

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

1

SOLICITUD DE:



Corrección de Error Material



Modificación a una solicitud

2

SOLICITANTE

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

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: 438.019 TP 31.929

4

Número de expediente: 07.058.589

Clase: A61K 009/000

Título del Invento: **MEDICAMENTO PARA ADMINISTRACIÓN HIGIÉNICA EN EL OIDO**

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. 09-44,620

Fecha: 16 de junio de 2009

7

Anexos:



Comprobante de pago de la tasa por concepto de modificación de solicitud en trámite.



Poderes, si fuere el caso



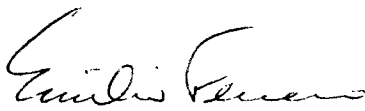
Certificado de existencia y representación legal, cuando el solicitante sea persona jurídica



Documento que acredita el traspaso.

8

NOMBRE: EMILIO FERRERO

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

JGG /ID.152081

CAVELIER

ABOGADOS

EDIFICIO SISKI

CARRERA 4a N° 72-35
BOGOTÁ, R. 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 GMBH

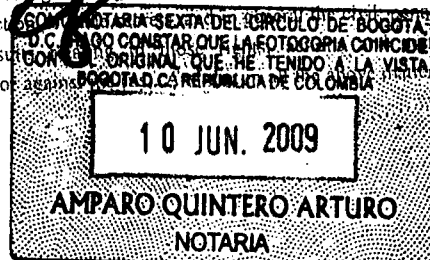
domiciliado (s) en/of 51368 Leverkusen, Germany

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, granting of licenses, the action for writ mandamus, the protection of industrial secrets, and in general the civil, and administrative suits instituted by me (us) or against



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

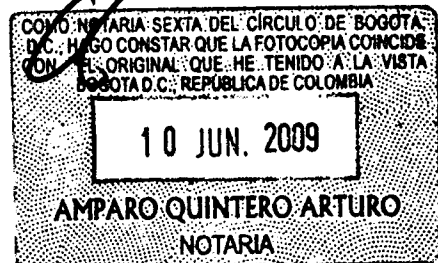
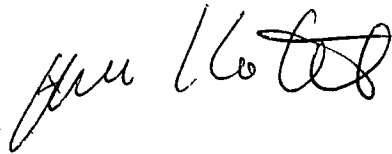
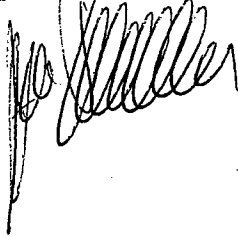
they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

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.

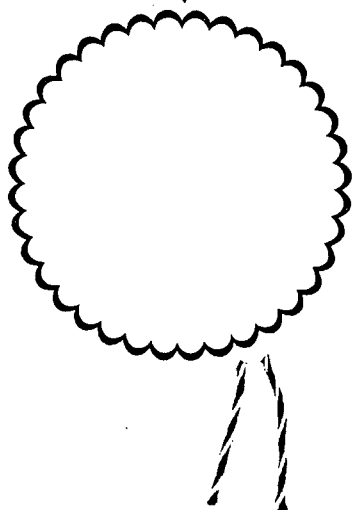
2. Ich beglaubige die vor mir vollzogenen Unterschriften von :

- 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,

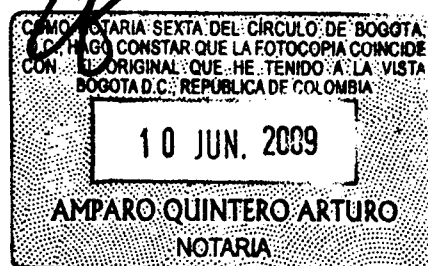
- von Person bekannt -.

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
(Notarin Leverkusen)



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

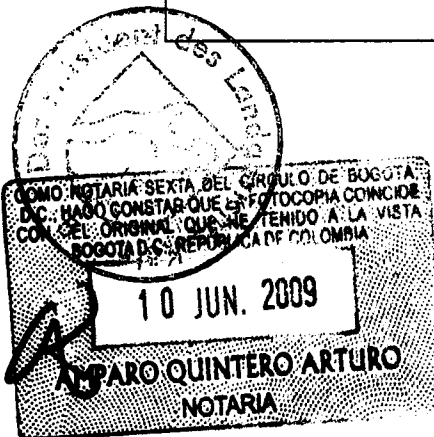
7. durch den Vizepräsidenten des Landgerichts Köln

8. unter Nr. 1455/09

9. Stempel

10. Unterschrift


Dr. Dumke



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.

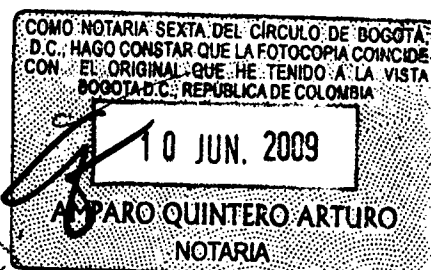
SIGUE LA APOSTILLA NO. 1455/09 DEL 16 DE MARZO DE 2009 POR MEDIO DE LA CUAL SE AUTENTICA LA FIRMA DE **KLAUS STRIEWSKI**, NOTARIO PUBLICO.

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

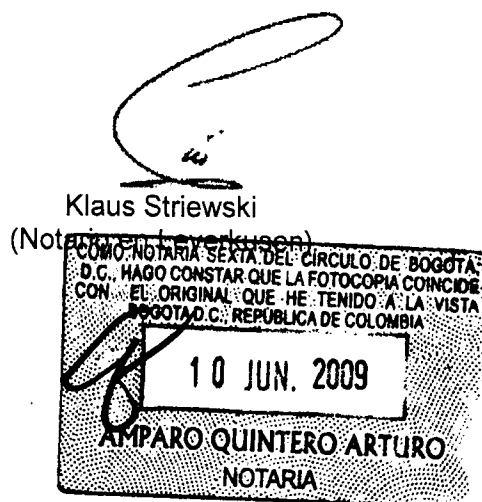
1) Certifico la autenticidad de las firmas, puestas en mi presencia, de:

- 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




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

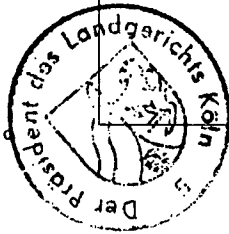
APOSTILLA

(Convention de la Haye du 5 octobre 1961)

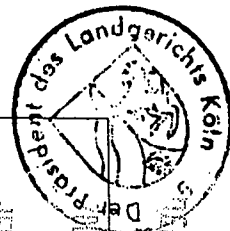
1. País: **República Federal de Alemania**
Este documento público
2. está firmado por **Klaus Striewski**
3. en su calidad de **Notario**
4. lleva el sello del
Notario Klaus Striewski en Leverkusen

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



[Signature]
Dr. Dumke



DELE. DE LOS JUDICIOS
NOTARIA D.C.
MAY 22 A 11:27

MINISTERIO DE
RELACIONES EXTERIORES

919776

[Signature]
Hernando Torres

RECEIVED
DEL JUDICIO

SELLO: EL PRESIDENTE DEL TRIBUNAL REGIONAL DE COLONIA

Cálculo de Gastos Notariales

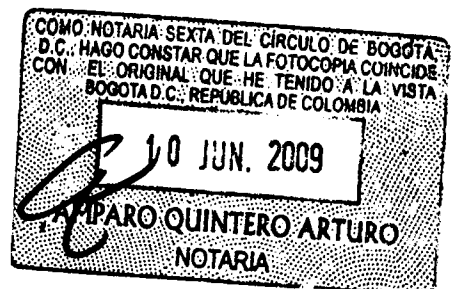
§§ 141, 154 KostO (Reglamento de Gastos Notariales)

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



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

stiv

**CAVELIER**

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

TRASPASOYo, (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, declaro(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 _____

ASSIGNMENTI (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

Dr. S. Beyreuther
BAYER HEALTHCARE AG

Cesionario

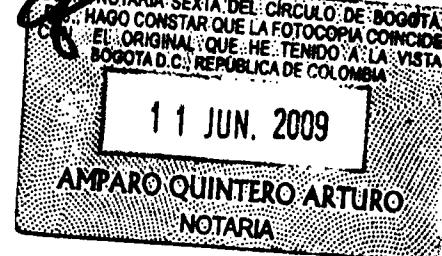
Dr. J. Thomaier
BAYER ANIMAL HEALTH GMBH

Assignor

Dr. F. Burkert (secretaries)

Assignee

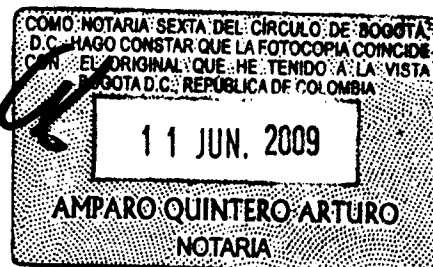
Dr. F. Köhler (secretaries)



Co

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 THIKENING AGENTS	✓
05.081.495 ✓	REPELLENT	9 s.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 beglaube 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.

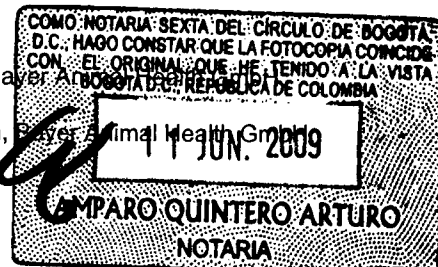
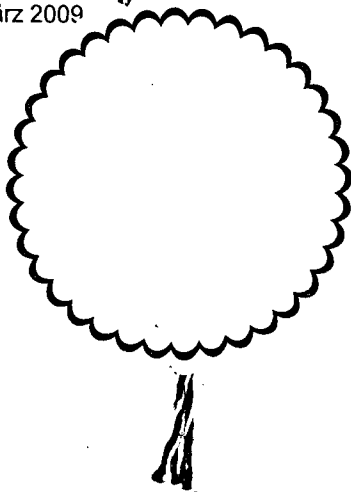
b) Ich beglaube die vor mir vollzogenen Unterschriften von:

- 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
LEVA SE
EL TEXTO O
TRADUCIR

st:u

APOSTILLE

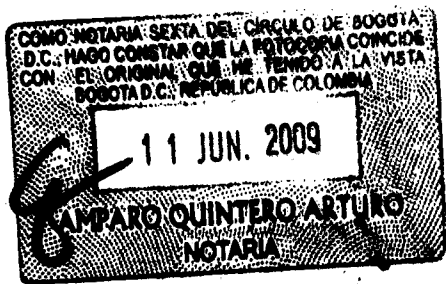
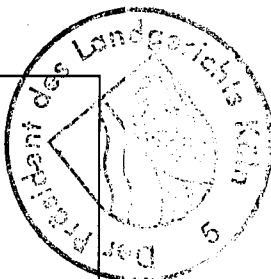
(Convention de La Haye du 5 octobre 1961)

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

Bestätigt

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


Dr. Dumke



Kostenberechnung

§§ 141, 154 KostO.

Wert: EUR 3.000,-

Geb. §§ 42, 45 (1)	EUR	10,00
Geb. §§ 59	EUR	10,00
Ges. § 150	EUR	26,00
Umsatzsteuer		6,00
§ 151a, 19	% EUR	8,74
Zus. EUR		50,74

gez.: Striewski, Notar

57:u

96

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:

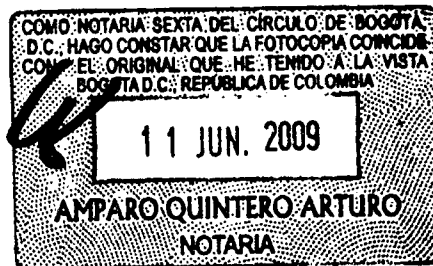
BAYER HEALTHCARE AG

DOCTOR S.BEYREUTHER DOCTOR F. BURKERT, (SECRETARIOS)

EL CESIONARIO:

BAYER ANIMAL HEALTH GMBH

DOCTOR J. THOMAIER DOCTOR F. KÖHLER, (SECRETARIOS)

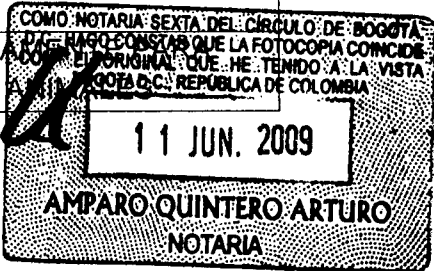


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ANEXO A

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- UINOLINA
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 EN ANIMALES
05.129.984	TABLETAS QUE CONTIENEN ENROFLOXACINA Y AGENTES SABORIZANTES Y/O SABORES
03.098.927	FORMULAS LIQUIDAS APLICABLES DÉRMICA CONTROLAR INSECTOS PARASITARIOS EN

[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.

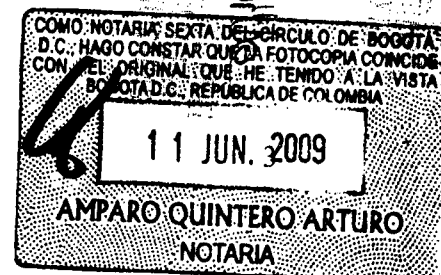
HAY SELLO EN RELIEVE DEL NOTARIO.

SIGUE LA APOSTILLA NO. 1453/09 DEL 16 DE MARZO DE 2009 POR 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



99

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:

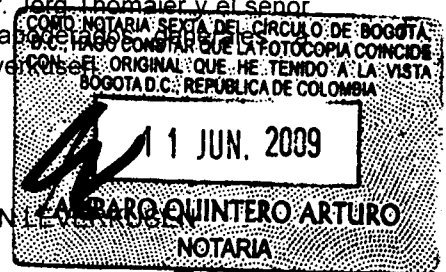
- el señor Dr. Jörg Thomaier, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania
- el señor Dr. Ferdinand Köhler, con domicilio profesional en: 51368 Leverkusen, Bayer Animal Health GmbH, Chempark, Alemania

- 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.

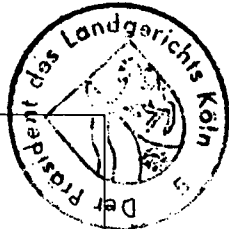
Leverkusen, 4 de marzo de 2009.

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

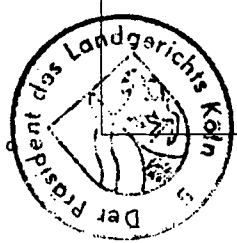
(Convention de la Haye du 5 octobre 1961)

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



SELLO: EL PRESIDENTE DEL TRIBUNAL REGIONAL DE COLONIA

Cálculo de Gastos Notariales

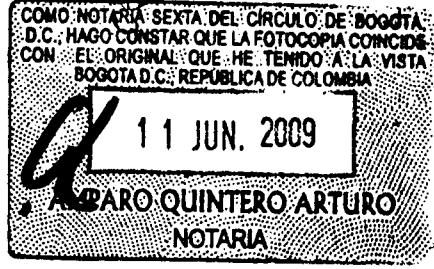
§§ 141, 154 KostO (Reglamento de Gastos Notariales)

Valor: EUR 3.000,--

Tasas §§ 32, 45 (1)	EUROS	10,00
Tasas §§ 58	EUROS	10,00
Tasas § 150	EUROS	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

NIT : 800175085-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-058589-00004-0000

Fecha: 2009-06-18 17:12:47 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 27

MEDIO CANTIDAD DE DAVA : 09 - 44,620

FECHA : JUNIO 16 DE 2009

***** CONSOLIDADO *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	VAL. PAGO	FECHA PAG.	VAL. PAGO
CAVELLER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754287	11.201536	16/06/2009	19,201,00.00

***** CONCEPTO *****

CONCEPTO	VAL. CONCEPTO
12 GANCIAS Y LEYAS COMERCIALES	111,70.00
	111,700.00

SON: CIENTO UNO MIL PESOS

RESPONSABLE : _____

RECEIBO DE DAVA APLICADO AL EXPEDIENTE No. _____

0010:16874-843-0076

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-58589

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **589** DE

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

LEY EXPIRA EL **03 DE JUNIO 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

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/635 // (A61K 31/635, 31:495)	A1	(11) International Publication Number: WO 97/24128 (43) International Publication Date: 10 July 1997 (10.07.97)
(21) International Application Number: PCT/US96/19946 (22) International Filing Date: 10 December 1996 (10.12.96) (30) Priority Data: 08/579,461 27 December 1995 (27.12.95) US (71) Applicant: BAYER CORPORATION [US/US]; One Mellon Center, 500 Grant Street, Pittsburgh, PA 15219 (US). (72) Inventors: GROH, Michael; 612 S.W. Third Street, Lee's Summit, MO 64063 (US). MCCURDY, Dennis; 9910 Ballentine, Overland Park, KS 66214 (US). CABRERA, Francisco, A.; 9953 Marty, Overland Park, KS 66212 (US). (74) Agent: AKORLI, Godfried, R.; Bayer Corporation, 100 Bayer Road, Pittsburgh, PA 15205 (US).		(81) Designated States: AU, BB, BG, BR, BY, CN, CZ, HU, IL, JP, KR, KZ, LK, NO, NZ, PL, RO, RU, SK, TR, UA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: OTIC MICROBIAL COMBINATIONS (57) Abstract Disclosed herein is an otic composition that is useful in treating otic infections comprising an antimicrobial such as a quinolone or a salt thereof and silver sulfadiazine in a therapeutically effective combination to treat otic infections in animals.		

- 2 -

animals, said composition comprising a therapeutically effective combination of an antimicrobial such as an antibacterial agent which preferably a quinolone or a salt thereof, and silver sulfadiazine. The invention further encompasses the use of a composition comprising a therapeutically effective combination of an antimicrobial such as an antibacterial agent which is preferably a quinolone or a salt thereof, and silver sulfadiazine in treating otic infections.

Also, encompassed by the present invention is a process for treating otic infections by administering the composition to animals, particularly, small animals such as dogs. The composition containing a combination of an antimicrobial such as an antibacterial agent which is preferably a quinolone and silver sulfadiazine can be administered as such or with a physiologically acceptable carrier such as an oil in water emulsion.

The composition can be used to safely and efficaciously treat otic infections such as infections of the outer ear canal. In particular, the composition can be used to treat infections caused by the bacteria *Pseudomonas*, or fungus, *Malessezia pachydermitis*. The invention is described more fully hereunder.

20

DETAILED DESCRIPTION OF THE INVENTION

As set forth above, the present invention relates to a composition that is useful in treating otic infections. The composition comprises a therapeutically effective combination of an antimicrobial such an antibacterial agent which is preferably a quinolone or a salt thereof and silver sulfadiazine. Typically, the quinolone is a fluorinated quinolone. The effective combination is described hereunder with specificity as to quinolones. The invention, however, encompasses combinations of silver sulfadiazine and other antimicrobial which can combined with the silver sulfadiazine to provide effective treatment of otic infections in the manner of the combination of silver sulfadiazine and quinolones.

- 3 -

Non-limiting examples of the fluorinated quinolone can be selected from the group consisting of Enrofloxacin; 6-Fluoro-1,4-dihydro-1-(methylamino)-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Amifloxacin); Benofloxacin; 6-Fluoro-1-(4-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Difloxacin); 5 Flerofloxacin; 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Fleroxacin); 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolonecarboxylic acid (Lomefloxacin); Marbofloxacin; 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)-3-quinolonecarboxylic acid (Norfloxacin); 10 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (Ofloxacin); Perfloxacin; Rufloxacin; Sarafloxacin; and Temafloxacin. The fluorinated quinolone preferred herein is Enrofloxacin. U.S. Patent 4,556,658 which is incorporated 15 herein by reference provides an illustrative but non-limiting description of the quinolone with particularity to Enrofloxacin and a method of preparing the same.

The quinolone or the salt thereof and the silver sulfadiazine are employed in an amount sufficient to provide a composition that would be 20 pharmaceutically effective. The quinolone or the salt thereof can be employed in an amount of 0.005 to 1.5 percent by weight of the composition and preferably 0.1 to 1 percent by weight of the composition. Silver sulfadiazine can be employed in an amount of 0.05 to 2 percent of the composition, and preferably in an amount of 0.5 to 1.5 percent of the 25 composition.

In the preparation of the composition, the quinolone and silver sulfadiazine can be combined in any convenient manner. For example, comminuted silver sulfadiazine and the quinolone can be mixed with each other. The composition can be used directly or preferably in formulation 30 with a pharmaceutically acceptable physiological carrier.

- 8 -

were for the most part, from three dilutions above to three dilutions below the MIC for each of the antimicrobials. The patterns of growth (inhibition) of the individual isolates, following exposure to the antimicrobials, were compared. Those of a single genera with the same response were
5 grouped together. All isolates were then subjected to a mathematical calculation designed to indicate whether the antimicrobials were antagonistic, synergistic, or somewhere between. The standard calculation called a Fractional Inhibitory Concentration (FIC) Index is presented below

$$\frac{X}{MIC_x} + \frac{Y}{MIC_y} = FIC_x + FIC_y = FIC \text{ index}$$

- 10 wherein X is equal to a concentration of drug X which is the lowest inhibitory concentration in its row of the checkerboard, and
Y is equal to a concentration in its row of the checkerboard.
FIC index equal to or less than 0.5 indicates synergism.
FIC index equal to or greater than 2.0 indicates antagonism.
15 FIC index equal to or greater than 0.5 but less than 2.0 indicates no effect.

For the purpose of comparison, the Enrofloxacin was also combined with clotrimazole. Clotrimazole has antifungal activity but essentially no activity on bacteria. The same series of pathogens were
20 used to evaluate both antimicrobial combinations. FIC data from the study indicating response observed for the two combinations are presented below. (Table 1).

- 11 -

WHAT IS CLAIMED IS:

1. A composition that is useful in treating otic infections comprising an antimicrobial and silver sulfadiazine in a therapeutically effective combination to treat otic infections in animals.
- 5 2. The composition of Claim 1 wherein the antimicrobial is a quinolone or a salt thereof.
3. The composition of Claim 2 wherein the quinolone is a fluorinated quinolone, an ester of fluorinated quinolone or a salt of a fluorinated quinolone.
- 10 4. The composition of Claim 3 wherein the fluorinated quinolone is selected from the group consisting of Amifloxacin, Benofloxacin, Difloxacin, Enrofloxacin, Flerofloxacin, Fleroxacin, Lomefloxacin, Marbofloxacin, Norfloxacin, Ofloxacin, Perfloxacin, Rufloxacin, Sarafloxacin, and Temafloxacin.
- 15 5. The composition of Claim 4 wherein the fluorinated quinolone is Enrofloxacin.
6. The composition of Claim 1 wherein the antimicrobial is present in an amount of 0.005 to 1.5 percent by weight of the composition.
- 20 7. The composition of Claim 6 wherein the antimicrobial is present in an amount of 0.1 to 1 percent by weight of the composition.
8. The composition of Claim 1 wherein the sulfadiazine is present in an amount of 0.05 to 2 percent of the composition.
9. The composition of Claim 8 wherein the sulfadiazine is present in an amount of 0.5 to 1.5 percent of the composition.
- 25 10. The composition of Claim 1 which further comprises a physiologically acceptable carrier.
11. The composition of Claim 10 wherein the carrier comprises an emulsion.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050021 A2

- (51) International Patent Classification⁷: **A61K** [GB/US]: 2531 Wexford Court, New Brighton, MN 55112 (US).
- (21) International Application Number: PCT/US2003/037819 (74) Agent: ELLINGER, Mark, S.; Fish & Richardson P.C., P.A., 60 South Sixth Street, Suite 3300, Minneapolis, MN 55402-1104 (US).
- (22) International Filing Date: 25 November 2003 (25.11.2003) (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, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 10/306,517 27 November 2002 (27.11.2002) US (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application: US 10/306,517 (CIP) Filed on 27 November 2002 (27.11.2002)
- (71) Applicant (*for all designated States except US*): RE-GENTS OF THE UNIVERSITY OF MINNESOTA [US/US]; 450 McNamara Alumni Center, 200 Oak Street S.E., Minneapolis, MN 55455-2070 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): SAWCHUK, Ronald, J. [US/US]: 1702 - 20th Avenue N.W., New Brighton, MN 55112 (US). CHEUNG, Belinda, W., Y.
- Published:
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOSITIONS FOR APPLYING PHARMACOLOGIC AGENTS TO THE EAR

(57) Abstract: Methods and materials useful for applying pharmacologic agents to the ear are described. The methods involve delivering a composition that contains at least one viscogenic agent and at least one pharmacologic agent to the epidermal surface of the tympanic membrane via the ear canal. The composition is delivered to the tympanic membrane in a flowable form and, after delivery to the tympanic membrane, becomes sufficiently viscous such that the pharmacologic agent is localized against the tympanic membrane. Such compositions can be used to prophylactically and/or therapeutically treat middle and inner ear conditions, including otitis media.



WO 2004/050021 A2

formulation has a viscosity less than 100,000 cps, and wherein the formulation has a yield stress sufficient to be maintained against the tympanic membrane.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those
5 described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials,
10 methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a graph of free (unbound) amoxicillin concentration in chinchilla middle
15 ear fluid as a function of time after drug dosing via the external ear canal; mean data and standard error bars ($n = 3$ to 5 at each time point).

FIG. 2 is a graph of clarithromycin concentration in chinchilla middle ear fluid as a function of time after drug dosing via the external ear canal; mean data and standard error bars ($n = 12$ to 23 at each time point).

DETAILED DESCRIPTION

20 In general, the invention provides methods for applying pharmacologic agents to the ear using compositions containing one or more pharmacologic agents and one or more viscogenic agents. Compositions are specifically formulated such that they can be delivered to the external, epidermal surface of the tympanic
25 membrane in a liquid-like state, i.e., a flowable form. After administration, however, the composition transforms into a solid-like state such that the composition remains in contact with the tympanic membrane. As a result, the composition remains localized against the tympanic membrane and the pharmacologic agent can transfer across the tympanic membrane into, for example, the middle ear space, providing a

Pharmacologic Agents

A composition of the invention also contains at least one pharmacologic agent (i.e., a chemical or biological molecule that has a desired effect when applied in an effective amount to the tympanic membrane). The amount of pharmacologic agent present in the composition is dependent on the type of pharmacologic agent and its known effective dosage. Typically, pharmacological agents are present in amounts ranging from 0.1% to 50% (e.g., 0.25% to 15%). A composition can include any type of pharmacologic agent, including, e.g., an adrenocorticoid (corticosteroid, steroid), analgesic, analgesic adjunct, analgesic-anesthetic, anesthetic, antibiotic, antibacterial, anti-infective, antibiotic therapy adjunct, antidote, anti-emetic, anti-fungal, anti-inflammatory, anti-vertigo, anti-viral, biological response modifier, cytotoxic, diagnostic aid, immunizing agent, immunomodulator, proteins, peptides, and other agents that may be useful in treating ear disorders. Analgesic, analgesic adjunct, analgesic-anesthetic, anesthetic, antibiotic, antibacterial, anti-infective, antibiotic therapy adjunct, anti-fungal, anti-inflammatory, anti-viral, and peptides are particularly useful. A composition of the invention can include a plurality of pharmacologic agents, including two or more agents within the same class (e.g., two different antibiotics) or two or more agents of various types, depending on the effect desired. For example, to fight a bacterial infection, to reduce tissue inflammation, and to alleviate irritation, a composition can contain an antibacterial, an anti-inflammatory, and an anesthetic or analgesic. Those skilled in the art can identify pharmacologic agents and combine them as needed to achieve a desired effect.

Exemplary adrenocorticoids include betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, paramethasone, prednisolone, prednisone, and triamcinolone. Exemplary analgesics include acetaminophen, aspirin, buprenorphine, butalbital, butorphanol, codeine, dezocine, diflunisal, dihydrocodeine, etodolac, fenoprefen, fentanyl, floctafenine, hydrocodone, hydromorphone, ibuprofen, ketoprofen, ketorolac, levorphanol, magnesium salicylate, meclufenamate, mefenamic acid, meperidine, meprobamate, methadone, methotrimeprazine, morphine, nalbuphine, naproxen, opium, oxycodone, oxymorphone, pentazocine, phenobarbital, propoxyphene, salsalate, and sodium salicylate. One exemplary analgesic adjunct is caffeine.

Exemplary anesthetics include articaine-epinephrine, bupivacaine, chloroprocaine, etidocaine, ketamine, lidocaine, mepivacaine, methohexital, prilocaine, propofol, propoxycaine, tetracaine, and thiopental. One exemplary analgesic-anesthetic is antipyrine-benzocaine.

- 5 Exemplary antibiotics, anti-bacterials, and anti-infectives include sulfonamides (e.g., sulfanilamide, sulfadiazine, sulfamethoxazole, sulfisoxazole, para-aminobenzoic acid, or sulfacetamide), trimethoprim-sulfamethoxazole, quinolones (e.g., ciprofloxacin, ofloxacin, or nalidixic acid), β -lactam antibiotics such as penicillins or cephalosporins, aminoglycosides (e.g., kanamycin, tobramycin, gentamycin C, amikacin, neomycin,
- 10 netilmicin, streptomycin, or vancomycin), tetracyclines, chloramphenicol, and macrolides (e.g., erythromycin, clarithromycin, or azithromycin). Non-limiting examples of suitable penicillins include penicillin G, penicillin V, methicillin, oxacillin, nafcillin, ampicillin, and amoxicillin. Non-limiting examples of suitable cephalosporins include cephalothin, cefdinir, cefozolin, cephalexin, cefadroxil, cefamandole, cefoxitin, cefaclor, cefonicid,
- 15 cefoetan, cefotaxime, ceftizoxime, ceftriaxone, cefditoren, and cefepime. Exemplary antibiotics useful for treating OM include penicillins such as amoxicillin and amoxicillin-clavulanate (Augmentin®); sulfa-based combinations such as erythromycin-sulfisoxazole (Pediazole), trimethoprim-sulfamethoxazole (Bactrim, Septra®); macrolides / azalides such as azithromycin (Zithromax®) or clarithromycin (Biaxin®); second-generation
- 20 cephalosporins such as cefaclor (Ceclor®), cefprozil (Cefzil®), cefuroxime axetil (Ceftin®), or loracarbef (Lorabid®); and third generation cephalosporins such as cefdinir (Omnicef®), cefixime (Suprax®), cefpodoxime proxetil (Vantin®), ceftibuten (Cedax®), cefditoren (Spectracef™), and ceftriaxone (Rocephin®).

- Suitable anti-emetics include buclizine, chlorpromazine, cyclizine,
- 25 dimenhydrinate, diphenhydramine, diphenidol, domperidone, dronabinol, haloperidol, hydroxyzine, meclizine, metoclopramine, nabilone, ondansetron, perphenazine, prochlorperazine, promethazine, scopolamine, thiethylperazine, triflupromazine, and trimethobenzamine. Exemplary antifungals include amphotericin B, clioquinol, clotrimazole, fluconazole, flucytosine, griseofulvin, ketoconazole, miconazole, and
- 30 potassium iodide. Exemplary anti-inflammatory agents include aluminum acetate, aspirin, betamethasone, bufexamac, celecoxib, dexamethasone, diclofenac, etodolac,



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(54) **ANTIBIOTIC COMPOSITIONS CONTAINING QUINOLONE DERIVATIVES FOR TREATMENT OF THE EYE, EAR AND NOSE**

(57) Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues.