunterschriften der Herren

1 Dr Dieter L a u d i e n Dipl Chemiker wohnhaft in 55127 Mainz

2 Dr Gerhard H u b e r Rechtsanwalt wohnhaft in 55411 Bingen

mir bekannt

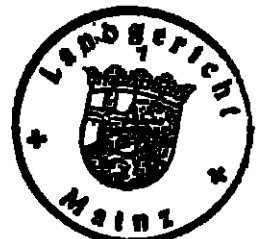
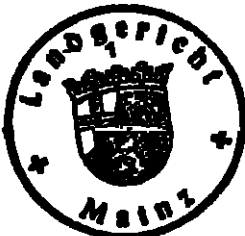
beglaubige ich hiermit

Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregister des Amtsgerichts Bingen daß die Firma Boehringer Ingelheim International GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen unter HR B 1063 eingetragen ist und daß die Herren Dr Laudien und Dr Huber als Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind

Ingelheim am Rhein den 12 Dezember 1995/hün



[Signature]
Notariatsverweser
anstelle des Notars
Prof Dr Weirich in Ingelheim



- 910 F 1 -

Die Echtheit vorstehender Unterschrift des Notarassessors Dr Peter Wirth - Notariatsverweser anstelle des Notars Prof Dr Weirich in Ingelheim und die Echtheit des beigedruckten Dienst - ~~scheines~~ - siegels werden hierdurch bestätigt. Zugleich wird bescheinigt, daß der Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Kostenberechnung

Gebühr für Legalisation

(Wert DM 500,-)

JVKostO v 26.7.1957

BGBI I S 881

DM 20,-

Mainz, den 13 DEZ. 1995

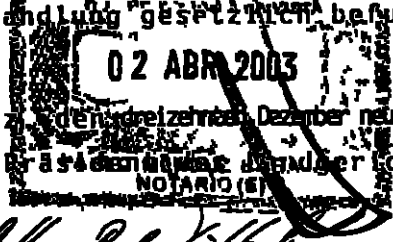
[Signature]

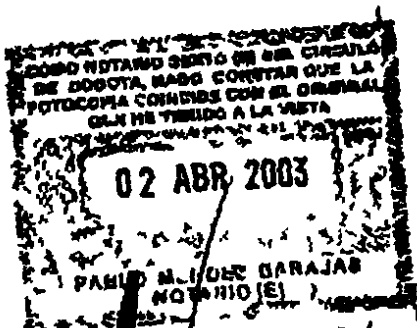
Amtinspektor



Mainz, den dreizehn. Dezember neunzehnhundertfünfundneunzig
Der Präsident des Landgerichts

[Signature]
(Dr. Hanns Paul Tullenberg)





MINISTERIO DE RELACIONES
EXTERIORES
Reinhardt
Mosquera
BOGOTÁ, A LOS 05 DE ABRIL DE 2003

NO SE ASUME
RESPONSABILIDAD DEL TITULO
MEXICO - EL A 11 44
DEFINICION DE GALIZACIONES
SECRETARÍA DE RELACIONES EXTERIORES

LAZARUS U-11 EN
TRAYECTORIA E INTER
1-245133
Resolución No 599 (Ministerio de)



CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr 169

El Cónsul General de Colombia

CERTIFICA

Que el Dr Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha allí indicada las funciones de Presidente del Tribunal Regional en Mainz -----

Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen ----- está constituida y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania

Que los señores Dr. DIETER LAUDIN Y Dr. GERHARD HUBER -----

quien(es) firman el presente documento tiene (n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre

Que ha tenido a la vista la documentación que prueba lo anterior

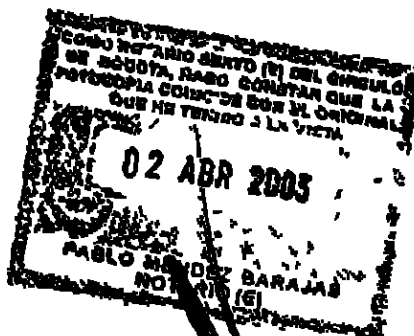
Munich, 18 de Diciembre de 1995

RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA A

Derechos para la Nación US \$ 6 -
Fondo Rotatorio US \$ 100 -
Tasa consular US \$ 1 x DM 1,60 = DM 169 60



PAGADO



TRADUCCION OFICIAL No 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente -

(A continuación del poder conferido a GERMAN CAVELIER, tpa 832, GONZALO PERDOMO, tpa 831, EMILIO FERRERO tpa, 31929, y LUZ CLEMENCIA DE PAEZ, tpa 23555, domiciliados en la Carrera 4 No 72-35, Bogotá, Colombia, por la BOEHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en D-55216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs Dr Dieter Laudien y Dr Gerhard Huber)

LUZ ANNA DIAZ DE
TRADUCTORA OFICIAL
Resolución No 599 Ministros

Legalización

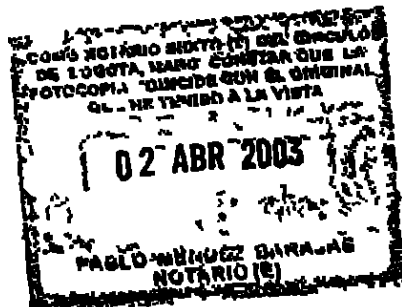
Protocolo notarial No 2659/95 V

, Certifico la autenticidad de las firmas antecedentes puestas ante mí por los señores

1 Dr. Dieter Laudien, Dipl. Chim , domiciliado en 55127 Mainz,

2 Dr Gerhard Huber, abogado, domiciliado en 55411 Bingen

a quienes conozco en persona



Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringer Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, está inscrita bajo el No. HR B 1063 en el Registro de Comercio del Juzgado Municipal de Bingen y que los señores Dr. Laudien y Dr. Huber, en su calidad de apoderados, están facultados para representar conjuntamente a la sociedad

LUZ ARRIAGA DE HERRERA
TRADUCTORA
Resolución No. 599 Ministerial

Ingelheim am Rhein, 12 de diciembre de 1995/hun

Fdo firma ilegible

(Hilo y oblea roja en relieve)

El notario suplente

El notario suplente - Ingelheim

del notario de Ingelheim

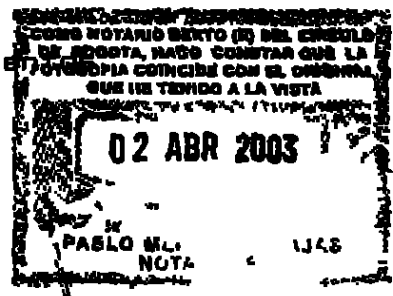
Prof Dr Weirich

(dos sellos redondos en tinta del Tribunal Regional de Mainz)

910 E 1

Se certifica la autenticidad de la firma antecedente del Dr. Peter Wirth, como notario suplente del Prof. Dr Weirich, notario de Ingelheim, y la del sello oficial que la acompaña Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de mil novecientos
noventa y cinco



[Illegible handwritten notes and signatures at the bottom of the page]

35 TH L 71 00427/743 OTX32 CIRATPH 04:02
13 17 11 100 RAT2N53 004H AIC009 32
El Presidente del Tribunal Regional

(E) Fdo firma ilegible

(Dr Hanns Paul Tuddenberg)

Costas

Derechos de legalización
(Valor DM 5 000,-)
JVKostO del 26 de julio 1957
Gacetas Oficial I Pag 861
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo . firma ilegible
Inspector

EN ESPAÑOL La legalización de las firmas antecedentes por el
Consulado de Colombia en Munich bajo el No de 10 de 10 de
diciembre de 1995, y por el Ministerio de Relaciones Exteriores
de Colombia bajo el No 051606 del 4 de enero de
Pagados derechos y Fondo Rotatorio US\$ 106,--

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

Santafé de Bogotá, 6 de enero de 1996

LUZ ARPIAGA DE HERBER
RADUCTORA E INTERPRETE OFICIAL
Calle 1559 Minutaria

02 ABR 2003

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE
DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

C C
COINCIDE CON LA REGISTRADA POR EL (ELLA)
EN ESTA NOTARIA

09 ENE 1996

SANTAFE DE BOGOTA D.C.



NO SE ASUME
RESPONSABILIDAD DEL TERCERO
1996 ENE 10 A 11 33
JEFE DE ASISTENCIAS
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

CUYA FIRMA
DOCUMENTO DE COMPENSA
LAS FUNCIONES DE

COMO NOTARIO SEXTO (C) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA CONCORDA CON EL ORIGINAL
QUE ME TIENGO A LA VISTA
02 ABR 2003
PABLO MENDEZ BARAJAS
NOTARIO (E)

TELEFAX (57) (1) 3009850
TELEX 45479 CAVE CO
(23) 7407375 CAVE UC

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 4ª No 72 35
BOGOTA 8 COLOMBIA

CORREO ELECTRONICO MUNDIAL CAVE

TELEFONO (57) (1) 2120100

CABLES CAVELEYES

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

Poderdante BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el 12-12-95

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado -- atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No 31 929, con todas las facultades que me fueron conferidas

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil, ya que los otros sustitutos faltan en este momento

Señor Jefe,

GERMAN CAVELIER

T P A No 832

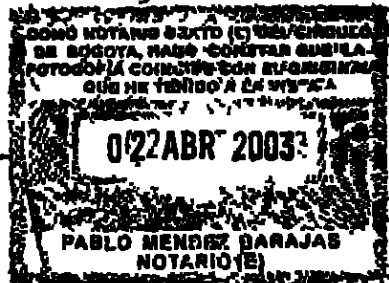
C C No 2 877 924 de Bogota

Acepto

EMILIO FERRERO

T P A No 31 929

C C No 438 019 de Usaquen



2e-780-2

-NOTARIA SEXTA DE BOGOTÁ

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D. C.

11 ENE 1996

Ante M. PABLO RIENDEZ BARRAJAS

NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTÁ

Compareció(eron)

quien(es) (אשר) (אשר) (אשר)

y la(s) Libreta(s) Militares

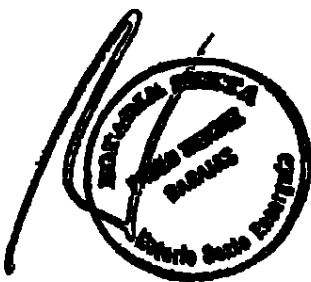
domiciliado(s) en Bogotá y declaró(aron) que la(s) firma(s) que aparecen(n) en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.
En constancia se firma esta Diligencia.

San Calo

Emilio F...

02 ABR 2003

PABLO RIENDEZ BARRAJAS
NOTARIO (E)



(19) World Intellectual Property Organization
International Bureau



ERFASST

INTERNATIONAL PATENT COOPERATION TREATY (PCT)

(43) International Publication Date
11 April 2002 (11 04 2002)

PCT

(10) International Publication Number
WO 02/28373 A1

- (51) International Patent Classification⁷ A61K 9/20
31/415 31/135 A61P 37/08
- (21) International Application Number PCT/EP01/11229
- (22) International Filing Date
28 September 2001 (28.09 2001)
- (25) Filing Language English
- (26) Publication Language: English
- (30) Priority Data
00121828.8 6 October 2000 (06 10 2000) EP
- (71) Applicant (for all designated States except US)
BOEHRINGER INGELHEIM INTERNATIONAL
GMBH [DE/DE] 55216 Ingelheim am Rhein (DE)
- (72) Inventors, and
- (75) Inventors/Applicants (for US only) ABELAIRA, Sara
[AR/AR] Salazar 1483 1686 Hurlingham, Buenos Aires
(AR). BIANCHI, Daniel [AR/AR] Buñes 2736 (P 15
Dpto 05), 1425 Buenos Aires (AR) GEL, Francisco
[AR/AR] Vicente Damonte 1520, (1824) Lanus Este,
Buenos Aires (AR) DENKER, Victor [AR/AR] Men
doza 2295 1428 Buenos Aires (AR) FERNANDEZ,
Mabel [AR/AR], Marcom 4848 1605 Munro Buenos
- (81) Designated States (national) AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW
- (84) Designated States (regional) ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW) Eurasian
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(54) Title NEW PHARMACEUTICAL COMPOSITIONS CONTAINING EPINASTINE AND PSEUDOEPHEDRINE

(57) Abstract: The present invention relates to novel oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epanastine or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and further comprising suitable pharmaceutically acceptable carriers or excipients. The invention further relates to methods for the preparation these compositions and methods of using them in the treatment of allergic diseases and/or disorders.

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congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs is preferred

In a preferred embodiment the pharmaceutical composition according to the invention contains as the active ingredients only an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof

In a preferred embodiment the present invention relates to an oral pharmaceutical composition, preferably a bilayer tablet, providing for a sustained release of the decongestant effective amount of pseudoephedrine and an immediate release of an antihistaminic effective amount of epinastine

Particularly preferred according to the invention is a bilayer tablet wherein a first layer A, providing for the sustained release of pseudoephedrine, comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and wherein a second layer B, providing for the immediate release of epinastine, comprises an antihistaminic effective amount of epinastine or a pharmaceutically acceptable salt thereof The bilayer tablet according to the invention may additionally contain a tablet coating C consisting of pharmaceutically acceptable excipients which mask the bitter taste of one of the active compounds

In a preferred embodiment of the invention layer A of the bilayer tablet according to the invention comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof in a matrix of a swellable hydrophilic polymer which provides a sustained release profile in a period of 3 to 24, preferably 6 to 18, most preferably about 12 hours

According to the invention the term pharmaceutically acceptable salts stands for acid addition salts of the active compounds pseudoephedrine and epinastine These acid addition salts can be formed with anorganic acids like hydrochloric acid, hydrobromic acid or sulfuric acid or with organic acids as for instance oxalic acid, fumaric acid or methanesulfonic acid Epinastine is preferably used as its hydrochloric acid addition

New pharmaceutical compositions containing epinastine and pseudoephedrine**Background of the invention**

The present invention relates to novel oral pharmaceutical compositions comprising
5 as pharmaceutically active compounds a combination of an antihistaminic-effective
amount of epinastine or a pharmaceutically acceptable salt thereof and of a
decongestant-effective amount of pseudoephedrine or a pharmaceutically
acceptable salt thereof and further comprising suitable pharmaceutically acceptable
carriers or excipients. The invention further relates to methods for the preparation
10 these compositions and methods of using them in the treatment of allergic diseases
and/or disorders

Description of the invention

The present invention provides for novel oral pharmaceutical compositions
comprising as pharmaceutically active compounds a combination of an
15 antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt
thereof and of a decongestant-effective amount of pseudoephedrine or a
pharmaceutically acceptable salt thereof and further comprising pharmaceutically
acceptable carriers or excipients under the proviso that the composition does not
contain a leukotriene antagonist

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As an additional active compound the compositions according to the invention may
optionally contain one or several compounds selected from the group consisting of
mucolytic and analgesic-antipyretic compounds and vitamins. Preferred mucolytic
ingredients are selected from bromhexine and ambroxol. Preferred analgesic-
25 antipyretic compounds are selected from paracetamol and ibuprofen. Preferred
vitamins are selected from vitamin B2, B6 and C

The pharmaceutical compositions according to the invention are useful for the
treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or
30 other diseases from allergic origin deserving the administration of antihistamine and
decongestant drugs. Furthermore the compositions according to the invention are
useful in the treatment of for instance common cold and in the symptomatic relief
associated with cough, cold and flu symptoms. The use of the pharmaceutical
compositions according to the invention for the treatment of allergic rhinitis, allergic

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salt. Pseudoephedrine is preferably used as the hydrochloride or the sulfate. Within the present invention pseudoephedrine sulfate is most preferred.

The release of pseudoephedrine takes place over 3 to 24, preferably 6 to 18, most preferably about 12 hours. This bilayer tablet is designed to be preferably administered twice daily.

The concentration range of pseudoephedrine salt in the compositions according to the invention is between 5 and 240 mg/tablet, preferably 10 to 200 mg/tablet, more preferably 60 to 180 mg/tablet, preferably 80 to 140 mg/tablet, most preferably 120 mg/tablet. The concentration range of epinastine salt in the compositions according to the invention is between 2 and 20 mg/tablet, preferably 5 to 10 mg/tablet, more preferably 10 mg/tablet.

Each layer of the tablet is in contact with each other in a portion of their surface, but provides independent release profiles for both active substances mentioned before. The sustained release layer A consists of pseudoephedrine or a pharmaceutically acceptable salt thereof and a swellable hydrophilic polymer.

Typical swellable hydrophilic polymers include cellulosic ethers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, carboxymethylcellulose and carboxyethylcellulose or mixtures thereof. The use of hydroxypropylmethylcellulose (HPMC) is preferred. Particularly useful are the HPMC polymers HPMC USP2910 and USP2208 like for instance Methocel E5, E4M, E15M, K15M, and K100M supplied by the Dow Chemical Company. In the aforementioned abbreviations the designation "E" refers to USP2910 whereas "K" refers to USP2208. The number designation refers to the viscosity in a 2% aqueous solution (e.g. 5 designates a viscosity of 5 cps, 15M designates a viscosity of 15000 cps).

The excipients that could be optionally used in the sustained release layer A are insoluble polymers, soluble or insoluble fillers, antiadherents, coloring agents, lubricants and additional binders. Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and cornstarch. Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are

colloidal silicon dioxide and talc Magnesium stearate, talc and stearic acid are typical lubricants Typical binders are povidone, and comstarch

The immediate release matrix layer B comprises epinastine within different combinations of excipients The excipients that could be optionally used in the immediate release layer B are insoluble polymers, soluble or insoluble fillers, antiadherents, lubricants, coloring agents, disintegrants and additional binders Typical fillers are for example lactose, microcrystalline cellulose, dibasic calcium phosphate and comstarch Examples of antiadherents, which are used to prevent tablets from sticking to the tablet press, are colloidal silicon dioxide and talc Typical disintegrants are crospovidone, sodium starch glycolate and crosscarmellose sodium Typical coloring agents are selected from FD&C red 40 HT Aluminum lake, 2-hydroxy-1,1'-azonaphthalene-3,6,4'-trisulfonic acid trisodium salt, erythrosine, iron oxides, 1-(4-sulpho-1-naphthylazo)-2-naphthol-6,8-disulphonic acid trisodium salt, 2',4',5',7'-tetrabromo-4,5,6,7-tetrachloro-fluorescein disodium salt, 2,4,5,7-Tetralodo-3,6-dihydroxyxanthene-9-spiro-1'-(4',5',6',7'-tetrachloro-3'H-isobenzofuran-3'one dipotassium salt, trisodium 3-carboxy-5-hydroxy-1-p-sulphophenyl-4-p-sulphophenylazopyrazole, 6-hydroxy-5-((4-sulphonphenyl)azo-2-naphthalenesulphonic acid disodium salt and optionally aluminium lakes thereof Magnesium stearate, talc and stearic acid are typical lubricants Typical binders are povidone, and comstarch

Water and ethanol are examples of volatile components which can be used in the manufacture process of both layers to granulate powders These volatile components are removed during processing and therefore do not appear in the finished product

The tablet coating is optional since the presence of it does not modifies significantly the release rates of the active substances present in the core layers The presence of the coating is preferred because it masks the bitter taste of one of the active substances and enhances the properties of dosage form Because of that a lot different coatings with different polymers, and plasticizers and other excipients could be used with the condition of not modifying significantly the release profile of the active substances present in the core tablet A typical coating comprises a polymer such as hydroxypropylmethylcellulose and a plasticizer such as polyethylene glycol

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Optional excipients could be added to the coating like antifoaming agents and opacifying Example of an antifoaming agent is silicone Examples of opacifying agents are Titanium dioxide, talc and aluminum lake dyes

5 The invention will be further described by the following examples These examples disclose certain preferred embodiments of the invention The methods of manufacturing the compositions according to the invention like for instance granulation, tablet compression, tablet coating etc are well known to the person skilled in the art Those skilled in the art will appreciate that various changes,

10 modifications and substitutions can be made therein without departing from the spirit of the invention Accordingly, it is intended that the invention be not limited to the following explicitly disclosed examples

Example N°1 - Composition

15 **Core**

A. First layer

<u>Layer pseudoephedrine</u>	<u>mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K 15 M PRCR *	198 00
Lactose Monohydrate	105 10
Microcrystalline cellulose	106 00
Colloidal silicon dioxide	1 65
Magnesium Stearate	2 75
Povidone	16 50
Total first layer	550 00

B Second layer

<u>Layer Epinastine</u>	<u>mg / tablet</u>
Epinastine HCl	10 00
FD&C red 40 HT Aluminum lake (allura red AC)	0 38
Microcrystalline cellulose	70 00
Lactose Monohydrate	154 62
Povidone	12 50

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Magnesium Stearate	2 50
Total second layer	250 00

Total core	800.00
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C Coating

Film Coating	mg/ tablet
Methocel E5	15 00
Polyethylene Glycol 6000	1 97
Silicone antifoam S184	0 03
Total film coating	17 00

Total Film coated tablet	817 00
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5 * PR means Premium grade and CR means Controlled Released grade

Method of Manufacture**A First layer**

- A1 Dissolve povidone in a hydroalcoholic mixture,
- A2 Blend pseudoephedrine sulfate, a portion of the microcrystalline cellulose, lactose and Methocel K15M for 5-30 minutes in a suitable mixer
- 10 A3 Use alcoholic or hydroalcoholic solution prepared previously in step A1 to granulate the powder mix
- A4 Dry and mill the pseudoephedrine sulfate granulation from step A3, using suitable size screen
- 15 A5 Blend the screened pseudoephedrine sulfate granulation with a portion of the microcrystalline cellulose and colloidal silicon dioxide for 3-15 minutes
- A6 Add magnesium stearate and blend for 3-15 minutes

B Second layer

- 20 B1 Pass through a suitable screen Epinastine HCL, Allura red AC (FD & C red 40 HT) aluminum lake and microcrystalline cellulose Blend for 5-30 minutes in a suitable mixer
- B2 Add lactose and povidone Blend for 60 minutes 15-120 minutes in a suitable mixer
- 25 B3 Add magnesium stearate Blend for 3-20 minutes in a suitable mixer

15

C Compression

Compress A and B into a suitable bilayer tableting machine in suitable size tablets

5 D Coating

- D1 Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water
D2 Dissolve silicone antifoam in suitable amount of isopropilic alcohol
D3 Add 2 to 1 and mix.
D4 Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3 in
10 a suitable coater

Example N° 2 - Composition

Core

A. First layer

<u>Layer pseudoephedrine</u>	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K 15 M PRGR *	198 00
Lactose Monohydrate	126 50
Microcrystalline cellulose	100 00
Colloidal silicon dioxide	2 75
Magnesium Stearate	2 75
Total first layer	550 00

B Second layer

<u>Layer Epinastine</u>	Mg / tablet
Epinastine HCl	10 00
Lactose Monohydrate	168 40
Microcrystalline cellulose	70 00
Punceau 4R red aluminum lake	0 38
Magnesium Stearate	1 25
Total second layer	250 00

Total core	800 00
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C. Coating

Film Coating	mg/ tablet
Methocel E5	4 42
Polyethylene Glycol 6000	2 72
Talc	8 76
Titanium dioxide	1 10
Total film coating	17 00

Total Film coated tablet	817 00
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5

* PR means Premium grade and CR means Controlled Released grade

Method of Manufacture**A First layer.**

- 10 A1 Blend pseudoephedrine sulfate, microcrystalline cellulose, lactose, colloidal silicon dioxide and HPMC K15M for 5-30 minutes in a suitable mixer
- A2 Add magnesium stearate and blend for 3-15 minutes

B Second layer

- 15 B1 Pass through a suitable screen Epinastine HCl, and microcrystalline cellulose Blend for 5-30 minutes in a suitable mixer
- B2 Add lactose Blend for 60 minutes 15-120 minutes in a suitable mixer
- B3 Add magnesium stearate Blend for 3-20 minutes in a suitable mixer

C Compression

- 20 Compress A and B into a suitable bilayer tableting machine in suitable size tablets

D Coating

- D1 Dissolve Methocel E5 and Polyethylene Glycol in suitable amount of water
- D2 Add Titanium Dioxide and Talc in suitable amount of water and mix
- 25 D3 Add 2 to 1 And mix

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D4 Coat tablets with the Methocel E5 /Polyethylene glycol solution from step D3 in a suitable coater

Example N° 3

5 Core

A. First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K4M PRCR	247 50
Lactose Monohydrate	166 00
Talc	11 00
Magnesium Stearate	5 50
Total first layer	550 00

* PR means Premium grade and CR means Controlled Released grade

Second layer and coating are identical to example 2, the manufacture method was
10 conducted analogously to the method outlined in example 2,

Example N° 4

Core

A First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K15 M PRCR	198 00
Lactose Monohydrate	99 50
Microcrystalline cellulose	99 50
Colloidal silicon dioxide	2 75
Povidone	27 50
Magnesium stearate	2 75
Total	550 00

* PR means Premium grade and CR means Controlled Released grade

15

Second layer and coating are identical to example 1, the manufacture method was
conducted analogously to the method outlined in example 1,

Example N° 5

Core

A. First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K15M CR	330 00
Lactose	83 50
Talc	11 00
Magnesium Stearate	5 50
Total	550 00

5 * CR means Controlled Released grade

Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

10 Example N° 6

Core

A. First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K15M CR	275 00
Microcrystalline Cellulose	138 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	sq
Total	550 00

* CR means Controlled Released grade

15 Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 7**Core****A. First layer**

<u>Layer pseudoephedrine</u>	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K15M CR	215 00
Dibasic Calcium phosphate	108 50
Ethylcellulose	40 00
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	500 00

* CR means Controlled Released grade

5

Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 8**10 Core****A. First layer**

<u>Layer pseudoephedrine</u>	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K15M CR	137 50
Methocel K100M CR	137 50
Lactose	138 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	550 00

* CR means Controlled Released grade

15 Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 9

Core

A. First layer

<u>Layer pseudoephedrine</u>	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K100M CR	275 00
Lactose	138 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	550 00

* CR means Controlled Released grade

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Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 10

10 Core

A. First layer

<u>Layer pseudoephedrine</u>	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K15M CR	206 20
Methocel K100M CR	68 80
Lactose	138 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	550 00

* CR means Controlled Released grade

15 Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 11

Core

A. First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K15M CR	235 00
Dibasic Calcium phosphate	108 50
Ethylcellulose	20 00
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	500 00

* CR means Controlled Released grade

5

Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 12

10 Core

A. First layer

<u>Layer pseudoephedrine</u>	<u>Mg/tablet</u>
Pseudoephedrine sulfate	120 00
Methocel K15M CR	255 00
Lactose	40 00
Microcrystalline Cellulose	68 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	500 00

* CR means Controlled Released grade

15 Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

Example N° 13

Core

A. First layer

Layer pseudoephedrine	Mg/tablet
Pseudoephedrine sulfate	120 00
Methocel K15M CR	255 00
Dibasic calcium phosphate	108 50
Talc	11 00
Magnesium Stearate	5 50
Ethanol	s q
Total	500 00

* CR means Controlled Released grade

5

Second layer and coating are identical to example 1, the manufacture method was conducted analogously to the method outlined in example 1,

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Claims

- 1) Oral pharmaceutical compositions comprising as pharmaceutically active compounds a combination of an antihistaminic-effective amount of epinastine
5 or a pharmaceutically acceptable salt thereof and of a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and further comprising pharmaceutically acceptable carriers or excipients under the proviso that the composition does not contain a leukotriene antagonist
- 10 2) Oral pharmaceutical composition according to claim 1, characterized in that it contains as the active ingredients only an antihistaminic-effective amount of epinastine or a pharmaceutically acceptable salt thereof and a decongestant-effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof
- 15 3) Oral pharmaceutical composition according to claim 1 or 2, providing for a sustained release of the decongestant effective amount of pseudoephedrine and an immediate release of an antihistaminic effective amount of epinastine
- 20 4) Oral pharmaceutical composition according to claims 1, 2 or 3, characterized in that it represents a bilayer tablet.
- 5) Bilayer tablet according to claim 4, wherein a first layer A, providing for the sustained release of pseudoephedrine, comprises a decongestant effective
25 amount of pseudoephedrine or a pharmaceutically acceptable salt thereof and wherein a second layer B, providing for the immediate release of epinastine, comprises an antihistaminic effective amount of epinastine or a pharmaceutically acceptable salt thereof
- 30 6) Bilayer tablet according to claim 5, characterized in that it additionally contains a tablet coating C consisting of pharmaceutically acceptable excipients

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- 7) Bilayer tablet according to claim 4, 5 or 6, characterized in that layer A comprises a decongestant effective amount of pseudoephedrine or a pharmaceutically acceptable salt thereof in a matrix of a swellable hydrophilic polymer

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- 8) Bilayer tablet according to claim 4, 5, 6 or 7, characterized in that the concentration range of pseudoephedrine salt is 5 and 240 mg/tablet and the concentration range of epinastine salt in the compositions according to the invention is between 2 and 20 mg/tablet

10

- 9) Bilayer tablet according to one of claims 4 to 8, characterized in that layer A comprises 120 mg pseudoephedrine sulfate and layer B comprises 10 mg epinastine-HCl

- 15 10) Use of a pharmaceutical composition according to one of claims 1 to 9 for the treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs, in the treatment of for instance common cold and in the symptomatic relief associated with cough, cold and flu symptoms

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- 11) Use of a pharmaceutical composition according to claim 10 for the treatment of allergic rhinitis, allergic congestion of the Eustachian tubes and / or other diseases from allergic origin deserving the administration of antihistamine and decongestant drugs, preferably of allergic rhinitis

25

INTERNATIONAL SEARCH REPORT

Intern at Application No

PCT/EP 01/11229

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K31/415 A61K31/135 A61P37/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

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)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 32125 A (SCHERING) 1 July 1999 (1999-07-01) claims 1,7,8 page 9, line 25 - line 33	1-11
A	EP 0 903 151 A (ASTA) 24 March 1999 (1999-03-24) the whole document	1-11
P,X	WO 01 51038 A (LABORATORIOS PHOENIX) 19 July 2001 (2001-07-19) claims 1,2,22 page 5, line 11 - line 13 examples 1,6	1-8,10, 11

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

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Date of the actual completion of the international search

6 February 2002

Date of mailing of the international search report

15/02/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/11229

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WO 0151038 A	19-07-2001	AU 2634901 A	24-07-2001
		WO 0151038 A1	19-07-2001

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only	
PCT/EP 0 1 / 1 1 2 2 9	
International Application No	
28 SEP 2001	(28.09.2001)
International Filing Date	
EUROPEAN PATENT OFFICE	
PCT INTERNATIONAL APPLICATION	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) Case 1/1147-PCT	

Box No I TITLE OF INVENTION	
New pharmaceutical compositions containing epinastine and pseudoephedrine	
Box No II APPLICANT ☐ This person is also inventor	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
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55216 Ingelheim am Rhein Deutschland	
Telephone No 06132-77 2003	
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
This person is applicant for the purposes of ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
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The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities 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.)	
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☒ 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.	

Continuation of Box No III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)			
<i>If none of the following sub-boxes is used this sheet should not be included in the request</i>			
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. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.) BIANCHI, Daniel Bulnes 2736 (P 15, Dpto 05) 1425 Buenos Aires Argentina		This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked do not fill in below) Applicant's registration No with the Office	
State (that is country) of nationality AR		State (that is country) of residence AR	
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
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. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.) GEL, Francisco Vicente Damonte 1520 (1824) Lanus Este Buenos Aires Argentina		This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below) Applicant's registration No with the Office	
State (that is country) of nationality AR		State (that is country) of residence AR	
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
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. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.) DENKER, Victor Mendoza 2295 1428 Buenos Aires Argentina		This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below) Applicant's registration No with the Office	
State (that is country) of nationality AR		State (that is country) of residence AR	
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
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. The country of the address indicated in this Box is the applicant's State (that is country) of residence if no State of residence is indicated below.) FERNANDEZ, Mabel Marconi 4848 1605 Munro Buenos Aires Argentina		This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked do not fill in below) Applicant's registration No with the Office	
State (that is country) of nationality AR		State (that is country) of residence AR	
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet			

Continuation of Box No III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
If none of the following sub-boxes is used this sheet should not be included in the request	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) VIDAL, Marta Cicconi de Ituzaingo 4156 1754 San Justo Buenos Aires Argentina	This person is ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked do not fill in below.) Applicant's registration No with the Office
State (that is country) of nationality AR	State (that is country) of residence AR
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No with the Office
State (that is country) of nationality	State (that is country) of residence
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked do not fill in below.) Applicant's registration No with the Office
State (that is country) of nationality	State (that is country) of residence
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check box is marked do not fill in below.) Applicant's registration No with the Office
State (that is country) of nationality	State (that is country) of residence
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	This person is ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check box is marked do not fill in below.) Applicant's registration No with the Office
State (that is country) of nationality	State (that is country) of residence
This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No V DESIGNATION OF STATES

Mark the applicable check-boxes below at least one must be marked

The following designations are hereby made under Rule 4 9(a)

Regional Patent

- ☒ AP ARIPO Patent GH Ghana GM Gambia, KE Kenya LS Lesotho, MW Malawi MZ Mozambique SD Sudan SL Sierra Leone SZ Swaziland TZ United Republic of Tanzania UG Uganda ZW Zimbabwe and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent AM Armenia AZ Azerbaijan BY Belarus KG Kyrgyzstan KZ Kazakhstan, MD Republic of Moldova RU Russian Federation TJ Tajikistan TM Turkmenistan and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent AT Austria, BE Belgium CH & LI Switzerland and Liechtenstein, CY Cyprus DE Germany, DK Denmark ES Spain FI Finland, FR France GB United Kingdom GR Greece, IE Ireland IT Italy LU Luxembourg MC Monaco NL Netherlands PT Portugal SE Sweden TR Turkey and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent BF Burkina Faso BJ Benin CF Central African Republic CG Congo, CI Côte d'Ivoire CM Cameroon GA Gabon GN Guinea GW Guinea Bissau ML Mali MR Mauritania NE Niger, SN Senegal, TD Chad, TG Togo and any other State which is a member State of OAPI and a Contracting State of the PCT (If other kind of protection or treatment desired specify on dotted line)

National Patent (If other kind of protection or treatment desired specify on dotted line)

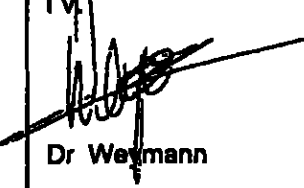
- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☒ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☒ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☒ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☒ PT Portugal |
| ☒ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | | ☒ SI Slovenia |
| ☒ CA Canada | ☒ KR Republic of Korea | ☒ SK Slovakia |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ KZ Kazakhstan | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LC Saint Lucia | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LK Sri Lanka | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LR Liberia | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LS Lesotho | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LT Lithuania | |
| ☒ DE Germany | ☒ LU Luxembourg | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MA Morocco | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MD Republic of Moldova | ☒ US United States of America |
| ☒ EC Ecuador | | |
| ☒ EE Estonia | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ FI Finland | | ☒ YU Yugoslavia |
| ☒ GB United Kingdom | ☒ MN Mongolia | ☒ ZA South Africa |
| ☒ GD Grenada | ☒ MW Malawi | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |

Check boxes below reserved for designating States which have become party to the PCT after issuance of this sheet

☒ PH Philippines☐☐☐☐☐

Precautionary Designation Statement In addition to the designations made above, the applicant also makes under Rule 4 9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. 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. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is		
		national application country	regional application * regional Office	international application receiving Office
item (1) 06 October 2000 (06.10.2000)	00121828 8	EP		
item (2)				
item (3)				
item (4)				
item (5)				
☐ Further priority claims are indicated in the Supplemental Box				
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as ☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other see Supplemental Box				
* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4 10(b)(ii))				
Box No VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen the two-letter code may be used)				
ISA /				
Request to use results of earlier search, reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority)				
Date (day/month/year)	Number	Country (or regional Office)		
06 October 2000	00121828 8-2114-	EP		
Box No. VIII DECLARATIONS				
The following declarations are contained in Boxes Nos VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)				Number of declarations
☐ Box No VIII (i)	Declaration as to the identity of the inventor			
☐ Box No VIII (ii)	Declaration as to the applicant's entitlement as at the international filing date, to apply for and be granted a patent			
☐ Box No VIII (iii)	Declaration as to the applicant's entitlement as at the international filing date to claim the priority of the earlier application			
☐ Box No VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)			
☐ Box No. VIII (v)	Declaration as to non prejudicial disclosures or exceptions to lack of novelty			

Box No IX CHECK LIST, LANGUAGE OF FILING		
This international application contains (a) the following number of sheets in paper form request (including declaration sheets) 12 description (excluding sequence listing part) 14 claims 2 abstract 1 drawings Sub-total number of sheets 29 sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form see (b) below) Total number of sheets 29 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette CD-ROM CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii) in right column)	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item) 1 ☒ fee calculation sheet 1 2 ☐ original separate power of attorney 3 ☐ original general power of attorney 4 ☐ copy of general power of attorney, reference number if any 5 ☐ statement explaining lack of signature 6 ☒ priority document(s) identified in Box No VI as item(s) 1 7 ☐ translation of international application into (language) 8 ☐ separate indications concerning deposited microorganism or other biological material 9 ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette CD ROM, CD R or other)) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including where applicable the copy for the purposes of international search under Rule 13ter (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column 10 ☐ other (specify)	Number of items
Figure of the drawings which should accompany the abstract	Language of filing of the international application English	
Box No X 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 request).		
BOEHRINGER INGELHEIM INTERNATIONAL GMBH IV IA   Dr Weymann Dr Fuchs		
For receiving Office use only		
1 Date of actual receipt of the purported international application 28 SEP 2001 (28 09 01)	2 Drawings ☐ received ☐ not received	
3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
4 Date of timely receipt of the required corrections under PCT Article 11(2)		
5 International Searching Authority (if two or more are competent) ISA /	6 ☒ Transmittal of search copy delayed until search fee is paid	
For International Bureau use only		
Date of receipt of the record copy by the International Bureau		

PATENT COOPERATION TREATY

22

PCT

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

(PCT Rule 47 1(c), first sentence)

From the INTERNATIONAL BUREAU

To
BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
55216 Ingelheim and Rhein
ALLEMAGNEingang B Patente

22 April 2002

SB gesehen erledigt

CF CF

25 April 2002

Date of mailing (day/month/year)

11 April 2002 (11 04 02)

Applicant's or agent's file reference

Case 1/1147-PCT

IMPORTANT NOTICE

International application No

PCT/EP01/11229

International filing date (day/month/year)

28 September 2001 (28 09 01)

Priority date (day/month/year)

06 October 2000 (06 10 00)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH 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

KP, KR, 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, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,

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 11 April 2002 (11 04.02) under No. WO 02/28373

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into 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 18 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 the designated Office. For further details see PCT Gazette No. 44/2001 of 1 November 2001 pages 18926 18932 and 18934 as well as the PCT News letter 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 limits

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

Facsimile No (41 22) 740 14.35

Authorized officer

J Zahra

Telephone No (41 22) 338 91 11

Continuation of Form PCT/IB/308

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

Date of mailing (day/month/year) 11 April 2002 (11 04 02)	IMPORTANT NOTICE
Applicant's or agent's file reference Case 1/1147-PCT	International application No PCT/EP01/11229
The applicant is hereby notified that at the time of establishment of this Notice the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments	

agents

4. Dec 2002

PCT-
12718

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To

**BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
55216 Ingelheim am Rhein
Germany**

Date of mailing (day/month/year)

22 November 2002 (22 11 02)

Applicant's or agent's file reference

Case 1/1147-PCT

IMPORTANT INFORMATION

International application No.

PCT/EP01/11229

International filing date (day/month/year)

28 September 2001 (28 09 01)

Priority date (day/month/year)

06 October 2000 (06 10 00)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH 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,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
National AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,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 GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,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,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZV

- 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 38(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 the 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

Facsimile No (41 22) 740 14.35

Authorized officer

Farid ABBOU

Telephone No (41 22) 338 83 38

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 and hereby elects all eligible States (except where otherwise indicated)

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 1/1147-PCT
International application No PCT/EP 01/11229	International filing date (day/month/year) 28 September 2001	(Earliest) Priority date (day/month/year) 6 Oktober 2000
Title of invention New pharmaceutical compositions containing epinastine and pseudoephedrine		
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 INTERNATIONAL GMBH Bingerstr 173 55216 Ingelheim am Rhein DE		Telephone No 06132/77-2003
		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.) ABELAIRA, Sara Salazar 1483 1686 Hurlingham Buenos Aires Argentina		
State (that is country) of nationality AR		State (that is country) of residence AR
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.) BIANCHI, Daniel Bulnes 2736 (P 15, Dpto 05) 1425 Buenos Aires Argentina		
State (that is country) of nationality AR		State (that is country) of residence AR
☒ Further applicants are indicated on a continuation sheet		

Continuation of Box No II APPLICANT(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the demand.</i>	
Name and address <i>(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)</i> GEL, Francisco Vicente Damonte 1520 (1824) Lanus Este Buenos Aires Argentina	
State <i>(that is country)</i> of nationality AR	State <i>(that is country)</i> of residence AR
Name and address <i>(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)</i> DENKER, Victor Mendoza 2295 1428 Buenos Aires Argentina	
State <i>(that is, country)</i> of nationality AR	State <i>(that is country)</i> of residence AR
Name and address <i>(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)</i> FERNANDEZ, Mabel Marconi 4848 1605 Munro Buenos Aires Argentina	
State <i>(that is country)</i> of nationality AR	State <i>(that is country)</i> of residence AR
Name and address <i>(Family name followed by given name, for a legal entity full official designation. The address must include postal code and name of country.)</i> VIDAL, Marta Cicconi de Ituzaingo 4156 1754 San Justo Buenos Aires Argentina	
State <i>(that is, country)</i> of nationality AR	State <i>(that is country)</i> of residence AR
☐ Further applicants are indicated on another continuation sheet	

Sheet No 3

International application No
PCT/EP 01/11229

Box No III AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The 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 earlierName 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 INTERNATIONAL GMBH
Bingerstr 173
55216 Ingelheim am Rhein
DE

Telephone No

06132/77-2003

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 filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342 ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed3 ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69 1(d)) *(This check-box may be marked only where the time limit under Article 19 has not yet expired)*

* 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 applicant hereby elects all eligible States *(that is all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect

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		For International Preliminary Examining Authority use only	
		received	not received
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	☐	☐

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 ☐ other (specify)
4 ☐ copy of general power of attorney reference number if any	

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 INTERNATIONAL GMBH

ppa/  Dr Klas	IV  Dr Fuchs
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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 I(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 period 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	

For International Bureau use only

Demand received from IPEA on.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Bingerstr 173
55216 Ingelheim am Rhein
ALLEMAGNE

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY(PCT Rules 59.3(e) and 61.1(b) first sentence
and Administrative Instructions Section 601(a))Date of mailing
(day/month/year)

26 04 02

Applicant's or agent's file reference
1/1147-PCT

IMPORTANT NOTIFICATION

International application No

PCT/EP 01/11229

International filing date (day/month/year)

28/09/2001

Priority date (day/month/year)

06/10/2000

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al

- 1 The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application.

17/04/2002

- 2 This date of receipt is

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

- 3 ☐ **ATTENTION** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details see the PCT Applicant's Guide Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on _____.

- 4 Only where paragraph 3 applies a copy of this notification has been sent to the International Bureau

Name and mailing address of the IPEA/

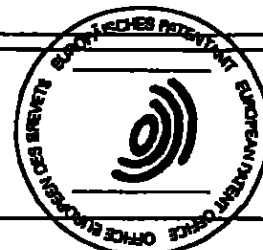


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PATENT COOPERATION TREATY

2
3

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To.		NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT	
BOEHRINGER INGELHEIM INTERNATIONAL GMBH Bingerstr 173 55216 Ingelheim am Rhein 16 Mai 2002 ALLEMAGNE			
SB	gesehen erledigt		
		(PCT Rule 71.1)	
Applicant's or agent's file reference 1/1147-PCT		Date of mailing (day/month/year) 15/05/2002	
International application No PCT/EP 01/11229		International filing date (day/month/year) 28/09/2001	Priority date (day/month/year) 06/10/2000
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al			

- 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
- A copy of the report and its annexes if any is being transmitted to the International Bureau for communication to all the elected Offices.
- 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.
- 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

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel (+49-89) 2399-0 Tx 523656 epmu d Fax (+49-89) 2399-4465	Authorized officer AIMALE MURILLO J Tel (+49-89) 2399 2828
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1/1147-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No PCT/EP 01/ 11229	International filing date (day/month/year) 28/09/2001	Priority date (day/month/year) 06/10/2000
International Patent Classification (IPC) or national classification and IPC A61K9/20		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH 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 <u>2</u> 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 consists of a total of _____ sheets.	
3 This report contains indications relating to the following items: I ☒ Basis of the report 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 Article 35(2) 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 17/04/2002	Date of completion of this report 10/05/2002
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel (+49-89) 2399-0 Tx 523656 epmu d Fax (+49-89) 2399-4465	Authorized officer FLETCHER A S Tel (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) (July 1998)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No PCT/EP 01/ 11229

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed

V Reasoned statement under Rule 66 2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable

**Nuevas composiciones farmaceuticas que contienen
epinastina y pseudoefedrina**

Antecedentes del invento

- 5 El presente invento se refiere a nuevas composiciones farmacéuticas orales que comprenden como compuestos farmacéuticamente activos una combinacion de una cantidad eficaz como antihistaminica de epinastina o una sal de la misma farmaceutica-mente aceptable, y de una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de ésta, y que comprenden además vehículos
10 o excipientes apropiados, farmacéuticamente aceptables El invento se refiere además a métodos para la preparación de estas composiciones, y a metodos de usarlas en el tratamiento de enfermedades y/o trastornos alergicos

Descripción del invento

- 15 El presente invento proporciona nuevas composiciones farmaceuticas orales que comprenden como compuestos farmaceuticamente activos una combinacion de una cantidad eficaz como antihistaminica de epinastina o una sal farmaceuticamente aceptable de ella y una cantidad eficaz como descongestionante de pseudoefedrina o una sal del farmacéuticamente aceptable de la misma, y que comprenden además
20 vehiculos o excipientes farmaceuticamente aceptables, con la condicion de que la composición no ha de contener un antagonista de leucotrienos

- Como compuesto activo adicional, las composiciones de acuerdo con el invento pueden contener opcionalmente uno o varios compuestos seleccionados entre el grupo que consta de compuestos mucolíticos y analgésicos-antipiréticos, así como de
25 vitaminas Los ingredientes mucolíticos preferidos se seleccionan entre bromhexina y ambroxol Los compuestos analgésicos y antipireticos preferidos se seleccionan entre paracetamol y obuprofeno Vitaminas prefendas se seleccionan entre las vitaminas B2, B6 y C

- Las composiciones farmaceuticas de acuerdo con el invento son utiles en el
30 tratamiento de la rinitis alergica, la congestion alergica de las trompas de Eustaquio y otras enfermedades de origen alergico que precisan de la administración de farmacos antihistaminicos y descongestionantes Además, las composiciones de acuerdo con el invento son utiles en el tratamiento, por ejemplo del resfriamiento comun y en el alivio sintomatico asociado con sintomas de tos, resfriamiento y gripe Se prefiere el uso de las
35 composiciones farmacéuticas de acuerdo con el invento para el tratamiento de la rinitis alérgica, la congestion alérgica de las trompas de Eustaquio y/u otras enfermedades de origen alérgico que precisan de la administracion de farmacos antihistaminicos y

descongestionantes

En una realizacion preferida la composición farmaceutica de acuerdo con el invento contiene en calidad de los ingredientes activos solamente una cantidad eficaz como antihistamínica de epinastina o una sal farmaceuticamente aceptable de la misma y una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuti-
camente aceptable de la misma

En una realizacion preferida, el presente invento se refiere a una composicion farmaceutica oral, preferiblemente una tableta de dos capas, que proporciona una liberacion prolongada de la cantidad eficaz como descongestionante de pseudoefedrina y una liberación inmediata de una cantidad eficaz como antihistaminica de epinastina

Es particularmente prefenda de acuerdo con el invento una tableta de dos capas en la que una primera capa A, que proporciona la liberacion prolongada de pseudoefedrina, comprende una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma, y en la que una segunda capa B, que proporciona la liberación inmediata de epinastina, comprende una cantidad eficaz como antihistamínica de epinastina o una sal farmacéuticamente aceptable de la misma La tableta de dos capas de acuerdo con el invento puede contener adicionalmente un revestimiento C de tabletas que consta de excipientes farmaceuticamente aceptables que enmascaran el sabor amargo de uno de los compuestos activos

En una realizacion preferida del invento, la capa A de la tableta de dos capas de acuerdo con el invento comprende una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma en una matriz de un polímero hidrófilo hinchable que proporciona un perfil de liberación prolongada en un periodo de tiempo de 3 a 24, preferiblemente 6 a 18, lo mas preferiblemente alrededor de 12 horas

De acuerdo con el invento la expresión "sales farmacéuticamente aceptables" se refiere a sales por adición de acidos de los compuestos activos pseudoefedrina y epinastina Estas sales por adición de ácidos se pueden formar con ácidos inorganicos tales como acido clorhídrico, ácido bromhídrico o ácido sulfurico o con acidos orgánicos tales como por ejemplo acido oxalico, ácido fumárico o acido metanosulfonico La epinastina se usa preferiblemente como su sal por adición con acido clorhídrico La pseudoefedrina se usa preferiblemente como el hidrocioruro o el sulfato Dentro del presente invento es sumamente preferido el sulfato de pseudoefedrina

La liberacion de pseudoefedrina tiene lugar en el transcurso de 3 a 24, preferiblemente 6 a 18, lo más preferiblemente alrededor de 12 horas Esta tableta de dos capas se diseña para ser administrada preferiblemente dos veces por dia

El margen de concentraciones de la sal de pseudoefedrina en las composiciones

de acuerdo con el invento esta situado entre 5 y 240 mg/tableta, preferiblemente entre 10 y 200 mg/tableta, mas preferiblemente entre 60 y 180 mg/tableta, todavia mas preferiblemente entre 80 y 140 mg/tableta y lo mas preferiblemente 120 mg/tableta El margen de concentraciones de la sal de epinastina en las composiciones de acuerdo con el invento está situado entre 2 y 20 mg/tableta, preferiblemente 5 a 10 mg/tableta, mas preferiblemente 10 mg/tableta

Cada capa de la tableta está en contacto con cada una de las otras en una porcion de su superficie, pero proporciona perfiles de liberacion independientes para ambas sustancias activas que antes se han mencionado La capa A de liberacion prolongada consta de pseudoefedrina o una sal farmaceuticamente aceptable de la misma y un polimero hidrófilo hinchable

Tipicos polimeros hidrófilos hinchables incluyen eteres celulósicos tales como metil-celulosa, hidroxipropil-celulosa, hidroxipropil-metil-celulosa hidroximetil-celulosa, hidroxietil-celulosa, carboximetil-celulosa y carboxietil-celulosa o sus mezclas Se prefiere el uso de hidroxipropil-metil-celulosa (HPMC) Son particularmente utiles los polimeros de la HPMC HPMC USP2910 y USP2208, por ejemplo Methocel E5, E4M, E15M, K15M y K100M suministrados por la entidad Dow Chemical Company En las abreviaturas antes mencionadas la designacion "E" se refiere a la USP2910 mientras que "K" se refiere a la USP2208 El numero de la designacion se refiere a la viscosidad en una solucion acuosa al 2% (p ej 5 designa una viscosidad de 5 cps, 15M designa una viscosidad de 15 000 cps)

Los excipientes que se podrian usar opcionalmente en la capa A de liberacion prolongada son polimeros insolubles, materiales de carga solubles o insolubles, antiadherentes, agentes colorantes, lubricantes y aglutinantes adicionales Tipicos materiales de carga son por ejemplo lactosa, celulosa microcristalina, fosfato de calcio dibásico y almidón de maiz Ejemplos de agentes antiadherentes, que se usan para impedir que las tabletas se peguen a la prensa para comprimir tabletas, son dióxido de silicio coloidal y talco El estearato de magnesio, el talco y el acido esteanco son lubricantes tipicos Agentes aglutinantes típicos son povidona y almidón de maíz

La capa B de matriz de liberacion inmediata comprende epinastina con diferentes combinaciones de excipientes Los excipientes que se podrian usar opcionalmente en la capa B de liberación inmediata son polímeros insolubles, materiales de carga solubles o insolubles, agentes antiadherentes, lubricantes, agentes colorantes, desintegrantes y aglutinantes adicionales Los materiales de carga típicos son por ejemplo lactosa, celulosa microcristalina, fosfato de calcio dibásico y almidón de maiz Ejemplos de agentes antiadherentes, que se usan para impedir que las tabletas se peguen a la prensa para comprimir tabletas son dióxido de silicio coloidal y talco Desintegrantes

tipicos son crospovidona, almidón-glicolato de sodio y crosscarmellosa de sodio. Los
tipicos agentes colorantes se seleccionan entre la laca con aluminio FD&C red 40 HT,
sal de trisodio de acido 2-hidroxi-1,1'-azo-naftaleno-3,6,4'-trisulfonico, entrosina, oxidos
de hierro, sal de trisodio de acido 1-(4-sulfo-1-naftilazo)-2-naftol-6,8-disulfonico, sal de
5 disodio de 2',4',5',7'-tetrabromo-4,5,6,7-tetracloro-fluoresceina, sal de dipotasio de
2,4,5,7-tetrayodo-3,6-dihidroxi-xanteno-9-espiro-1'-(4',5',6',7'-tetracloro-3'H-
isobenzofuran-3'-ona, sal de trisodio de 3-carboxi-5-hidroxi-1-p-sulfofenil-4-p-sulfofenil-
azo-pirazol, sal de disodio de acido 6-hidroxi-5-((4-sulfofenil)azo-2-naftaleno-sulfonico y
opcionalmente lacas con aluminio de estas. El estearato de magnesio, el talco y el acido
10 esteánico son lubricantes típicos. Agentes aglutinantes típicos son povidona y almidon
de maíz.

El agua y el etanol son ejemplos de componentes volátiles que se pueden usar
en el procedimiento de preparacion de ambas capas para granular polvos. Estos
componentes volatiles se eliminan durante el tratamiento y por lo tanto no aparecen en
15 el producto acabado.

El revestimiento de las tabletas es opcional, puesto que la presencia de éste no
modifica de manera importante los regimenes de liberacion de las sustancias activas
presentes en las capas de nucleo. Es preferido la presencia del revestimiento, puesto
que enmascara el sabor amargo de una de las sustancias activas e intensifica las
20 propiedades de la forma de dosificacion. A causa de esto, se podrian usar gran numero
de diferentes revestimientos con diferentes polimeros y plastificantes y otros excipientes,
con la condición de que no modifiquen de manera importante el perfil de liberacion de las
sustancias activas presentes en el nucleo de tabletas. Un revestimiento típico comprende
un polímero tal como hidroxipropil-metil-celulosa y un plastificante tal como polietilen-
25 glicol. Se podrían añadir al revestimiento excipientes opcionales tales como agentes
antiespumantes y opacificantes. Un ejemplo de un agente antiespumante es silicona.
Ejemplos de agentes opacificantes son dióxido de titanio, talco y tintes de lacas con
aluminio.

El invento se describira adicionalmente mediante los siguientes ejemplos. Estos
30 ejemplos describen ciertas realizaciones, preferidas del invento. Los metodos para
preparar las composiciones de acuerdo con el invento, tales como por ejemplo
granulacion, compresión de tabletas, revestimiento de tabletas, etc., son bien conocidos
para la persona experta en el sector de la técnica. Los expertos en el sector de la técnica
apreciarán que se pueden hacer en ellas diversos cambios, modificaciones y sustitucio-
35 nes, sin apartarse del espíritu del invento. Correspondientemente se pretende que el
invento no quede limitado a los siguientes ejemplos descritos explícitamente.

Ejemplo N° 1 - Composicion

Nucleo

A Primera capa

5	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
	Methocel K15M PRCR*	198 00
	Lactosa monohidrato	105,10
	Celulosa microcristalina	106 00
10	Dióxido de silicio coloidal	1,65
	Estearato de magnesio	2 75
	Povidona	16 50
	Total de la primera capa	550,00

15

B Segunda capa

	Capa de epinastina	mg/tableta
	Epinastina HCl	10,00
	Laca con aluminio FD&C red 40 HT (Allura red AC)	0,38
20	Celulosa microcristalina	70 00
	Lactosa monohidrato	154 62
	Povidona	12,50
	Estearato de magnesio	2,50
	Total de la segunda capa	250,00

25

Total del núcleo	800,00
-------------------------	---------------

C **Revestimiento**

5	Revestimiento de película	mg/tableta
	Methocel E5	15 00
	Poli(etilén)-glicol 6000	1,97
	Antiespumante de sílica S184	0,03
	Total del revestimiento de película	17,00
Total de la tableta revestida con película		817,00

* PR significa calidad primerísima (Premium) y CR significa calidad con liberación controlada

10

Método de preparación

A Primera capa

- 15
- A1 Hay que disolver la povidona en una mezcla hidroalcohólica,
- A2 Hay que mezclar el sulfato de pseudoefedrina, una porción de la celulosa microcristalina, la lactosa y el Methocel K15M durante 5-30 minutos en un mezclador apropiado
- A3 Hay que usar una solución alcohólica o hidroalcohólica preparada con antelación en la operación A1, para granular la mezcla de polvos
- 20
- A4 Hay que secar y moler el granulado de sulfato de pseudoefedrina procedente de la operación A3, usando un tamiz de tamaño apropiado
- A5 Hay que mezclar el granulado tamizado de sulfato de pseudoefedrina con una porción de la celulosa microcristalina y dióxido de silicio coloidal durante 3-15 minutos
- 25
- A6 Hay que añadir estearato de magnesio y mezclar durante 3-15 minutos

B Segunda capa

- 30
- B1 Se han de hacer pasar a través de un tamiz apropiado la epinastina HCl, el Allura red AC (FD&C red 40 HT), la laca con aluminio y la celulosa microcristalina Hay que mezclar durante 5-30 minutos en un mezclador apropiado
- B2 Hay que añadir la lactosa y la povidona Hay que mezclar durante 60 minutos, 15-120 minutos, en un mezclador apropiado
- B3 Hay que añadir estearato de magnesio Hay que mezclar durante 3-20 minutos en un mezclador apropiado

35

C Compresion

Hay que comprimir A y B en una apropiada maquina de compresion para tabletas de dos capas formando tabletas de tamaño apropiado

5 D Revestimiento

- D1 Hay que disolver el Methocel E5 y el polietilen-glicol en una cantidad apropiada de agua
- D2 Hay que disolver el antiespumante de silicona en una cantidad apropiada de alcohol isopropilico
- 10 D3 Hay que añadir el componente 2) al componente 1) y mezclar
- D4 Hay que revestir las tabletas con la solución de Methocel E5/polietilen-glicol procedente de la operacion D3 en un aparato revestidor apropiado

Ejemplo N° 2 - Composicion

15

Nucleo

A Primera capa

20	<u>Capa de pseudoefedrina</u>	<u>mg/tableta</u>
	Sulfato de pseudoefedrina	120 00
	Methocel K15M PRCR*	198,00
	Lactosa monohidrato	126,50
	Celulosa microcristalina	100 00
	Dióxido de silicio coloidal	2,75
	Estearato de magnesio	2,75
25	Total de la primera capa	550,00

B Segunda capa

30	<u>Capa de epinastina</u>	<u>mg/tableta</u>
	Epinastina HCl	10,00
	Lactosa monohidrato	168,40
	Celulosa microcristalina	70,00
	Laca con aluminio Ponceau 4R red	0,38
	Estearato de magnesio	1 25
	Total de la segunda capa	250,00

45

Total del nucleo	800,00
------------------	--------

C Revestimiento

	Revestimiento de pelicula	mg/tableta
5	Methocel E5	4 42
	Poli(etil)en-glicol 6000	2,72
	Talco	8,76
	Dióxido de titanio	1 10
	Total del revestimiento de película	17,00

10

Total de la tableta revestida con pelicula	817,00
--	--------

* PR significa calidad primerisima (Premium) y CR significa calidad con liberación controlada

Método de preparacion

15

A Pnmera capa

- A1 Hay que mezclar el sulfato de pseudoefedrina, la celulosa microcristalina, la lactosa, el dióxido de silicio coloidal y el HPMC K15M durante 15-30 minutos en un mezclador apropiado
- 20 A2 Hay que añadir el estearato de magnesio y mezclar durante 3-15 minutos

B Segunda capa

- B1 Hay que hacer pasar a traves de un tamiz apropiado la epinastina HCl y la celulosa microcristalina Hay que mezclar durante 5-30 minutos en un mezclador apropiado
- 25 B2 Hay que añadir la lactosa Hay que mezclar durante 60 minutos, 15-120 minutos en un mezclador apropiado
- B3 Hay que añadir estearato de magnesio Hay que mezclar durante 3-20 minutos en un mezclador apropiado

30

C Compresion

Hay que comprimir A y B en una máquina apropiada de compresion de tabletas de dos capas para dar tabletas de tamaño apropiado

D Revestimiento

- D1 Hay que disolver el Methocel E5 y el polietilen-glicol en una cantidad apropiada de agua
- D2 Hay que añadir el dióxido de titanio y el talco en una cantidad apropiada de agua y mezclar
- D3 Hay que añadir el componente 2) al componente 1) y mezclar
- D4 Hay que revestir tabletas con la solución de Methocel E5 y polietilen-glicol procedente de la operación D3, en un aparato revestidor apropiado

Ejemplo N° 3

Núcleo

A Primera capa

15	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
	Methocel K4M PRCR*	247 50
	Lactosa monohidrato	166 00
	Talco	11 00
20	Estearato de magnesio	5,50
	Total de la primera capa	550,00

* PR significa calidad primerísima (Premium) y CR significa calidad con liberación controlada

La segunda capa y el revestimiento son idénticos a como en el Ejemplo 2, el método de preparación se realizó análogamente al método bosquejado en el Ejemplo 2

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Ejemplo N° 4

Nucleo

5 A Primera capa

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120 00
	Methocel K15M PRCR*	198,00
	Lactosa monohidrato	99 50
10	Celulosa microcristalina	99,50
	Dioxido de silicio coloidal	2,75
	Povidona	27 50
	Estearato de magnesio	2,75
	Total	550,00

15 * PR significa calidad primerisima (Premium) y CR significa calidad con liberacion controlada

La segunda capa y el revestimiento son idénticos a como en el Ejemplo 1, el método de preparacion se realizo análogamente al metodo bosquejado en el Ejemplo 1

20 Ejemplo N° 5

Nucleo

A Primera capa

25	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
	Methocel K15M CR*	330,00
	Lactosa	83,50
	Talco	11,00
30	Estearato de magnesio	5 50
	Total	550,00

* CR significa calidad con liberación controlada

35 La segunda capa y el revestimiento son idénticos a como en el Ejemplo 1, el método de preparacion se realizó análogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 6

Nucleo

5 A Primera capa

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120 00
	Methocel K15M CR*	275,00
	Celulosa microcristalina	138 50
10	Talco	11 00
	Estearato de magnesio	5,50
	Etanol	q s
	Total	550,00

* CR significa calidad de liberación controlada

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La segunda capa y el revestimiento son identicos a como en el Ejemplo 1, el método de preparacion se realizo analogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 7

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Nucleo

A Primera capa

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120 00
25	Methocel K15M CR*	215,00
	Fosfato de calcio dibasico	108 50
	Etil-celulosa	40,00
	Talco	11,00
	Estearato de magnesio	5,50
30	Etanol	q s
	Total	500,00

* CR significa calidad de liberación controlada

35 La segunda capa y el revestimiento son idénticos a como en el Ejemplo 1, el método de preparacion se realizo análogamente al método bosquejado en el Ejemplo 1

Ejemplo N° 8

Nucleo

A Primera capa

5	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
	Methocel K15M CR*	137 50
	Methocel K100M CR*	137 50
	Lactosa	138,50
10	Talco	11,00
	Estearato de magnesio	5 50
	Etanol	q s
	Total	550,00

* CR significa calidad de liberacion controlada

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La segunda capa y el revestimiento son identicos a como en el Ejemplo 1, el metodo de preparacion se realizo analogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 9

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Nucleo

A Primera capa

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
25	Methocel K100M CR*	275,00
	Lactosa	138,50
	Talco	11,00
	Estearato de magnesio	5,50
	Etanol	q s
30	Total	550,00

* CR significa calidad de liberación controlada

La segunda capa y el revestimiento son identicos a como en el Ejemplo 1, el método de preparacion se realizo analogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 10

Nucleo

A Primera capa

5	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120 00
	Methocel K15M CR*	206,20
	Methocel K100M CR*	68 80
	Lactosa	138,50
10	Talco	11,00
	Estearato de magnesio	5,50
	Etanol	q s
	Total	550,00

* CR significa calidad de liberación controlada

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La segunda capa y el revestimiento son idénticos a como en el Ejemplo 1 el método de preparacion se realizó analogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 11

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Nucleo

A Primera capa

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
25	Methocel K15M CR*	235,00
	Fosfato de calcio dibásico	108,50
	Etil-celulosa	20,00
	Talco	11 00
	Estearato de magnesio	5,50
30	Etanol	q s
	Total	500,00

* CR significa calidad de liberación controlada

La segunda capa y el revestimiento son identicos a como en el Ejemplo 1, el método de preparacion se realizó análogamente al metodo bosquejado en el Ejemplo 1

Ejemplo N° 12

Nucleo

5 **A Primera capa**

	Capa de pseudoefedrina	mg/tableta
	Sulfato de pseudoefedrina	120,00
	Methocel K15M CR*	255,00
	Lactosa	40,00
10	Celulosa microcristalina	68 50
	Talco	11,00
	Estearato de magnesio	5,50
	Etanol	q s
15	Total	500,00

CR significa calidad de liberacion controlada

La segunda capa y el revestimiento son identicos a como en el Ejemplo 1, el metodo de preparacion se realizo análogamente al metodo bosquejado en el Ejemplo 1

20 **Ejemplo N° 13**

Nucleo

1 **A Primera capa**

	Capa de pseudoefedrina	mg/tableta
25	Sulfato de pseudoefedrina	120 00
	Methocel K15M CR*	255,00
	Fosfato de calcio dibásico	108,50
	Talco	11,00
	Estearato de magnesio	5 50
30	Etanol	q s
	Total	500,00

* CR significa calidad de liberación controlada

La segunda capa y el revestimiento son idénticos a como en el Ejemplo 1, el método de preparación se realizo analogamente al metodo bosquejado en el Ejemplo 1

REIVINDICACIONES

- 1 Composiciones farmacéuticas orales que comprenden como compuestos farmacéuticamente activos una combinación de una cantidad eficaz como antihistamínica de epinastina o una sal farmacéuticamente aceptable de la misma y de una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma, y que comprenden además vehículos o excipientes farmacéuticamente aceptables, con la condición de que la composición no ha de contener ningún antagonista de leucotrienos
- 2 Composición farmacéutica oral de acuerdo con la reivindicación 1, caracterizada porque contiene como ingredientes activos solamente una cantidad eficaz como antihistamínica de epinastina o una sal farmacéuticamente aceptable de la misma y una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma
- 3 Composición farmacéutica oral de acuerdo con la reivindicación 1 ó 2, que proporciona una liberación prolongada de la cantidad eficaz como descongestionante de pseudoefedrina y una liberación inmediata de una cantidad eficaz como antihistamínica de epinastina
- 4 Composición farmacéutica oral de acuerdo con las reivindicaciones 1, 2 o 3, caracterizada porque representa una tableta de dos capas
- 5 Tableta de dos capas de acuerdo con la reivindicación 4, en la que una primera capa A, que proporciona la liberación prolongada de pseudoefedrina, comprende una cantidad eficaz como descongestionante de pseudoefedrina o una de sus sales farmacéuticamente aceptables, y en la que una segunda capa B, que proporciona la liberación inmediata de epinastina, comprende una cantidad eficaz como antihistamínica de epinastina o una de sus sales farmacéuticamente aceptables
- 6 Tableta de dos capas de acuerdo con la reivindicación 5, caracterizada porque adicionalmente contiene un revestimiento C de tabletas que consta de excipientes farmacéuticamente aceptables
- 7 Tableta de dos capas de acuerdo con las reivindicaciones 4, 5 ó 6, caracterizada porque A comprende una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma en una matriz de un polímero hidrófilo hinchable
- 8 Tableta de dos capas de acuerdo con las reivindicaciones 4, 5, 6 ó 7, caracterizada porque el margen de concentraciones de la sal de pseudoefedrina está entre 5 y 240 mg/tableta y el margen de concentraciones de la sal de epinastina en las composiciones de acuerdo con el invento está entre 2 y 20 mg/tableta

9 Tableta de dos capas de acuerdo con una de las reivindicaciones 4 a 8, caracterizada porque la capa A comprende 120 mg de sulfato de pseudoefedrina y la capa B comprende 10 mg de epinastina-HCl

5 10 Uso de una composicion farmacéutica de acuerdo con una de las reivindicaciones 1 a 9 para el tratamiento de la rinitis alergica, la congestion alergica de las trompas de Eustaquio y/u otras enfermedades de origen alérgico que merecen la administración de fármacos antihistamínicos y descongestionantes, en el tratamiento, por ejemplo, del resfriamiento corriente y en el alivio sintomático asociado con sintomas de tos, resfriamiento y gripe

10 11 Uso de una composicion farmacéutica de acuerdo con la reivindicación 10 para el tratamiento de la rinitis alérgica, l congestión alérgica de las trompas de Eustaquio y/u otras enfermedades de origen alergico que precisan de la administracion de fármacos antihistaminicos y descongestionantes, preferiblemente de la rinitis alergica

RESUMEN

El presente invento se refiere a nuevas composiciones farmacéuticas orales que comprenden como compuestos farmacéuticamente activos una combinación de una
5 cantidad eficaz como antihistamínica de epinastina o una sal farmacéuticamente aceptable de la misma y de una cantidad eficaz como descongestionante de pseudoefedrina o una sal farmacéuticamente aceptable de la misma, y que comprenden además apropiados vehículos o excipientes farmacéuticamente aceptables

El invento se refiere además a métodos para la preparación de estas composicio-
10 nes y métodos de usarlos en el tratamiento de enfermedades y/o trastornos alérgicos

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FECHA : MARZO 25 DE 2003

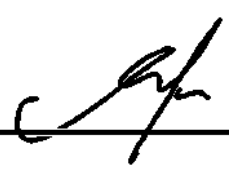
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	990-001.0-6	9005690	25/03/2003	27,448,920 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01 01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN	400,000 00
		TOTAL :	\$ 400,000 00

SOL CUATROCIENTOS MIL PESOS

RESPONSABLE 

RECIBO DE CAJA APLICADO A EXPEDIENTE No _____

Colo 09255-841-003-8

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicacion de que se solicita la concesion de una patente.	()	
Datos de Identificacion del solicitante o de la persona que se presenta la solicitud.	()	
- Descripcion de la invencion.	()	
Dibujos de ser estos pertinentes	()	
- Comprobante de Pago de las tasas establecidas	()	
COMPLETA ()		
INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
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- Datos de Identificacion del solicitante o de la persona que presenta la solicitud.	()	()
- Representacion grafica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseno	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		
INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicacion de que solicita el registro de un Esquema de trazado	()	()
- Datos de Identificacion del solicitante o de la persona que presenta La solicitud	()	()
Representacion grafica del esquema de trazado	()	()
Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		
INCOMPLETA ()		

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