



No. 07-058595- -00004-0000

Fecha: 2009-06-18 17:03:42 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 17

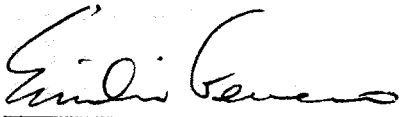
**FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES
2000-10**

1	SOLICITUD DE:		
☐	Corrección de Error Material		
☒	Modificación a una solicitud		
2 SOLICITANTE	<table><tr><td>Nombre: BAYER ANIMAL HEALTH GMBH sociedad constituida y existente bajo las leyes de Alemania Dirección: 51368 Leverkusen, Alemania Teléfono: 546 09 70 E-mail: clientes@cavelier.com Fax: 249 40 70 Domicilio: Leverkusen, Alemania</td><td>IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____</td></tr></table>	Nombre: BAYER ANIMAL HEALTH GMBH sociedad constituida y existente bajo las leyes de Alemania Dirección: 51368 Leverkusen, Alemania Teléfono: 546 09 70 E-mail: clientes@cavelier.com Fax: 249 40 70 Domicilio: Leverkusen, Alemania	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
Nombre: BAYER ANIMAL HEALTH GMBH sociedad constituida y existente bajo las leyes de Alemania Dirección: 51368 Leverkusen, Alemania Teléfono: 546 09 70 E-mail: clientes@cavelier.com Fax: 249 40 70 Domicilio: Leverkusen, Alemania	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____		
3 REPRESENTANTE O APODERADO	<table><tr><td>Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 E-mail: cavelier@cavelier.com Fax: 217 92 11 Domicilio: Bogotá, Colombia</td><td>IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019</u> TP <u>31.929</u></td></tr></table>	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 E-mail: cavelier@cavelier.com Fax: 217 92 11 Domicilio: Bogotá, Colombia	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019</u> TP <u>31.929</u>
Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 E-mail: cavelier@cavelier.com Fax: 217 92 11 Domicilio: Bogotá, Colombia	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019</u> TP <u>31.929</u>		
4	Número de expediente: <u>07.058.595</u> Clase: <u>A61K 047/012</u> Título del Invento: ESTABILIZACIÓN DE ESTERES DE GLUCOCORTICOIDES CON ÁCIDOS		
5	Descripción de la corrección o modificación solicitada: Informo a ese Despacho que la sociedad BAYER HEALTHCARE AG , domiciliada en 51368 Leverkusen, Alemania, traspasó la solicitud de patente que se tramita en el presente expediente a favor de la sociedad BAYER ANIMAL HEALTH GMBH , domiciliada en 51368 Leverkusen, Alemania. Por lo anterior solicito efectuar la anotación del mencionado traspaso en los libros de la Propiedad Industrial y expedir el certificado de patente a favor de la sociedad BAYER ANIMAL HEALTH GMBH .		
6	Comprobante de pago No. <u>09-44,626</u> Fecha: <u>16 de junio de 2009</u>		
7	Anexos: ☒ Comprobante de pago de la tasa por concepto de modificación de solicitud en trámite. ☒ Poderes, si fuere el caso ☒ Certificado de existencia y representación legal, cuando el solicitante sea persona jurídica ☒ Documento que acredita el traspaso.		

57

8

NOMBRE: EMILIO FERRERO

FIRMA: 
C.C. 438.019 de Usaquén T.P. 31.929

CAVELIER

ABOGADOS

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

179

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

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

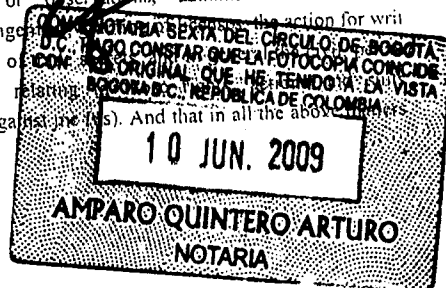
BAYER ANIMAL HEALTH GMBHdomiciliado (s) en/of 51368 Leverkusen, Germany

por el presente nombramos a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el 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, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, 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) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, mandamus, the protection of industrial secrets and administrative suits relating to industrial property. And that in all the above matters instituted by me (us) or against me (us).



los derechos, acciones y procesos que promovamos o se nos
muevan. Y para que en todos los asuntos arriba determinados, puedan
constituir este mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de
agentes oficiosos.

they may substitute this Power of Attorney, compromise, conciliate, admit
the facts of the case, desist, cancel, receive, resign, and ratify acts done by
representatives without a power of attorney.

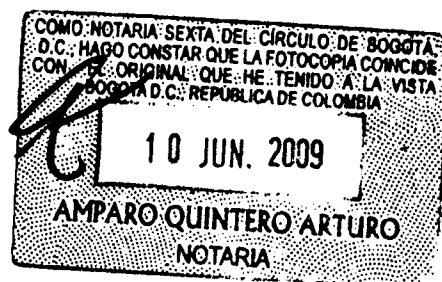
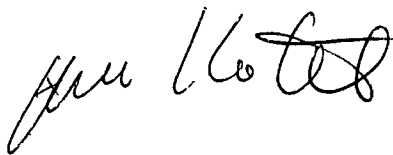
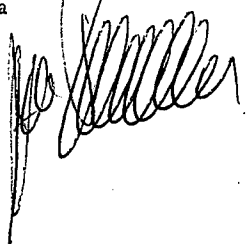
Dado y firmado hoy/Given and signed this _____

en/in Leverkusen

por/by Dr. J. Thomaier Dr. F. Köhler
(secretary) (secretary)

Firma

Signature



URNr. 367/2009

1. I certify that the individuals, named

- Mr. Dr. Jörg Thomaier, business address : 51368 Leverkusen,
Bayer Animal Health GmbH, Chempark, Germany,
- Mr. Dr. Ferdinand Köhler, business address : 51368 Leverkusen,
Bayer Animal Health GmbH, Chempark, Germany

appeared before me and executed the foregoing document and signed personally

- personally known to me -.

I further confirm that Mr. Dr. Jörg Thomaier and Mr. Dr. Ferdinand Köhler are authorised representatives of Bayer Animal Health GmbH in Leverkusen and having today inspected the commercial register of the local court in Cologne, are recorded in Section B 52145 as authorised representatives.

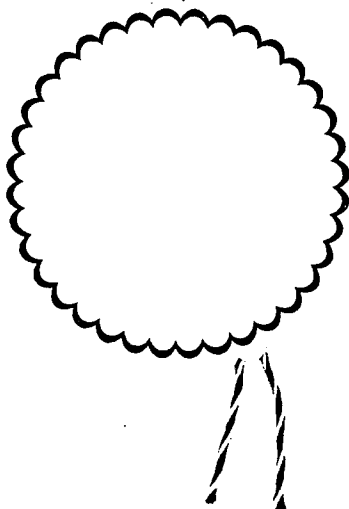
2. Ich beglaubige die vor mir vollzogenen Unterschriften von :

- Herrn Dr. Jörg Thomaier, geschäftsansässig : 51368 Leverkusen,
Bayer Animal Health GmbH, Chempark, Germany,
- Herrn Dr. Ferdinand Köhler, geschäftsansässig : 51368 Leverkusen,
Bayer Animal Health GmbH, Chempark, Germany,

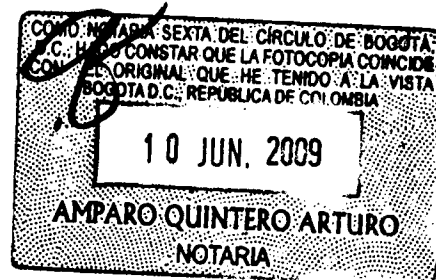
- von Person bekannt -.

Ich bescheinige aufgrund Einsicht vom heutigen Tage in das Handelsregister des Amtsgerichts Köln - HRB 52145 -, dass Herr Dr. Jörg Thomaier und Herr Dr. Ferdinand Köhler berechtigt sind, die Bayer Animal Health GmbH in Leverkusen als Prokuristen einzeln zu vertreten.

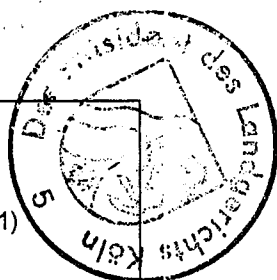
Leverkusen, den 04. März 2009



Klaus Striewski
(Notar in Leverkusen)



5



stir



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

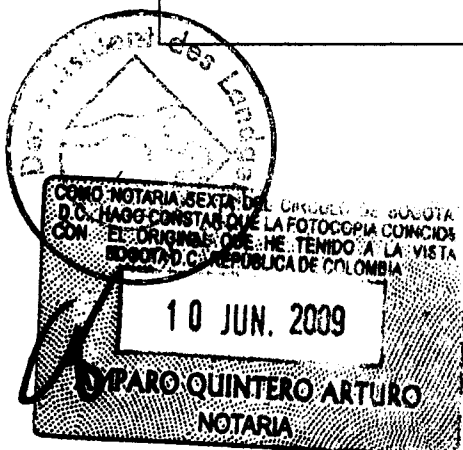
- 1. Land: Bundesrepublik Deutschland
- Diese öffentliche Urkunde
- 2. ist unterschrieben von **Klaus Striewski**
- 3. in seiner Eigenschaft als **Notar**
- 4. Sie ist versehen mit dem Siegel des **Notars Klaus Striewski in Leverkusen**

Bestätigt

- 5. in Köln
- 6. am 16.03.2009
- 7. durch den Vizepräsidenten des Landgerichts Köln
- 8. unter Nr. 1455/09
- 9. Stempel
- 10. Unterschrift

[Signature]
Dr. Dumke

[Handwritten mark]



Kostenberechnung

§§ 141, 154 KostO.

Wert: EUR 3.000,-

Geb. §§ 32, 45 (1)	EUR 10,00
Geb. §§ 58	EUR 10,00
Geb. § 150	EUR 13,00
Umsatzsteuer	33,00
§ 151a, 19 %	EUR 6,27
Zus. EUR	39,27

gez.: Striewski, Notar

TRADUCCION OFICIAL NO. 310/2009

EL TEXTO QUE SIGUE ES TRADUCCIÓN FIEL Y COMPLETA DE UN DOCUMENTO ESCRITO EN INGLES; LLEVA SELLO Y FIRMA DE HELENA URIBE DE LEMOINE, TRADUCTORA E INTERPRETE OFICIAL, SEGÚN RESOLUCION No. 3618 EXPEDIDA POR EL MINISTERIO DE JUSTICIA EL 6 DE SEPT. DE 1972.

TRADUCCION DE LOS SELLOS QUE SE ENCUENTRAN EN EL DOCUMENTO DE REPRESENTACION Y PODER OTORGADO POR BAYER ANIMAL HEALTH GMBH, DOMICILIADA EN 51368 LEVERKUSEN, ALEMANIA, A LOS DOCTORES EMILIO FERRERO, LUZ CLEMENCIA DE PAEZ Y DANIEL PEÑA.

DADO Y FIRMADO EN MI PRESENCIA EN LEVERKUSEN

FIRMADO: DOCTOR J. THOMAIER, SECRETARIO

FIRMADO: DOCTOR F. KÖHLER, SECRETARIO.

No. 367/2009

Certifico que las personas mencionadas a continuación:

- Señor Doctor Jörg Thomaier, dirección comercial 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- Señor Doctor Ferdinand Köhler, dirección comercial 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania

Se presentaron ante mí, ejecutaron el anterior documento y lo firmaron personalmente; por lo tanto los conozco en persona.

Confirmando además que el señor Doctor Jörg Thomaier y el señor Doctor Ferdinand Köhler, son los representantes autorizados de BAYER Animal Health GmbH en Leverkusen y después de inspeccionar electrónicamente el registro comercial de la Corte en Colonia, están registrados en la Sección B 52145 como representantes autorizados.

Leverkusen, 4 de Marzo de 2009

FIRMADO: KLAUS STRIEWSKI, NOTARIO PUBLICO EN LEVERKUSEN

HAY SELLO EN RELIEVE DEL NOTARIO.

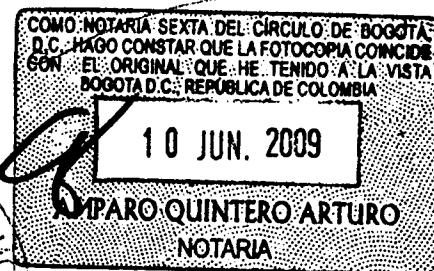
SIGUE LA APOSTILLA NO. 1455/09 DEL 16 DE MARZO DE 2009 POR MEDIO DE LA CUAL SE AUTENTICA LA FIRMA DE KLAUS STRIEWSKI, NOTARIO PUBLICO.

FIRMADO: DR. DUMKE.

LA TRADUCTORA OFICIAL

Helena Uribe de Lemoine

HELENA URIBE DE LEMOINE



La presente traducción oficial No. 0053C/09 fue elaborada por Hernando Torres Barrera, Traductor e Intérprete Oficial, según Resolución 01305 de 1998 del Ministerio de Justicia y del Derecho.

A continuación se traducen una certificación notarial y una apostilla en alemán, que acompañan a un DOCUMENTO DE REPRESENTACIÓN Y PODER.

Protocolo Notarial No. 367/2009

1) Certifico la autenticidad de las firmas, puestas en mi presencia, de:

- el señor Dr. Jörg Thomaier, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- el señor Dr. Ferdinand Köhler, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- a quienes conozco personalmente -.

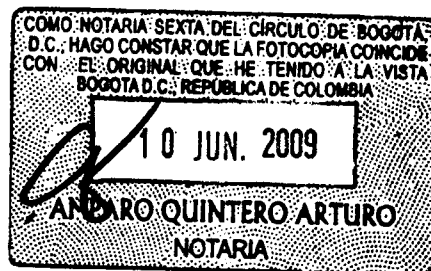
Con base en la inspección realizada por mí en la fecha del Registro Mercantil en el juzgado municipal de Colonia - HRB 52145 -, hago constar que el señor Dr. Jörg Thomaier y el señor Dr. Ferdinand Köhler están autorizados, en su calidad de apoderados generales, a representar individualmente a la Bayer Animal Health GmbH en Leverkusen.

Leverkusen, 4 de marzo de 2009.

HILO Y SELLO EN ALTO RELIEVE: KLAUS STRIEWSKI * NOTARIO EN LEVERKUSEN



Klaus Striewski
(Notario en Leverkusen)




HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

APOSTILLA

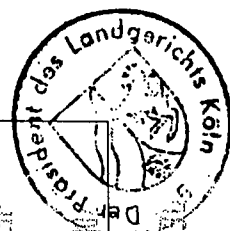
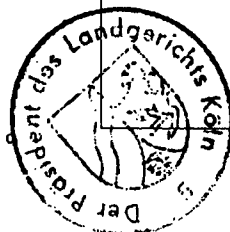
(Convention de la Haye du 5 octobre 1961)

1. País: **República Federal de Alemania**
Este documento público
2. está firmado por **Klaus Striewski**
3. en su calidad de **Notario**
4. lleva el sello del
Notario Klaus Striewski en Leverkusen

Certificado

5. en **Colonia**
6. el 16 de marzo de 2009
7. por **el Vicepresidente del Tribunal Regional de Colonia**
8. bajo el No. 1455/09
9. Sello/timbre
10. Firma


Dr. Dumke



MINISTERIO DE
RELACIONES EXTERIORES
BOGOTÁ D.C.
MAY 22 A H: 27
DEPARTAMENTO DE
NOTARIAS

919776
Hernando Torres

SELLO: EL PRESIDENTE DEL TRIBUNAL REGIONAL DE COLONIA

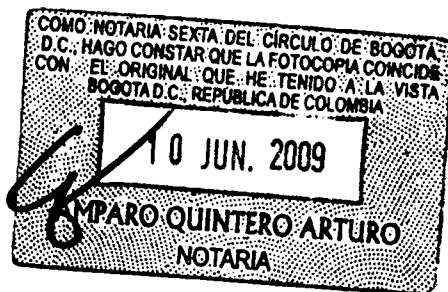
Cálculo de Gastos Notariales

§§ 141, 154 KostO (Reglamento de Gastos Notariales)

Valor: EUR 3.000,--

Tasas §§ 32, 45 (1)	EUROS	10,00
Tasas §§ 58	EUROS	10,00
Tasas § 150	EUROS	13,00
IVA		33,00
§ 151a, 19	%	EUROS 6,27
Total	EUROS	39,27

Firmado: Striewski, Notario



Bogotá, D.C., 20 de mayo de 2009


HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998



CAVELIER

ABOGADOS
EDIFICIO SISKI
CARRETA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

TRASPASO

Yo, (nosotros), abajo firmado (s) BAYER HEALTHCARE AGdomiciliada (s) en 51368 Leverkusen, Alemania

aquí llamado (s) CEDENTE(s), propietario(s) de las invenciones que se tramitan en Colombia bajo los expedientes listados en el Anexo A de este documento, declara(n) por el presente instrumento que cedo(n) en propiedad a

BAYER ANIMAL HEALTH GMBHsociedad organizada y existente bajo las leyes de Alemaniadomiciliada en 51368 Leverkusen, Alemania

(aquí llamada la CESIONARIA) la(s) referida(s) invención(es) así como todos los derechos y privilegios que a ella(s) se refieran, pudiendo por consiguiente de hoy en adelante la CESIONARIA, arriba nombrada, considerarse única dueña, explotarla(s) como cosa propia o disponer de ella(s) como mejor conviene a sus intereses.

Dado y firmado hoy _____

en _____

ASSIGNMENT

I (we), the undersigned BAYER HEALTHCARE AGof 51368 Leverkusen, Alemania

hereinafter ASSIGNOR(S), owner of the inventions prosecuted in Colombia under the files listed in Annex A of this document, does(do) hereby state that it assigns its ownership

to BAYER ANIMAL HEALTH GMBH

a corporation organized and existent under the laws of Germany and domiciled in 51368 Leverkusen, Germany

(hereinafter the ASSIGNEE) in and to the mentioned inventions and all the rights and privileges relating thereto. Accordingly, the aforesaid ASSIGNEE may hold itself to be as from this day on the sole owner and may use it (them) or dispose of it (them) as it may best deem fit for the interests thereof.

Given and signed this _____

in Leverkusen

Cedente

BAYER HEALTHCARE AG
Dr. S. Beyreuther

Cesionario

BAYER ANIMAL HEALTH GMBH
Dr. J. Thomaier

Assignor

Dr. F. Burkert (secretaries)

Assignee

Dr. Kähler (secretaries)

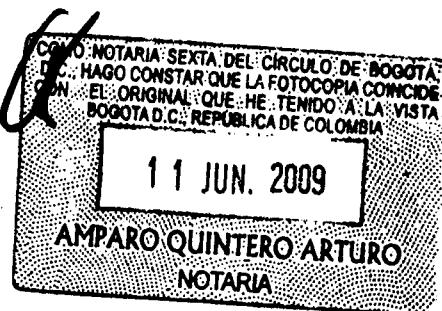
NOTARIA SEXTA DEL CIRCULO DE BOGOTA
D.C. AGO CONSTAR QUE LA FOTOCOPIA COINCIDE
CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA

11 JUN. 2009

AMPARO QUINTERO ARTURO
NOTARIA

ANNEX A

APPLICATION NO.	TITLE	
06.041.546 ✓	PHARMACEUTICAL FORMULATIONS CONTAINING FLAVOURING SUBSTANCES WITH IMPROVED PHARMACEUTICAL PROPERTIES	✓
06.098.062 ✓	NOVEL CRYSTALLINE FORM OF 8-CYANO-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-UINOLINE CARBOXILIC AC ID	✓
06.057.503 ✓	ENDOPARASITICIDAL AGENTS FOR TOPICAL APPLICATION	✓
06.093.626 ✓	PARASITICIDAL AGENTS	✓
06.128.575 ✓	ACTIVE SUBSTANCE-CONTAINING SOLID SHAPED BODIES FOR EXTERNAL USE AGAINST PARASITES IN ANIMALS	✓
07.058.589 ✓	MEDICAMENT FOR HYGIENIC APPLICATION INSIDE THE EAR	✓
07.047.769 ✓	PREVENTION OF VERTICAL ENDOPARASITE INFECTIONS	✓
07.024.053 ✓	PHARMACEUTICAL COMPOSITIONS IN THE FORM OF A WATER SOLUBLE SOLID DOSAGE FORM	✓
07.020.788 ✓	PHARMACEUTICAL COMPOSITION IN THE FORM OF A WATER SOLUBLE SOLID DOSAGE FORM	✓
07.024.055 ✓	PHARMACEUTICAL COMPOSITION CONTAINING A WATER SOLUBLE CARRIER	✓
07.093.657 ✓	ENDOPARASITICIDE	✓
07.058.595 ✓	MEDICAMENT FOR HYGIENIC APPLICATION INSIDE THE EAR	✓
04.128.947 ✓	PHARMACEUTICAL PREPARATIONS FOR ORAL ADMINISTRATION, CONTAINING ION-EXCH ANGE RESINS LOADED WITH ACTIVE INGREDIENTES AND INTRINSICALLY VISCOUS GELLING AGENTS AS THICKENING AGENTS	✓
05.081.495 ✓	REPELLENT	95.0
05.113.512 ✓	AGENTS FOR CONTROLLING PARASITES ON ANIMALS	✓
05.129.984 ✓	TABLETS CONTAINING ENROFLOXACIN AND FLAVOURING AGENTS AND/OR FLAVOURS	✓
03.098.927 ✓	DERMALLY APPLICABLE LIQUID FORMULATIONS FOR CONTROLLING PARASITIC INSECTS ON ANIMALS	✓



URNr. 365/2009

1a) I certify that the individuals, named

- Mr. Dr. Stefan Beyreuther, business address : 51368 Leverkusen, Chempark, Germany,
- Mr. Dr. Frank Burkert, business address : 51368 Leverkusen, Chempark, Germany,

appeared before me and executed the foregoing document and signed personally

- personally known to me -.

I further confirm that Mr. Dr. Stefan Beyreuther and Mr. Dr. Frank Burkert are authorised representatives of Bayer Schering Pharma Aktiengesellschaft in Berlin and having today electronically inspected the commercial register of the local court in Charlottenburg, Berlin, are recorded in Section B 283 B as authorised representatives.

b) Ich beglaubige die vor mir vollzogenen Unterschriften von :

- Herrn Dr. Stefan Beyreuther, geschäftsansässig in 51368 Leverkusen, Chempark, Deutschland,
- Herrn Dr. Frank Burkert, geschäftsansässig in 51368 Leverkusen, Chempark, Deutschland,
- von Person bekannt -.

Ich bescheinige aufgrund Einsicht vom heutigen Tage in das Handelsregister des Amtsgerichts Charlottenburg, Berlin - HRB 283 B -, dass Herr Dr. Stefan Beyreuther und Herr Dr. Frank Burkert berechtigt sind, die Bayer Schering Pharma Aktiengesellschaft in Berlin als Prokuristen einzeln zu vertreten.

2a) I certify that the individuals, named

- Mr. Dr. Jörg Thomaier, business address: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Germany,
- Mr. Dr. Ferdinand Köhler, business address: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Germany,

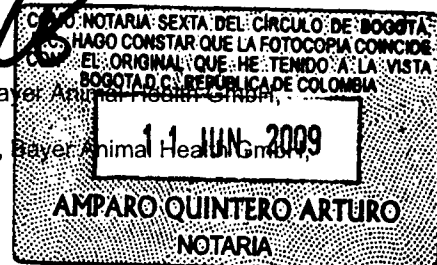
appeared before me and executed the foregoing document and signed personally

- personally known to me -.

I further confirm that Mr. Dr. Jörg Thomaier and Mr. Dr. Ferdinand Köhler are authorised representatives of Bayer Animal Health GmbH in Leverkusen and having today inspected the commercial register of the local court in Köln, are recorded in Section B 52145 as authorised representatives.

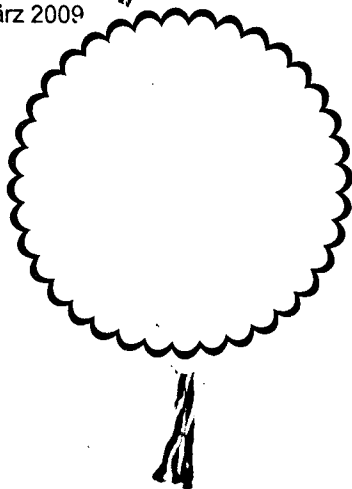
b) Ich beglaubige die vor mir vollzogenen Unterschriften von :

- Herrn Dr. Jörg Thomaier, geschäftsansässig: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Deutschland,
- Herrn Dr. Ferdinand Köhler, geschäftsansässig: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Deutschland,
- von Person bekannt -.



Ich bescheinige aufgrund Einsicht vom heutigen Tage in das Handelsregister des Amtsgerichts Köln - HRB 52145 -, dass Herr Dr. Jörg Thomaier und Herr Dr. Ferdinand Köhler berechtigt sind, die Bayer Animal Health GmbH in Leverkusen als Prokuristen einzeln zu vertreten.

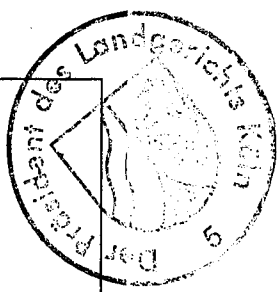
Leverkusen, den 04. März 2009



Klaus Striewski
(Notar in Leverkusen)

RESOLUCION
LEIVA SEI
EL TEXTO O
TRADUCCION

st.v



APOSTILLE

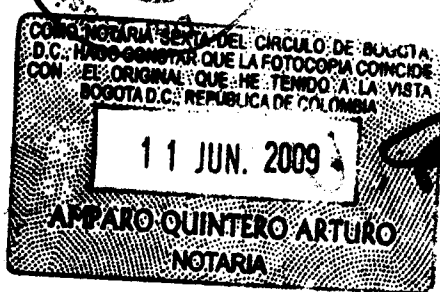
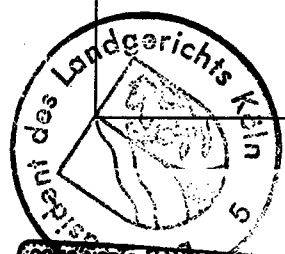
(Convention de La Haye du 5 octobre 1961)

- 1. Land: Bundesrepublik Deutschland
- Diese öffentliche Urkunde
- 2. ist unterschrieben von **Klaus Striewski**
- 3. in seiner Eigenschaft als **Notar**
- 4. Sie ist versehen mit dem Siegel des **Notars Klaus Striewski in Leverkusen**

Bestätigt

- 5. in Köln
- 6. am 16.03.2009
- 7. durch den Vizepräsidenten des Landgerichts Köln
- 8. unter Nr. 1453/09
- 9. Stempel
- 10. Unterschrift

Dr. Dumke



Kostenberechnung

§§ 141, 154 KostO.

Wert:	EUR 3.000,-
Geb. §§ 42, 45 (1)	EUR 10,00
Geb. §§ 58	EUR 10,00
Ges. § 150	EUR 20,00
Umsatzsteuer	46,00
§ 151a, 19 %	EUR 8,24
Zus. EUR	54,24

gez.: Striewski, Notar

57:0

67

TRADUCCION OFICIAL NO. 311/2009

EL TEXTO QUE SIGUE ES TRADUCCIÓN FIEL Y COMPLETA DE UN DOCUMENTO ESCRITO EN INGLES; LLEVA SELLO Y FIRMA DE HELENA URIBE DE LEMOINE, TRADUCTORA E INTERPRETE OFICIAL, SEGÚN RESOLUCION No. 3618 EXPEDIDA POR EL MINISTERIO DE JUSTICIA EL 6 DE SEPT. DE 1972.

TRASPASO

Nosotros, abajo firmantes **BAYER HEALTHCARE AG**, domiciliada en 51368 Leverkusen, Alemania, aquí llamados los **CEDENTES**, propietarios de las invenciones que se tramitan en Colombia bajo los expedientes listados en el Anexo A de este documento, declaramos por el presente instrumento que cedemos en propiedad a **BAYER ANIMAL HEALTH GMBH**, domiciliada en 51368 Leverkusen, Alemania, aquí llamada el **CESIONARIO**, las referidas invenciones así como todos los derechos y privilegios que a ellas se refieran, pudiendo por consiguiente de hoy en adelante el Cesionario arriba nombrado, considerarse único dueño, explotarlas como cosa propia o disponer de ellas como mejor conviene a sus intereses.

Dado y firmado en Leverkusen

EL CEDENTE:

BAYER HEALTHCARE AG

DOCTOR S.BEYREUTHER

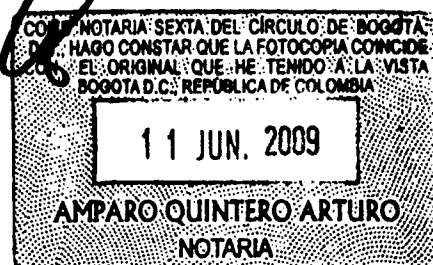
DOCTOR F. BURKERT, (SECRETARIOS)

EL CESIONARIO:

BAYER ANIMAL HEALTH GMBH

DOCTOR J. THOMAIER

DOCTOR F. KÖHLER, (SECRETARIOS)



TRADUCCION OFICIAL NO. 311/2009

ANEXO A

SOLICITUD NO.	TITULO
06.041.546	FORMULAS FARMACEUTICAS QUE CONTIENEN SUSTANCIAS SABORIZANTES CON PROPIEDADES FARMACEUTICAS MEJORADAS
06.098.062	NUEVA FORMA CRISTALINA DE ACIDO CARBOXILICO 8-CIANO-1-CICLOPROPIL-7-(IS,6S-2,8-DIAZABICICLO [4.3.0]NONAN-8-YL)-6-FLUORO-1.4-DIHIDRO-4-OXO-3-UIINOLINA
06.057.503	AGENTES ENDOPARASITARIOS PARA APLICACION TOPICA
06.093.626	AGENTSE PARASITARIOS
06.128.575	SUSTANCIA ACTIVA QUE CONTIENE ELEMENTOS DE FORMA SOLIDA PARA USO EXTERNO CONTRA PARASITOS EN ANIMALES
07.058.589	MEDICAMENTO PARA APLICACIÓN HIGIENICA DENTRO DEL OIDO
07.047.769	PREVENCION DE INFECCIONES ENDOPARASITARIAS VERTICALES
07.024.053	COMPUESTOS FARMACEUTICOS CUYA FORMA DE DOSIFICACION ES UN SOLIDO SOLUBLE EN AGUA
07.020.788	COMPUESTOS FARMACEUTICOS CUYA FORMA DE DOSIFICACION ES UN SOLIDO SOLUBLE EN AGUA
07.024.055	COMPUESTO FARMACEUTICO QUE CONTIENE UN VEHICULO SOLUBLE EN AGUA
07.093.657	ENDOPARASITICIDA
07.058.595	MEDICAMENTO PARA APLICACIÓN HIGIENICA DENTRO DEL OIDO
04.128.947	PREPARACIONES FARMACEUTICAS PARA ADMINISTRACION ORAL QUE CONTIENEN RESINAS CON INTERCAMBIO DE IONES CARGADAS CON INGREDIENTES ACTIVOS Y AGENTES GELIFICANTES INTRISICAMENTE VISCOSOS COMO AGENTES ENGROSADORES
05.081.495	REPELENTE
05.113.512	AGENTES PARA EL CONTROL DE PARASITOS
05.129.984	TABLETAS QUE CONTIENEN ENROFLOXACINA Y AGENTES SABORIZANTES Y/O SABORES
03.098.927	FORMULAS LIQUIDAS APLICABLES DÉRMICAMENTE PARA CONTROLAR INSECTOS PARASITARIOS EN ANIMALES

NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ
 DEBO CONSTAR QUE LA FOTOCOPIA COINCIDE
 EL ORIGINAL QUE HE TENIDO A LA VISTA
 BOGOTÁ, REPÚBLICA DE COLOMBIA
 11 JUN. 2009
 AMPARO QUINTERO ARTURO
 NOTARIA

[Handwritten signature]



TRADUCCION OFICIAL NO. 311/2009

No. 365/2009

1a). Por medio del presente certifico que las personas mencionadas a continuación

- Señor Doctor Stefan Beyreuther, dirección commercial: 51368 Leverkusen, Chempark, Alemania
- Señor Doctor Frank Burkert, dirección commercial: 51368 Leverkusen, Chempark, Alemania

Se presentaron ante mí, ejecutaron el anterior documento y lo firmaron personalmente; por lo tanto los conozco en persona.

Confirmando además que el señor Doctor Stefan Beyreuther y el señor Doctor Frank Burkert son los representantes autorizados de BAYER Schering Pharma Aktiengesellschaft en Berlin y después de inspeccionar electrónicamente el registro comercial de la Corte Local en Charlottenburg, Berlin, pude comprobar que están registrados en la Sección B 283 B como representantes autorizados.

2a) Certifico que las personas mencionadas a continuación :

- Señor Doctor Jörg Thomaier, dirección comercial 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- Señor Doctor Ferdinand Köhler, dirección comercial 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania

Se presentaron ante mí, ejecutaron el anterior documento y lo firmaron personalmente; por lo tanto los conozco en persona.

Confirmando además que el señor Doctor Jörg Thomaier y el señor Doctor Ferdinand Köhler, son los representantes autorizados de BAYER Animal Health GmbH en Leverkusen y después de inspeccionar electrónicamente el registro comercial de la Corte Local en Colonia, pude comprobar que están registrados en la Sección B 52145 como representantes autorizados.

Leverkusen el 4 de Marzo de 2009

FIRMADO: KLAUS STRIEWSKI (NOTARIO PUBLICO.

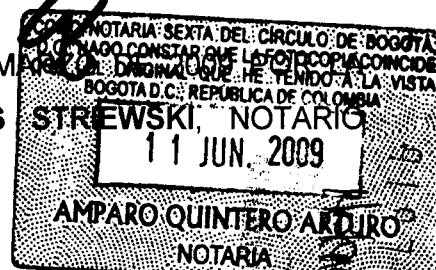
HAY SELLO EN RELIEVE DEL NOTARIO.

SIGUE LA APOSTILLA NO. 1453/09 DEL 16 DE MARZO DE 2009
CUAL SE AUTENTICA LA FIRMA DE KLAUS STRIEWSKI, NOTARIO PUBLICO. FIRMADO DR. DUMKE

LA TRADUCTORA OFICIAL

Helena Uribe de Lemoine

HELENA URIBE DE LEMOINE



La presente traducción oficial No. 0053B/09 fue elaborada por Hernando Torres Barrera, Traductor e Intérprete Oficial, según Resolución 01305 de 1998 del Ministerio de Justicia y del Derecho.

A continuación se traducen una certificación notarial y una apostilla en alemán, que acompañan a un DOCUMENTO DE TRASPASO.

Protocolo Notarial No. 365/2009

1) Certifico la autenticidad de las firmas, puestas en mi presencia, de:

- el señor Dr. Stefan Beyreuther, con domicilio profesional en 51368 Leverkusen, Chempark, Alemania,
- el señor Dr. Frank Burkert, con domicilio profesional en 51368 Leverkusen, Chempark, Alemania

- a quienes conozco personalmente -.

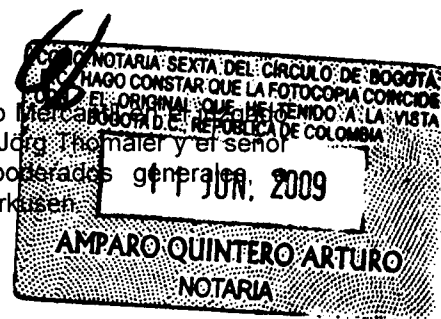
Con base en la inspección realizada por mí en la fecha del Registro Mercantil en el juzgado municipal de Charlottenburg, Berlín, - HRB 283 B -, hago constar que el señor Dr. Stefan Beyreuther y el señor Dr. Frank Burkert están autorizados, en su calidad de apoderados generales, a representar individualmente a la Schering Pharma Aktiengesellschaft en Berlín.

2) Certifico la autenticidad de las firmas, puestas en mi presencia, de:

- el señor Dr. Jörg Thomaier, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- el señor Dr. Ferdinand Köhler, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania

- a quienes conozco personalmente -.

Con base en la inspección realizada por mí en la fecha del Registro Mercantil en el juzgado municipal de Colonia - HRB 52145 -, hago constar que el señor Dr. Jörg Thomaier y el señor Dr. Ferdinand Köhler están autorizados, en su calidad de apoderados generales, a representar individualmente a la Bayer Animal Health GmbH en Leverkusen.

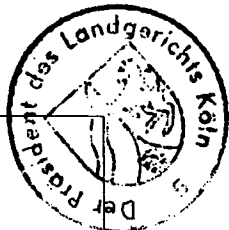


Leverkusen, 4 de marzo de 2009.

HILO Y SELLO EN ALTO RELIEVE: KLAUS STRIEWSKI * NOTARIO EN LEVERKUSEN


 Klaus Striewski
 (Notario en Leverkusen)


 HERNANDO TORRES BARRERA
 TRADUCTOR E INTERPRETE OFICIAL
 RES. No. 1305 MINJUSTICIA 1998



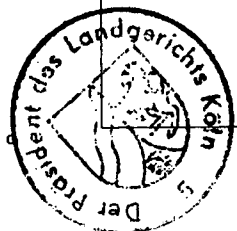
APOSTILLA
(Convention de la Haye du 5 octobre 1961)

1. País: **República Federal de Alemania**
Este documento público
2. está firmado por **Klaus Striewski**
3. en su calidad de **Notario**
4. lleva el sello del
Notario Klaus Striewski en Leverkusen

Certificado

5. en **Colonia**
6. el 16 de marzo de 2009
7. por el **Vicepresidente del Tribunal Regional de Colonia**
8. bajo el No. 1453/09
9. Sello/timbre
10. Firma

Dr. Dumke



MINISTERIO DE
JUSTICIA
BOGOTÁ D.C.
20 MAY 22 A 11:28
CELESTINO GARCIA
BOGOTÁ D.C.
919777
Hernando Torres

SELLO: EL PRESIDENTE DEL TRIBUNAL REGIONAL DE COLO

Cálculo de Gastos Notariales

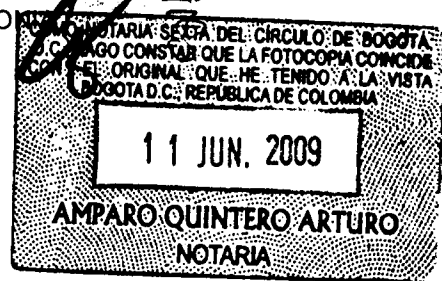
§§ 141, 154 KostO (Reglamento de Gastos Notariales)

Valor: EUR 3.000,--

Tasas §§ 32, 45 (1)	EUROS	10,00
Tasas §§ 58	EUROS	10,00
Tasas § 150	EUROS	26,00
IVA		46,00
§ 151a, 19	%	EUROS 8,74
Total	EUROS	54,74

Firmado: Striewski, Notario

Bogotá, D.C., 20 de mayo de 2009



HERNANDO TORRES BARRERA
TRADUCTOR E INTERPRETE OFICIAL
RES. No. 1305 MINJUSTICIA 1998

72

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MTT : 0011 8004-2

RECIBO OFICIAL DE CAJA : 09 - 44,626
FECHA : JUN.0 16 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-058595- -00004-0000

Fecha: 2009-06-18 17:03:42 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 17

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	VAL. PAGO	FECHA PAGO	VAL. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062154287	111001505	16.06.2009	11,100,000.00

***** CONCEPTO *****

CANT. DEBITO	CONCEPTO	VAL. DEBITO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEYAS COMERCIALES	11,100.00
	TOTAL	11,100.00

SUM: CIENTO ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EFEDIENTE NO. _____

0010: 16874-843-03-4

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-58595

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **595** DE

FECHA **29 DE AGOSTO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **26 DE NOVIEMBRE DE 2008**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



US005972920A

D₁

(7A)

United States Patent [19]

Seidel

[11] **Patent Number:** **5,972,920**[45] **Date of Patent:** ***Oct. 26, 1999**

[54] **FORMULATION CONTAINING A CARRIER, ACTIVE INGREDIENT, AND SURFACTANT FOR TREATING SKIN DISORDERS**

4,424,234 1/1984 Alderson et al. 424,317
4,686,211 8/1987 Hara et al. 514 148

[75] **Inventor:** William E. Seidel, Scarborough, Me.

FOREIGN PATENT DOCUMENTS

[73] **Assignee:** Dermalogix Partners, Inc., Scarborough, Me.

581587 2/1994 European Pat. Off. .
2279567 1/1995 United Kingdom .

[*] **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Primary Examiner—William R. A. Jarvis

Attorney, Agent, or Firm—Pierce Atwood; Chris A. Caseiro

[57] **ABSTRACT**

[21] **Appl. No.:** 09/022,995

[22] **Filed:** Feb. 12, 1998

[51] **Int. Cl.^o** A61K 31/56; A61K 31/60;
A61K 31/555; A61K 33/04

[52] **U.S. Cl.** 514/171; 514/159; 514/178;
514/180; 514/181; 514/188; 514/762; 424/702;
424/705

[58] **Field of Search** 514/171, 178,
514/180, 181, 188, 159, 762; 424/702,
705

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,730,182 5/1973 Boghosian .

One or more formulations for treating psoriasis and other skin disorders characterized by redness, itching, flaking, scaling, and plaque-type growth. The formulation includes a carrier component, one or more active ingredient components, and a surfactant component. The carrier preferably includes an alcohol in substantially equal volume with isopropyl myristate. The active ingredient component preferably includes a superpotent or high-potency corticosteroid such as clobetasol propionate, an anti-flaking ingredient such as zinc pyrithione, or a combination of the two. It may also include an anti-fungal compound. The surfactant component preferably includes an alkyl sulfate such as sodium lauryl sulfate. The formulations made by applied topically either in spray form or as a direct-contact liquid.

20 Claims, No Drawings

sodium lauryl sulfate that may be as much as about 2% of the total formulation weight, and preferably it is about 0.1% of the total weight. The active component may also include, in addition to, or instead of, the primary active component, a secondary active component that is preferably an anti-fungal agent, undecylenic acid, that may be as much as about 10% of the total formulation weight, and is preferably about 0.3% of the total if used.

The active ingredient component is preferably a primary active component that is up to about 0.10% by weight of the total formulation weight of either a superpotent or a high-potency topical corticosteroid, and is preferably about 0.05% of the total formulation weight. A superpotent topical corticosteroid such as clobetasol propionate, augmented betamethasone dipropionate, or diflorasone diacetate, may be used. Alternatively, a high-potency topical corticosteroid such as betamethasone valerate, betamethasone dipropionate, diflucortolone valerate, fluticasone valerate, hydrocortisone 17-butyrate, mometasone furoate, halobetasol propionate, desoximetasone, or flucinonide may be used. The active ingredient component may also include, in addition to, or instead of, the corticosteroid, zinc pyrithione, coal tar, salicylic acid, selenium sulfide, or sulfur that may be as much as about 2% by weight of the total formulation weight, and is preferably about 0.25% by weight if used. The active component may also include, in addition to, or instead of, the primary active component, a secondary active component that is preferably a mild anti-fungal agent, undecylenic acid, that may be as much as about 10% of the total formulation weight, and is preferably about 0.3% of the total if used.

Finally, the carrier component makes up the balance of the total formulation weight and preferably includes any denatured alcohol, such as a denatured ethyl alcohol, or isopropyl alcohol, or other low-molecular weight compound, such as those with C₂-C₈ bases in combination with a fatty-acid ester or an alcohol ester selected from the group including isopropyl myristate, isopropyl palmitate, octyl palmitate, octyl isononanoate, and isocetyl stearate. The ratio of the fatty-acid ester or alcohol ester to the alcohol may range from as high as 95/5 to as low as about 50/50 by volume. Initially, the isopropyl alcohol, a commonly-available home-care product was used and found to be suitable. Subsequently, denatured ethyl alcohol was learned to be as effective and was less harsh to the skin and emitted less odor than the formulation with the isopropyl alcohol.

Formulations created with the noted components may be applied in either spray or liquid form to skin evidencing the effects of psoriasis, eczema, lichenplanus, and seborrheic dermatitis, and other disorders related thereto. When used over a period of 14 days, it has been determined that the preferred formulations reversed the skin conditions noted in substantially all users. More generally, a number of compound formulations were prepared and evaluated for applicability and effectiveness. Initially, the formulations were evaluated to determine whether there was suitable compound miscibility, dispersion and solubility. This evaluation was based on mixing the ingredients together, examining for solids suspension over a period of 24 hours and ensuring that the viscosity of the mix was low enough for it to be sprayed by finger pump without the use of a propellant. That determination was made by evaluating the ability to create a mist pattern upon spraying, which mist pattern was preferably similar to that of water. It was immediately determined that the fatty-acid esters and alcohol esters of the carrier component would not permit the creation of such a mist pattern; however, when combined with noted alcohols,

such a pattern was achieved. Application of the present invention substantially ensures a uniform dispersion of the active component or components with minimal loss of compound.

Once the first of the evaluated formulations exhibited stable solubility and "sprayability" over a period of time leading to an indication of a product shelf life of at least one year with acceptable sprayability, it was applied to the afflicted areas of the skin of 13 test patients. The patients were examined by a physician for reductions in redness, itching, flaking, scaling, and plaque-type growth of the skin. A positive result was signified by a reduction in the particular affliction. That first formulation included as the active ingredient the zinc pyrithione without the corticosteroid. Seven of the 13 patients exhibited positive results. A second version of the formulation of the present invention included the corticosteroid and 11 of the 13 patients exhibited positive results. Variations on the formulations found to be most effective are presented in Tables 1 to 6.

TABLE 1

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	99.65
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	0.0
Clobetasol Propionate	0.05
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1
Undecylenic Acid	0.3
Results: Sprayable; strong, undesirable odor of alcohol; harsh to skin; positive results in approximately 30% of patients tested.	

TABLE 2

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	0.0
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	99.65
Clobetasol Propionate	0.0
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1
Undecylenic Acid	0.3
Results: Sprayable; reduction in the number of complaints of skin irritation; positive results in approximately 35% of patients tested.	

TABLE 3

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	0.0
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	99.6
Clobetasol Propionate	0.05
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1
Undecylenic Acid	0.3
Results: Sprayable; no lingering odor; no complaints of harshness; positive results in approximately 80% of patients tested.	

TABLE 4

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	99.6
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	0.0
Clobetasol Propionate	0.05
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1

TABLE 4-continued

Compound	Weight Percent
Undecylenic Acid	0.0
Results: Sprayable; complaints of lingering alcohol odor and harshness to the skin; positive results in approximately 75% of patients tested.	

TABLE 5

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	99.3
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	0.0
Clobetasol Propionate	0.05
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1
Undecylenic Acid	0.3
Results: Sprayable; complaints of lingering alcohol odor and harshness to the skin; positive results in approximately 80% of patients tested.	

TABLE 6

Compound	Weight Percent
Isopropyl Myristate/Isopropyl Alcohol (50/50 by vol.)	0.0
Isopropyl Myristate/Ethyl Alcohol (50/50 by vol.)	99.3
Clobetasol Propionate	0.05
Zinc Pyrithione	0.25
Sodium Lauryl Sulfate	0.1
Undecylenic Acid	0.3
Results: Sprayable; no complaints associated with odor or harshness; positive results in more than 90% of patients tested.	

It is to be understood that the present invention has been described with specific reference to preferred formulations. It is intended that those formulations, their variants and equivalents are covered hereby with reference to the following appended claims.

I claim:

1. A formulation for treating skin disorders consisting essentially of:

- a. about 0.01% to about 2% by weight of an active ingredient compound selected from the group consisting of clobetasol propionate, augmented betamethasone dipropionate, diflorasone diacetate, betamethasone valerate, betamethasone dipropionate, difluocortolone valerate, fluticasone valerate, hydrocortisone 17-butyrate, mometasone furoate, halobetasol propionate, desoximetasone, flucinonide, zinc pyrithione, coal tar, salicylic acid, selenium sulfide, and sulfur;
- b. 0.1% to about 2% by weight of an anionic surfactant compound selected from the group consisting of soap, alkyl aryl sulphonate, alkyl ether sulfate, alkyl sulfate, and alcohol sulfate;
- c. 0.3% to about 10% by weight of undecylenic acid; and
- d. a carrier compound to make up the balance of weight of said formulation, said carrier compound formed of a combination of two components in a volume ratio of about 50/50, wherein a first carrier component of said combination of two components is selected from the group consisting essentially of ethyl alcohol and isopropyl alcohol and a second carrier component of said combination of two components is selected from the group consisting essentially of isopropyl myristate, isopropyl palmitate, octyl palmitate, octyl isononanoate, and isocetyl stearate.

2. The formulation as claimed in claim 1 wherein said first carrier component is ethyl alcohol and said second carrier component is isopropyl myristate.

3. The formulation as claimed in claim 1 wherein said first carrier component is isopropyl alcohol and said second carrier component is isopropyl myristate.

4. The formulation as claimed in claim 1 wherein said active ingredient compound is about 0.05% by weight of clobetasol propionate and about 0.25% by weight of zinc pyrithione.

5. The formulation as claimed in claim 4 wherein said anionic surfactant compound is about 0.1% by weight of sodium lauryl sulfate, the formulation including about 0.3% by weight of undecylenic acid.

6. The formulation as claimed in claim 1 wherein said anionic surfactant compound is about 0.1% by weight of sodium lauryl sulfate, the formulation including about 0.3% by weight of undecylenic acid.

7. The formulation as claimed in claim 6 wherein said active ingredient compound is about 0.05% by weight of clobetasol propionate and about 0.25% by weight of zinc pyrithione.

8. A formulation for treating skin disorders consisting essentially of:

- a. about 0.01% to about 0.10% by weight of clobetasol propionate;
- b. 0.1% to about 2% by weight of an anionic surfactant compound selected from the group consisting of soap, alkyl aryl sulphonate, alkyl ether sulfate, alkyl sulfate, and alcohol sulfate;
- c. 0.3% to about 10% by weight of undecylenic acid; and
- d. a carrier compound to make up the balance of weight of said formulation, said carrier compound formed of a combination of two components in a volume ratio of about 50/50, wherein a first carrier component of said combination of two components is selected from the group consisting essentially of ethyl alcohol and isopropyl alcohol and a second carrier component of said combination of two components is isopropyl myristate.

9. The formulation as claimed in claim 8 consisting of about 0.05% by weight of clobetasol propionate.

10. The formulation as claimed in claim 8 wherein said anionic surfactant compound is about 0.1% by weight of sodium lauryl sulfate.

11. The formulation as claimed in claim 10 including about 0.3% by weight of undecylenic acid.

12. The formulation as claimed in claim 8 wherein said first carrier component is ethyl alcohol.

13. The formulation as claimed in claim 8 wherein said first carrier component is isopropyl alcohol.

14. A formulation for treating skin disorders consisting essentially of:

- a. about 0.01% to about 2% by weight of zinc pyrithione;
- b. 0.1% to about 12% by weight of an anionic surfactant compound selected from the group consisting of soap, alkyl aryl sulphonate, alkyl ether sulfate, alkyl sulfate, and alcohol sulfate;
- c. 0.3% to about 10% by weight of undecylenic acid; and
- d. a carrier compound to make up the balance of weight of said formulation, said carrier compound formed of a combination of two components in a volume ratio of about 50/50, wherein a first carrier component of said combination of two components is selected from the group consisting essentially of ethyl alcohol and iso-

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㉕ Applicant: **EFAMOL LIMITED, Efamol House Woodbridge Meadows, Guildford Surrey GU1 1BA (GB)**

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㉙ Inventor: **Horrobin, David Frederick, Efamol Limited Efamol House Woodbridge Meadows, Guildford Surrey GU1 1BA (GB)**

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㉜ Representative: **Caro, William Egerton et al, J. MILLER & CO. Lincoln House 296-302 High Holborn, London WC1V 7JH (GB)**

㉞ **Treatment of skin disorders.**

㉟ A topical composition for skin treatment contains an anti-inflammatory glucocorticoid in combination with an essential fatty acid (EFA) of the n-6 or n-3 series or equivalent polyunsaturated fatty acid, as such or in the form of a physiologically acceptable derivative convertible in the body thereto.

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THE INVENTION

In the light of the above it will be seen that at its broadest the invention is to use anti-inflammatory glucocorticoids in combination, for their effect on the skin, with one or more EFAs of the n-6 or n-3 series (preferably other than arachidonic acid because of its potential action in increasing 2-series PG synthesis) or equivalent polyunsaturated fatty acids, in their effects on the skin, of which columbinic acid is an example. Preferably, for the specific effect on PG balance, the acids are the earlier n-6 EFAs linoleic acid, GLA and DGLA of which for the reasons explained GLA and DGLA are preferred and GLA is best.

Anti-inflammatory glucocorticoids are a well recognised class of natural or synthetic steroids having biological effects similar to naturally occurring hydrocortisone (cortisol) and are fully described in, for example, Martindale's Extra Pharmacopeia, 27th Edition, 1977, pages 389-440 or in Goodman and Gilman, Pharmacological Basis of Therapeutics, 6th Edition, pp 1470-1492, 1980, to which reference may be made. Examples include hydrocortisone itself, cortisone, betamethasone, dexamethasone, fluprednisolone, methylprednisolone, paramethasone, prednisone, prednisolone, triamcinolone, beclomethasone, clobetasol, cloprednol, cortivazol, deoxycortone, desonide, desoxymethasone, diflucortolone, flucilorolone, fludrocortisone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortolone, fluoromethalone, fluperolone, fluprednidene, flurandrenolone, formocortal, halcinonide, hydrocortamate, medrysone, methylprednisone, paramethasone, prednisolamate and prednylidene. Concentration ranges are suitably, by weight, 0.01 to 30% fatty acid, 0.01 to 10% steroid in a topical application base.

The invention also extends to use of such compositions in, and the preparation of such compositions for, treating inflammatory skin

CLAIMS

1. A topical composition for skin treatment containing an anti-inflammatory glucocorticoid in combination with an essential fatty acid (EFA) of the n-6 or n-3 series or equivalent polyunsaturated fatty acid, as such or in the form of a physiologically acceptable derivative convertible in the body thereto.
2. A composition according to claim 1, wherein the fatty acids are selected from GLA, DGLA, the 22:4 and 22:5 n-6 EFAs, the 18:4, 20:4, 20:5, 22:5 and 22:6 n-3 EFAs and columbinic acid.
3. A composition according to claim 1 or 2 wherein the glucocorticoid is hydrocortisone, cortisone, betamethasone, dexamethasone, fluprednisolone, methylprednisolone, paramethasone, prednisone, prednisolone, triamcinolone, beclomethasone, clobetasol, clocprednol, cortivazol, deoxycortone, desonide, desoxymethasone, difluocortolone, flucolorolone, fludrocortisone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortolone, fluoromethalone, fluperolone, fluprednidene, flurandrenolone, formocortal, halcinonide, hydrocortamate, medrysone, methylprednisone, paramethasone, prednisolamate and prednylidene.
4. A composition according to any preceding claim containing by weight, 0.01 to 30% fatty acid, 0.01 to 10% glucocorticoid in a topical application base.
5. A pack comprising a glucocorticoid and an EFA as set out

- [54] POWDERY PHARMACEUTICAL COMPOSITION SUITABLE FOR APPLICATION TO MUCOSA OF ORAL OR NASAL CAVITY

- [75] Inventors: Yoshiki Suzuki; Hiroshi Ikura, both of Hino, Japan

- [73] Assignee: Teijin Limited, Osaka, Japan

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- [22] Filed: Feb. 4, 1988

Related U.S. Application Data

- [63] Continuation of Ser. No. 692,091, Jan. 25, 1985, abandoned.

- [51] Int. Cl.⁴ A61K 31/715; A61K 31/56

- [52] U.S. Cl. 514/53; 514/180

- [58] Field of Search 514/180, 53

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Primary Examiner—Leonard Schenkman

Assistant Examiner—Joseph A. Lipovsky

Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak, and Seas

[57] ABSTRACT

A powdery pharmaceutical composition for application to the mucosa of the oral or nasal cavity including: (a) a base selected from the group consisting of lower alkyl ethers of cellulose; (b) a pharmaceutically effective amount of a drug selected from the group consisting of steroid or glycyrrhizic acid type anti-inflammatory agents; and (c) a stabilizer for the drug composed of at least one low irritant solid organic acid selected from the group consisting of saturated higher aliphatic monocarboxylic acids having 12 or more carbon atoms, aliphatic polycarboxylic acid, hydroxy aliphatic polycarboxylic acids, aromatic carboxylic acids, unsaturated lower aliphatic monocarboxylic acids having six or less carbon atoms, and cellulose derivatives having carboxyl group.

This powdery pharmaceutical composition has extremely excellent stability in the steroid or glycyrrhizic acid type anti-inflammatory agent contained therein, low irritation of the mucosa of the oral or nasal cavity, and sustained release of the drug over an extended period of time.

22 Claims, No Drawings

POWDERY PHARMACEUTICAL COMPOSITION SUITABLE FOR APPLICATION TO MUCOSA OF ORAL OR NASAL CAVITY

This is a continuation of application Ser. No. 06/692,091, filed Jan. 25, 1985 now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a powdery pharmaceutical composition suitable for application to the mucosa of the oral or nasal cavity. More specifically, it relates to a powdery pharmaceutical composition, suitable for application to the mucosa of the oral or nasal cavity, containing (a) lower alkyl ethers of cellulose as a base, (b) a steroid or glycyrrhizic acid type anti-inflammatory agent as a drug component, and (c) a solid low irritant organic acid as a stabilizer for the drug component.

The powdery pharmaceutical composition exhibits extremely excellent stability in the steroid or glycyrrhizic acid type anti-inflammatory agent contained therein, low irritation of the mucosa of the oral or nasal cavity, and sustained release of the drug over an extended period of time. Accordingly, the powdery pharmaceutical composition according to the present invention can be effectively used for the treatment of oral diseases such as stomatitis, erosion or sores generated by radiotherapy, and licken planus or nasal diseases such as allergic rhinitis and vasomotor rhinitis.

2. Description of the Related Art

Various pharmaceutical preparations, such as buccal tablets, troche tablets, sublingual tablets, and oral ointments, have been heretofore known in the art for application to the oral cavity. Buccal tablets, troche tablets, and sublingual tablets, however, give a foreign feeling to the oral cavity. Therefore, patients often chew on and swallow the tablets. Oral ointments, on the other hand, usually contain mixtures of beeswax or plastibase with gelatin, pectin, or sodium carboxymethyl cellulose. These mixtures are unsatisfactory because the adhesion properties thereof to the oral mucosa are not sufficient and also because they have unpleasant tastes.

On the other hand, various pharmaceutical preparations, such as nasal ointments, jellies, nose drops, and sprays, have been known in the art for application to the nasal cavity. Nasal ointments and jellies, however, are difficult to apply to deep parts of the nasal cavity, such as the concha nasalis superior. With, nose drops and sprays, the active components do not remain in the nasal cavity for an extended period of time.

Various sustained release pharmaceutical preparations for oral or nasal cavity administration are known in the art. With these, the efficacy of the drugs is spread over a long period of time by the gradual or sustained releasing the active drug components from the pharmaceutical preparations. For example, Japanese Unexamined Patent Publication (Kokai) No. 57-118511 discloses powdery sustained release preparations suitable for adhesion to the oral cavity. These preparations use, as a base, hydroxypropyl cellulose and have the advantages of an excellent sustained release of the drugs and possible application over a wide range of the oral cavity. Furthermore, U.S. Pat. No. 4,294,829 discloses powdery sustained release preparations suitable for application to the nasal cavity. These contain lower alkyl

ethers of cellulose and drugs and also have the advantage of excellent sustained release of the drugs.

It is, however, more desirable to improve the stability of drugs in the above-mentioned sustained release preparations for application to the mucosa of the oral or nasal cavity.

SUMMARY OF THE INVENTION

Accordingly, the object of the present invention is to provide a powdery pharmaceutical composition, suitable for application to the mucosa of the oral or nasal cavity, having extremely excellent stability of the carried drug, i.e., a steroid or glycyrrhizic acid type anti-inflammatory agent.

Another object of the present invention is to provide a powdery pharmaceutical composition, suitable for application to the mucosa of the oral or nasal cavity, containing a lower alkyl ether of cellulose as a base, a steroid or glycyrrhizic acid type anti-inflammatory agent as a drug, and a specific solid low irritant organic acid as a stabilizer for the drug.

A further object of the present invention is to provide a powdery pharmaceutical composition having low irritation of the mucosa of the oral or nasal cavity.

A still further object of the present invention is to provide a powdery pharmaceutical composition having excellent sustained release of the drug.

A still further object of the present invention is to provide a powdery pharmaceutical composition having a particle diameter suitable for administration to the oral or nasal cavity.

A still further object of the present invention is to provide a method for preparing a powdery pharmaceutical composition suitable for application to the mucosa of the oral or nasal cavity.

A still further objects of the present invention is to provide a method for stabilizing a powdery pharmaceutical composition containing a steroid or glycyrrhizic acid type anti-inflammatory agent as a drug.

Other objects and advantages of the present invention will be apparent from the following description.

According to the present invention, the above-mentioned objects and advantages can be achieved by a powdery pharmaceutical composition including: (a) a base selected from the group consisting of lower alkyl ethers of cellulose; (b) a pharmaceutically effective amount of a drug selected from the group consisting of steroid or glycyrrhizic acid type anti-inflammatory agents; and (c) a stabilizer for the drug composed of at least one low irritant solid organic acid selected from the group consisting of saturated higher aliphatic monocarboxylic acids having 12 or more carbon atoms, aliphatic polycarboxylic acids, hydroxy aliphatic polycarboxylic acids, aromatic carboxylic acids, unsaturated lower aliphatic monocarboxylic acids having six or less carbon atoms, and cellulose derivatives having carboxyl groups.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to the present invention, the desired powdery pharmaceutical composition, i.e., a composition having extremely excellent stability of the drug, low irritation to the mucosa of the oral or nasal cavity, and excellent sustained release of the drug, can be obtained by using a lower alkyl ether of cellulose as a base, a steroid or glycyrrhizic acid type anti-inflammatory agent as a drug, and a specific solid low irritant organic

acid as a stabilizer for the drug, i.e., by combining the specified base and the specified drug with the specified organic acid.

The lower alkyl ethers of cellulose usable as a base in the present invention are those obtained by at least partially substituting the same or different lower alkyl ether groups for a plurality of hydroxyl groups of cellulose. The lower alkyl groups in the lower alkyl ether groups may be substituted with substituents. An example of such preferable substituents is a hydroxyl group.

Preferable examples of the optionally substituted lower alkyl groups are a methyl group, and hydroxy lower alkyl groups having 2 or 3 carbon atoms.

Examples of the optionally substituted lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, β -hydroxyethyl, and β -hydroxypropyl.

Examples of the optionally substituted lower alkyl ethers of cellulose are methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose. Of these lower alkyl ethers of cellulose, the use of methyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose is preferable due to the facts that these lower alkyl ethers of cellulose have substantially no odor and irritation when applied to the mucosa of the oral or nasal cavity, which is particularly sensitive to odor and irritation, and that the desired sustained release of the drug can be obtained. Of these lower alkyl ethers of cellulose, the use of hydroxypropyl cellulose is especially preferable.

The lower alkyl ethers of cellulose can be used alone or in any mixture thereof.

When the above-mentioned lower alkyl ethers of cellulose are used as a base in the powdery pharmaceutical composition according to the present invention, the pharmaceutical preparations thus obtained can adhere to the mucosa of the oral or nasal cavity and will swell to gradually release the active drug components therefrom over a long period of time. Thus, the affected or diseased parts can be treated by the drugs over a long period of time.

Although there is no limitation in the molecular weight of the lower alkyl ethers of cellulose usable in the present invention, lower alkyl ethers having a viscosity in 2% aqueous solution thereof of 3 to 10,000 cps at 37° C. $\pm 0.2^\circ$ C., more preferably, 1000 to 4000 cps at 37° C. $\pm 0.2^\circ$ C., are preferably used.

In preparing unit dosage forms of powdery pharmaceutical compositions in which lower alkyl ethers of cellulose are contained as a base, the compositions are generally filled in hard capsules. These capsules are set in a specially designed spraying device. The spraying device is provided with needle for spraying the powdery pharmaceutical compositions into the oral or nasal cavity. In this case, when the moisture content of the lower alkyl ethers of cellulose in the capsules is too small, the moisture contained in the membranes of the capsules tends to be absorbed by the lower alkyl ethers of cellulose and, as a result, the capsules become too rigid. Therefore, lower alkyl ethers of cellulose having a moisture content of 3% to 9% by weight, especially 4% to 8% by weight, are preferably used as a base.

The drugs usable in the present powdery pharmaceutical compositions are steroid or glycyrrhizic acid type anti-inflammatory agents. Examples of such steroid type anti-inflammatory agents are beclomethasone dipropionate, betamethasone, betamethasone valerate, triamcinolone, triamcinolone acetonide, dexamethasone, fluocinolone acetonide, fluocinonide, flumetha-

sone, hydrocortisone, prednisolone, and prednisone. Examples of glycyrrhizic acid type anti-inflammatory agents are glycyrrhizic acid, disodium glycyrrhizinate, trisodium glycyrrhizinate, monopotassium glycyrrhizinate, dipotassium glycyrrhizinate and monoammonium glycyrrhizinate. These drugs can be used alone or in any mixture thereof in the present powdery pharmaceutical composition.

According to the present invention, the above-mentioned anti-inflammatory agents contained in the powdery pharmaceutical compositions comprising the above-mentioned lower alkyl ethers of cellulose as a base can be advantageously stabilized by incorporating therein, as a stabilizer, a specified organic acid, i.e., at least one solid low irritant organic acid selected from the group consisting of saturated higher aliphatic monocarboxylic acids having 12 or more carbon atoms, aliphatic polycarboxylic acids, hydroxy aliphatic polycarboxylic acids, aromatic carboxylic acids, unsaturated lower aliphatic monocarboxylic acids having six or less carbon atoms, and cellulose derivatives having carboxyl groups.

The organic acids usable as a stabilizer for the drug in the present invention are those selected from the above-mentioned group of the organic acids which are solid at room temperature, less irritant to the mucosa of the oral or nasal cavity, and substantially odorless or with only a very slight odor. By the term "organic acids" is meant acids comprising organic groups and free carboxylic groups. Use of the organic acids solid at room temperature facilitates the production of the desired powdery pharmaceutical compositions in a uniform particle size. Use of the less irritant organic acids means higher safety when the composition is applied to the mucosa of the oral or nasal cavity.

Examples of the preferable saturated higher aliphatic monocarboxylic acids are saturated higher aliphatic hydrocarbon monocarboxylic acid having 12 to 24 carbon atoms, such as stearic acid, palmitic acid, lauric acid, and myristic acid. Examples of the preferable aliphatic polycarboxylic acids are aliphatic hydrocarbon dicarboxylic acids having 4 to 6 carbon atoms, such as, succinic acid, fumaric acid, and maleic acid. Examples of the preferable hydroxy aliphatic polycarboxylic acid are hydroxy aliphatic hydrocarbon di- or tri-carboxylic acids having 4 to 8 carbon atoms, such as, tartaric acid and citric acid. Examples of the preferably aromatic acids are benzoic acid and its derivatives, such as parahydroxy benzoic acid and salicylic acid. Examples of the preferable unsaturated lower aliphatic monocarboxylic acids are unsaturated lower aliphatic hydrocarbon monocarboxylic acid having 4 to 6 carbon atoms, such as sorbic acid. Examples of the preferable cellulose derivatives having carboxyl groups are carboxymethyl cellulose and carboxymethylethyl cellulose. These organic acids can be used alone or in any mixture thereof.

Of the above-mentioned organic acids, saturated higher aliphatic monocarboxylic acids having 12 or more carbon atoms, aliphatic polycarboxylic acids, hydroxy aliphatic polycarboxylic acids, aromatic carboxylic acids, and cellulose derivatives having carboxyl groups are preferably used. For powdery pharmaceutical compositions for application to the nasal cavity, use of saturated higher aliphatic monocarboxylic acids having 12 or more carbon atoms and cellulose derivatives having carboxyl groups is especially preferably from

the viewpoints of low irritation and substantial odorlessness.

There is no specific limitation in the amount of the above-mentioned organic acids in the present pharmaceutical composition as long as the anti-inflammatory agents are stabilized. The preferable amount of the organic acid in the present pharmaceutical composition is within the range of from 0.05% to 5% by weight, especially from 0.1% to 3% by weight, based upon the total weight of the composition. Although there is also no critical limitation in the particle size of the organic acid, the organic acid preferably has such a particle size that at least about 90% by weight of the powder particles has an effective particle diameter of about 75 μm or less, more preferably about 20 μm to about 75 μm , to obtain a powdery pharmaceutical composition capable of being effectively administered to the mucosa of the oral or nasal cavity.

As mentioned above, the powdery-pharmaceutical compositions according to the present invention contain, as essential constituents, the above-mentioned lower alkyl ethers of cellulose, steroid or glycyrrhizic acid type anti-inflammatory agents, and organic acid stabilizers. Although there is no specific limitation in the particle size of the present pharmaceutical composition, the particle size of the present pharmaceutical composition is preferably such that at least about 90% by weight of the powder particles thereof has an effective particle diameter of about 20 μm to about 250 μm . The present powdery pharmaceutical composition having such a particle size distribution is preferably due to the fact that the amount of the powder particles adhering to the mucosa of the oral or nasal cavity becomes large. That is, when the pharmaceutical composition having the above-mentioned preferable particle size distribution is applied to the oral or nasal cavity, the amount of the pharmaceutical composition reaching, for example, the lung becomes small or the amount of the pharmaceutical composition scattered out of the oral or nasal cavity becomes small. Furthermore, the pharmaceutical composition having the above-mentioned preferable particle size can well adhere to the mucosa of the oral or nasal cavity and can be effectively and gradually released. The powdery pharmaceutical composition according to the present invention more preferably has such a particle size distribution that at least about 90% by weight of the powder particles has an effective particle diameter of about 20 μm to about 150 μm .

The term "effective particle diameter" used herein means that determined by the opening sizes of sieves. For example, a powder having an effective diameter (d) of $37 < d \leq 44$ passes through a sieve having an opening size of 44 microns but does not pass through a sieve having an opening size of 37 microns.

A vibratory sieve is used when the effective particle diameter of a powder is more than 37 microns, and a sonic sieve (Micro Hand Sifter SWM-2, a product of Tsutsui Rikagaku Kikai Co., Ltd.) is used when the effective particle diameter of a powder is not more than 37 microns.

The sieves used has an opening size of 500, 420, 350, 297, 250, 210, 177, 149, 125, 105, 88, 74, 63, 53, 44, 37, 25, and 20 microns, respectively.

The powdery pharmaceutical composition according to the present invention can optionally contain, in addition to the above-mentioned lower alkyl ethers of cellulose, anti-inflammatory agents, and organic acids, any conventional ingredients for improving the physical

properties, visual appearance, or odor of the pharmaceutical preparations. Examples of such ingredients are: lubricants such as talc and waxes; binders such as starch, dextrin, tragacanth gum, gelatin, polyvinylpyrrolidone, and polyvinyl alcohol; diluents such as starch, crystalline cellulose, dextrin, lactose, mannitol, sorbitol, and anhydrous calcium phosphate; odor improvers such as menthol and citrus perfumes; preservatives such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate; and various surfactants.

The powdery pharmaceutical composition according to the present invention can be prepared in any conventional manner. For example, the pharmaceutical composition can be prepared by mechanically mixing the above-mentioned three essential constituents, i.e., the lower alkyl ethers of cellulose, the anti-inflammatory agents, and the solid organic acids and the above-mentioned optional ingredients, if any. The mixing of the composition can be carried out by using any conventional means such as ball mills, and V-type mixers. The desired pharmaceutical composition can also be prepared by mechanically mixing all the above-mentioned constituents of the composition, compressing the resultant mixture under pressure, e.g., 0.2 to 0.4 ton, to and pulverizing the compressed mixture so as to obtain the desired particle size distribution. The mixed or pulverized powder particles can be sieved to obtain the powdery composition having the desired particle size distribution, if necessary.

The desired pharmaceutical composition can further be prepared by impregnating the lower alkyl ethers of cellulose with a solution or dispersion, in an organic solvent (e.g., methanol, ethanol, ethyl cellosolve, and dichloromethane), of the anti-inflammatory agents and the organic acids and, if any, the optional ingredients, followed by drying the impregnated product. The said organic solvent may contain water. The impregnation can be carried out by, for example, spraying the above-mentioned solution or dispersion to the lower alkyl ethers of cellulose in the form of powder particles in a spray apparatus. The particle size distribution of the lower alkyl ethers of cellulose can be controlled to the desired range prior to the impregnation. Alternatively, the powder particles of the impregnated product can be pulverized and/or sieved after the impregnation so as to obtain the desired particle size distribution.

Furthermore, the desired pharmaceutical compositions can be prepared by dissolving or dispersing the lower alkyl ethers of cellulose, the anti-inflammatory agents, the solid organic acid, and any optional ingredients in organic solvents such as methanol, ethanol, ethyl cellosolve, and dichloromethane, water, or the mixture thereof followed by evaporating the organic solvents off. The resultant composition can be pulverized and/or sieved to obtain the desired particle size distribution.

According to the present invention, a powdery preparation in a unit dosage form including the above-mentioned powdery pharmaceutical composition can be obtained. The present pharmaceutical composition can be directly converted to the powdery preparation in the form of a unit dosage. The unit dosage of the powdery preparations according to the present invention is preferably about 10 mg to about 400 mg, especially about 30 mg to about 300 mg, when applied to the oral cavity and about 5 mg to about 200 mg, especially about 10 mg to about 100 mg, when applied to the nasal cavity.

The amount of the steroid or glycyrrhizic acid type anti-inflammatory agent in the powdery preparation in

diameter of 37 to 149 μm was charged into a fluidized bed type granulator. Then, 50 parts of, ethanol mixture containing 0.025 part of beclomethasone dipropionate and 5 parts of hydroxypropyl cellulose having a viscosity of a 2% aqueous solution thereof of 7 cps at 37° C. $\pm 0.2^\circ$ C. dissolved therein and also containing 0.5 part of stearic acid dissolved therein were sprayed from the spraying nozzle of the granulator, followed by drying. Thus, the powder particles impregnated with the solid components in the ethanol mixture was obtained. The powder particles were sieved to obtain those having a particle size of 60 to 400 meshes. The powder particles thus obtained were filled in #2 hard gelatin capsules in an amount of 200 mg each to prepare a powdery preparation in a unit dosage form for the application to the oral cavity.

Example 24

A 80 part amount of hydroxypropyl cellulose having a viscosity of a 2% aqueous solution thereof of 1550 cps at 37° C. $\pm 0.2^\circ$ C. and having a particles size such that 90% or more of the powder particles had a particle diameter of 37 to 149 μm and 1000 parts of an ethanol suspension containing 0.2 part of the dissolved beclomethasone dipropionate and 0.4 part of the suspended stearic acid were casted on the surface of releasing paper. After drying, the casted film was obtained.

The film obtained above was ground and pulverized by a grinding machine and, then, sieved to the powder particles having a particle size of 60 to 400 meshes. The powder particles were filled in #2 hard gelatin capsules in an amount of 200 mg each to prepare a powdery preparation in a unit dosage form for the application to the oral cavity.

We claim:

1. A powdery pharmaceutical composition for application to the mucosa of the oral or nasal cavity comprising:
 - (a) a base selected from the group consisting of lower alkyl ethers of cellulose;
 - (b) a pharmaceutically effective amount of a drug selected from the group consisting of steroidal anti-inflammatory agents or glycyrrhizic acid anti-inflammatory agents; and
 - (c) a stabilizer for the drug in the form of at least one low irritant solid organic acid selected from the group consisting of saturated higher aliphatic monocarboxylic acids having 12 to 24 carbon atoms, aliphatic hydrocarbon dicarboxylic acids having 4 to 6 carbon atoms, hydroxyl aliphatic hydrocarbon di- or tricarboxylic acids having 4 to 8 carbon atoms, benzoic acid and its derivatives, unsaturated lower aliphatic monocarboxylic acids having six or less carbon atoms, and carboxymethyl cellulose and carboxymethylethyl cellulose, said stabilizer being present in an amount of 0.05% to 5% by weight in the composition.
2. A powdery pharmaceutical composition as claimed in claim 1, wherein at least about 90% by weight of the stabilizer particles has an effective particle diameter of about 75 μm or less.
3. A powdery pharmaceutical composition for application to the mucosa of the oral cavity as claimed in claim 1, wherein said stabilizer is at least one member selected from the group consisting of saturated higher aliphatic monocarboxylic acids having 12 to 24 carbon atoms, aliphatic dicarboxylic acids having 4 to 6 carbon atoms, hydroxy aliphatic hydrocarbon di- or tricarbox-

ylic acids having 4 to 8 carbon atoms, benzoic acid and its derivatives, and carboxymethyl cellulose and carboxymethylethyl cellulose.

4. A powdery pharmaceutical composition for application to the mucosa of the nasal cavity as claimed in claim 1, wherein said stabilizer is a saturated higher aliphatic monocarboxylic acid having 12 or more carbon atoms or a cellulose derivative having carboxyl groups.

5. A powdery pharmaceutical composition as claimed in claim 1, wherein said saturated higher aliphatic hydrocarbon monocarboxylic acid is stearic acid, palmitic acid, lauric acid, or myristic acid.

6. A powdery pharmaceutical composition as claimed in claim 1, wherein said aliphatic hydrocarbon dicarboxylic acid is succinic acid, fumaric acid, or maleic acid.

7. A powdery pharmaceutical composition as claimed in claim 1, wherein said hydroxy aliphatic hydrocarbon di- or tricarboxylic acid is tartaric acid or citric acid.

8. A powdery pharmaceutical composition as claimed in claim 1, wherein said benzoic acid and its derivatives is benzoic acid, parahydroxybenzoic acid, or salicylic acid.

9. A powdery pharmaceutical composition as claimed in claim 1, wherein said steroid type anti-inflammatory agent is beclomethasone dipropionate, betamethasone, betamethasone valerate, triamcinolone, triamcinolone acetone, dexamethasone, fluocinolone acetone, fluocinonide, flumethasone, hydrocortisone, prednisolone, or prednisone.

10. A powdery pharmaceutical composition as claimed in claim 1, wherein the moisture content of the lower alkyl ether of cellulose is within the range of from 3% to 9% by weight.

11. A powdery pharmaceutical composition as claimed in claim 1, wherein said lower alkyl ether of cellulose is hydroxypropyl cellulose, methyl cellulose, or hydroxypropyl methyl cellulose.

12. A powdery pharmaceutical composition as claimed in claim 1, wherein at least about 90% by weight of the powder particles of the pharmaceutical composition has an effective particle diameter of about 20 to 250 μm .

13. A powdery pharmaceutical preparation in unit dosage form for application to the mucosa of the oral or nasal cavity comprising the powdery pharmaceutical composition of claim 1.

14. A powdery pharmaceutical preparation as claimed in claim 13, wherein said pharmaceutical composition is filled in a capsule.

15. A powdery pharmaceutical composition as claimed in claim 1, wherein the drug is a glycyrrhizic acid anti-inflammatory agent.

16. A powdery pharmaceutical composition as claimed in claim 15, wherein said glycyrrhizic acid anti-inflammatory agent is glycyrrhizic acid, disodium glycyrrhizinate, trisodium glycyrrhizinate, monopotassium glycyrrhizinate, dipotassium glycyrrhizinate or monoammonium glycyrrhizinate.

17. A powdery pharmaceutical composition as claimed in claim 1, wherein said base is present in an amount of 89.374% to 99.925% by weight in the composition.

18. A method for preparing a powdery pharmaceutical composition for application to the mucosa of the oral or nasal cavity, comprising the step of mechanically mixing: