



FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☒ Capitulo I. ☐ Capitulo II.

2) SOLICITANTE
(71)

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C.C. ☐ NIT: ☒

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3) REPRESENTANTE
O APODERADO

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Nacionalidad o Domicilio: Todos los anteriores Italianos

5) PCT (86)

Solicitud Internacional No. PCT/EP2006/060709 Fecha: Marzo 14, 2006

Publicación Internacional No. WO 2006/100195 A1 Fecha: Sept. 28, 2006

6) Título (54) USO DE MACROLIDAS PARA TRATAR INFLAMACIÓN INTESTINAL

7) Clasificación Internacional: A61K 31/7048 A61P 35/00 A61P 1/04

8) PRIORIDAD

33) País de Origen

(32) Fecha

**(31) Número de
Solicitud**

SI ☒ NO ☐

EP

MARZO 21, 2005

05102244.0

9) Comprobante de pago N°.

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☒ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Reporte internacional de búsqueda
 2. Cambio del solicitante
 3. IB/304, ISA/237, IB/308

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-105847 - 00000-0000
 Fecha: 2007-10-09 16:10:28 Dep. 2020 NUECREACION
 Tra 11 PATENTE IYII Evt. 378 FASENACIONALI
 Act. 411 PRESENTACION Folios: 55

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 81,174
 FECHA : OCTUBRE 2 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	66408802	02/10/2007	18,575,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

3

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/100195 A1

(51) International Patent Classification:

A61K 31/7048 (2006.01) A61P 35/00 (2006.01)
A61P 1/04 (2006.01)

(21) International Application Number:

PCT/EP2006/060709

(22) International Filing Date: 14 March 2006 (14.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

05102244.0 21 March 2005 (21.03.2005) EP

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(72) Inventors; and

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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: USE OF MACROLIDES FOR TREATING INTESTINAL INFLAMMATION

(57) Abstract: The present invention relates to a compound of formula (IA) as defined in the specification or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for both the treatment of inflammatory bowel diseases and the prevention of colon cancer.

WO 2006/100195 A1

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Use of macrolides for treating intestinal inflammation"

DESCRIPTION

The present invention relates to novel methods of treating an inflammatory response in
5 intestinal tissues associated with a disease such as inflammatory bowel disease involving
either or both the small and large bowel. In particular the present invention relates to a new
use of certain macrolides for the treatment of the inflammatory bowel disease.

Inflammatory bowel disease (IBD) is the generic term for a disease of unknown cause that
produces chronic inflammation or ulceration of the mucosa of the large and small intestine.
10 This inflammatory bowel disease includes such diseases as ulcerative colitis and Crohn's
disease.

Ulcerative colitis is a chronic, non-specific IBD which involves a diffuse inflammation in the
mucosa of the large intestine causing ulcerative lesions of the colon. Crohn's disease, also
known as regional enteritis or colitis granulomatosa, is most frequently located in the small
15 intestine (small bowel), especially in the ileum, but it can affect any part of the bowel,
including the rectum. In the latter case the differentiation of Crohn's disease from ulcerative
colitis may give rise to diagnostic problems. Generally, the inflammation differs from that of
ulcerative colitis by progressing to layers deeper than the mucosa and affecting the
epithelium to a lesser degree. Both diseases have become increasingly frequent especially in
20 the developed countries. Therefore, treatment of IBD has become an important problem of
modern medicine.

The presently available medical treatments for IBD generally involve drug therapy directed
towards the suppression of gastrointestinal inflammation. The most commonly used
medicaments to treat IBD are anti-inflammatory drugs such as the salicylates. The salicylate
25 preparations may be effective in treating mild to moderate disease. Examples of salicylates
include sulfasalazine, olsalazine, and mesalamine. All of these medications are given orally
in high doses for maximal therapeutic benefit. These medicines are not without side effects
including heartburn, nausea, vomiting, diarrhea, and headache.

People with more severe IBD can be treated with corticosteroids, such as prednisone and
30 hydrocortisone, which are more potent and faster-acting than salicylates in the treatment of
IBD, but are endowed with potentially serious side effects.

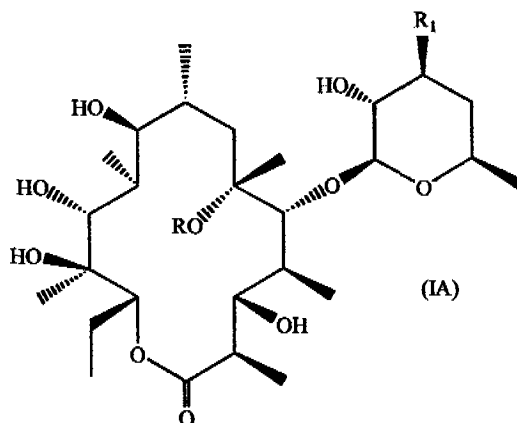
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In IBD patients that do not respond to salicylates or corticosteroids, medications that suppress the immune system are used. However, immunosuppressants cause increased risk of infection, renal failure, and may increase the need for hospitalization. In severe cases of disease, the patient may need surgery to remove the affected gut. Drugs like antidiarrheals, laxatives, and pain relievers can be also given to help relieve symptoms.

Since all the available medical treatments for IBD are rather unsatisfactory and often ineffective, there is currently a great need for novel drugs capable of treating IBD and preventing its relapse.

We have now found that some macrolides, encompassed by the general formula (I), as reported in the International patent application WO 2004/013153 and endowed with anti-inflammatory activity particularly in skin and lung inflammation, are also surprisingly effective in treating intestinal inflammation.

It is therefore a first object of the present invention the use of a compound of formula (IA)



wherein

R is hydrogen or methyl;

R₁ is an N-(C₁-C₄)acyl-N-(C₁-C₃)alkylamino group;

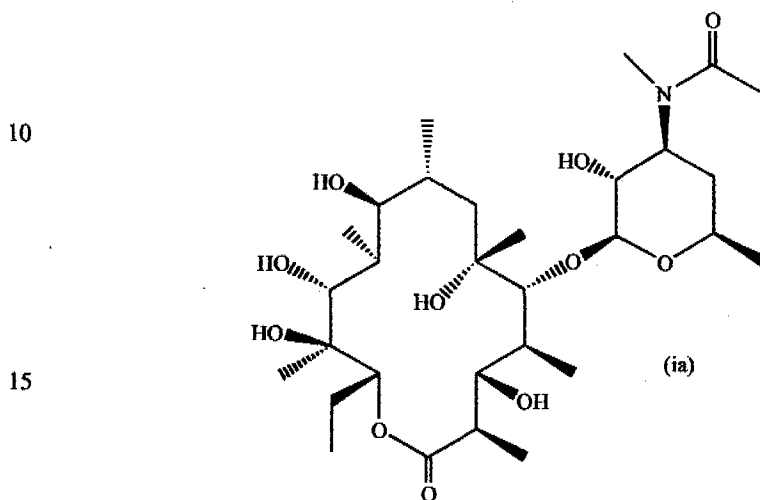
or a pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating IBD.

Examples of pharmaceutically acceptable salts of the compounds of formula (IA) are salts with organic or mineral acids such as hydrogen chloride, hydrogen bromide, hydrogen

iodine, nitric acid, sulphuric acid, phosphoric acid, acetic acid, tartaric acid, citric acid, benzoic acid, succinic acid and glutaric acid.

In particular, the compounds of formula (IA) or a pharmaceutically acceptable salt thereof can be used for treating ulcerative colitis or Crohn's disease.

Particularly preferred compound of formula (IA) according to the invention is the compound of formula (ia)



namely, (9S)-O5-[3-(1-oxoethyl)-methylamino- β -D-xylo-3,4,6-trideoxy-hexapyranosyl]-9-hydroxy-9-deoxy-erythronolide-A, or a pharmaceutically acceptable salt thereof.

Unless otherwise specified, the term "treatment" as used herein relates to both treatment in order to cure or alleviate a disease or a condition, and to treatment in order to prevent the development or relapse of a disease or a condition.

The term "patient", as used herein, relates to any human or non-human mammal in need of treatment according to the invention.

In IBD, the constant process of inflammatory injury and repair of the lining of the colon (colonic mucosa) is believed to make the individual more susceptible to the cancer. Colon cancer doesn't distinguish between active disease and remission. Patients whose disease has been quiet have the same risk as those who have more active disease.

For example, patients with prolonged ulcerative colitis are at increased risk for developing

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colon cancer. The risk of cancer increases with the duration and the extent of involvement of colonic mucosa. For example, if only the lower colon and rectum are involved, the risk of cancer is no higher than normal. However, if the whole colon is involved, the risk of cancer may be higher.

It is therefore a further object of the present invention the use of a compound of formula (IA) as defined above or a pharmaceutically acceptable salt thereof for the preparation of a medicament for preventing colon cancer.

In a further aspect, the present invention relates to a method for treating IBD, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof.

In a still further aspect the present invention relates to a method for preventing colon cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof.

The pharmacological activity of the compound of formula (ia), as a representative compound of the compounds of the present invention, was evaluated in *in vivo* models of intestinal inflammation, as illustrated in the following EXPERIMENTAL PART.

Brief description of the drawings

In the Experimental Part below reference is made to the appended drawings on which:

Fig. 1 shows the scheme of drug treatments. Oral drugs were suspended in 1% methocel and given in a volume of 0.5 ml.

Fig. 2 shows the macroscopic damage score criteria. The final score is obtained by the sum of all values.

Fig. 3 shows values of macroscopic damage score indicating the severity of DNBS-induced colitis in rats. Each column indicates the mean value obtained from 6-8 animals $\pm$ S.E.M. (vertical lines). Significant difference from control values * $P < 0.05$ (one way ANOVA following by Student-Newman-Keuls test).

EXPERIMENTAL PART

Methods

Induction of colitis

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Albino male Sprague-Dawley rats, 200-250 g body weight, were treated with intrarectal DNBS (2,4-dinitrobenzenesulfonic acid, 30 mg in 0.25 ml of 50% ethanol) under a light anaesthesia with diethyl ether. In control experiments, the animals received 0.25 ml of saline (NaCl 0.9%). Animals were subjected to subsequent experimental procedures 6 days after induction of colitis with DNBS (Blandizzi et al., Altered prejunctional modulation of intestinal cholinergic and noradrenergic pathways by alpha-2-adrenoceptors in the presence of experimental colitis. *Br J Pharmacol* 139, 309-320, 2003).

Experimental design

- 10 The compound of formula (ia), from now on the macrolide, was suspended in 1% methocel and administered to animals by intragastric gavage in a volume of 0.5 ml at the doses of 100 or 300 $\mu\text{mol/kg/day}$ for 7 consecutive days. Induction of colitis was performed on day 2 as reported above. Animals were subjected to subsequent experimental procedures on day 7, four hours later from administration of the last dose of the macrolide or its vehicle (Fig. 1).
- 15 Each experimental series included the following treatment groups:
- 1) controls (intragastric drug vehicle for 7 days plus intra-colonic saline on day 2);
 - 2) intragastric macrolide for 7 days plus intra-colonic saline on day 2;
 - 3) intragastric drug vehicle for 7 days plus intra-colonic DNBS on day 2;
 - 4) intragastric macrolide for 7 days plus intra-colonic DNBS on day 2.
- 20 Each data point represents the mean value of results obtained from at least 6-8 animals. The effect of the macrolide was compared with that of dexamethasone (1 mg/kg/day, by oral route), known to exert a good anti-inflammatory action in the rat model of TNBS-induced colitis (Bobin-Dubigeon et al., Effects of tumor necrosis factor- α synthesis inhibitors on rat trinitrobenzene sulfonic acid-induced chronic colitis. *Eur J Pharmacol* 431, 103-110, 2001).
- 25 Dexamethasone was administered once daily following the same time schedule adopted for the macrolide.

Macroscopic and histological assessment of intestinal inflammation

- At the end of treatments, animals were sacrificed and the severity of colonic inflammation was macroscopically evaluated in accordance with the criteria previously reported by
- 30 Wallace and Keenan (Wallace JL and Keenan CM, An orally active inhibitor of leukotriene

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synthesis accelerates healing in a rat model of colitis. *Am J Physiol*, 258, G527-G534, 1990) with minor modifications (Blandizzi et al., 2003). Briefly, the macroscopic evaluation is based on the following criteria: presence of adhesions between the colon and other intra-abdominal organs; consistency of colonic faecal material (as an indirect marker of diarrhea); thickening of the colonic wall; presence and extension of hyperemia and macroscopic mucosal damage (assessed with the aid of a ruler) (Fig. 2). All parameters of macroscopic damage were recorded and scored for each rat by two independent observers blinded to the treatment.

10 Results

The obtained results are illustrated in Fig. 3. Control rats exhibited a negligible macroscopic damage score, accounting for 1.0 ± 0.2 . In DNBS-treated animals, the extent of inflammatory lesions was significantly higher than that observed in control rats (10.7 ± 0.4), indicating the occurrence of colitis. The macrolide exerted significant anti-inflammatory effects both at 100 and 300 $\mu\text{mol/kg}$ (-24% and -51%, respectively). Dexamethasone induced anti-inflammatory effect similar to that observed with the macrolide 100 $\mu\text{mol/kg}$.

Conclusions

Data obtained from the present study indicate a good pattern of anti-inflammatory activity of the macrolide against experimental colitis. In this setting, the efficacy of the macrolide seems to be comparable with that of dexamethasone, a well known anti-inflammatory drug.

It is thus clear from the experimental evidence reported above that a compound of formula (IA), especially the compound of formula (ia) or a pharmaceutically acceptable salt thereof, may be effectively used in the treatment of IBD and in the prevention of colon cancer.

The therapeutical effective amounts of a compound of formula (IA) or a pharmaceutically acceptable salt thereof will depend on the age and the general physiological state of the patient, the route of administration and the pharmaceutical formulation used; the therapeutic doses will generally be between about 10 and 2000 mg/day and preferably between about 30 and 1500 mg/day.

The compounds of the present invention for use in the treatment and/or prophylaxis of the above mentioned diseases will preferably be used in a pharmaceutical form that is suitable

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for oral, rectal, sublingual, parenteral, topical, transdermal and inhalational administration.

It is therefore a further object of the present invention to provide pharmaceutical formulations containing a therapeutical effective amount of a compound of formula (IA) or a
5 pharmaceutically acceptable salt thereof together with a pharmaceutical acceptable vehicle.

The pharmaceutical formulations of the present invention may be liquid, suitable for oral and/or parenteral administration, for instance drops, syrups, solutions, injectable solutions ready to use or prepared via dilution of a lyophilizate, but preferably solid, for instance
10 tablets, capsules, granules, powders, pellets, pessaries, suppositories, creams, pomades, gels or ointments; or alternatively solutions, suspensions, emulsions or other forms suitable for inhalation and transdermal administration.

Depending on the type of formulation, these formulations will contain, besides a therapeutical effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof, solid or liquid excipients or diluents for pharmaceutical use and
15 optionally other additives normally used in the preparation of pharmaceutical formulations, for instance thickeners, aggregating agents, lubricants, disintegrants, flavourings and colourings.

The pharmaceutical formulations according to the invention, may be produced according to conventional techniques. As an example, hard gelatine capsules for oral administration
20 comprising from 100 mg to 300 mg of the macrolide and a pharmaceutically acceptable vehicle may be prepared to be administered to a patient in need thereof.

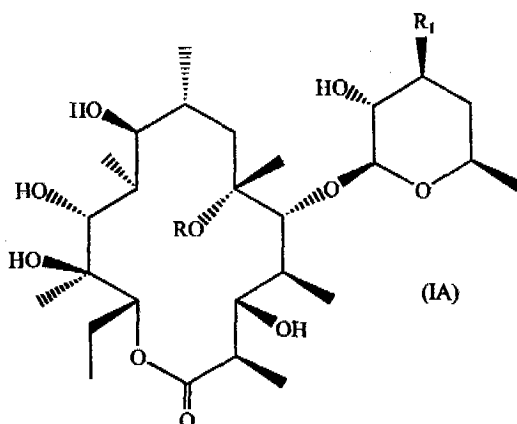
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CLAIMS

1. The use of a compound of formula (IA)

5

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wherein

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R is hydrogen or methyl;

R₁ is an N-(C1-C4)acyl-N-(C1-C3)alkylamino group;

or a pharmaceutically acceptable salts thereof, in the preparation of a medicament for the treatment of inflammatory bowel diseases.

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2. The use according to claim 1, wherein the compound of formula (IA) is (9S)-O5-[3-(1-oxoethyl)-methylamino-β-D-xylo-3,4,6-trideoxy-hexapyranosyl]-9-hydroxy-9-deoxy-erythronolide-A, or a pharmaceutically acceptable salt thereof.

3. The use according to claim 1 or 2, wherein the inflammatory bowel disease is ulcerative colitis.

25

4. The use according to claim 1 or 2, wherein the inflammatory bowel disease is Crohn's disease.

5. The use of a compound of formula (IA) as defined in claim 1, for the prevention of colon cancer.

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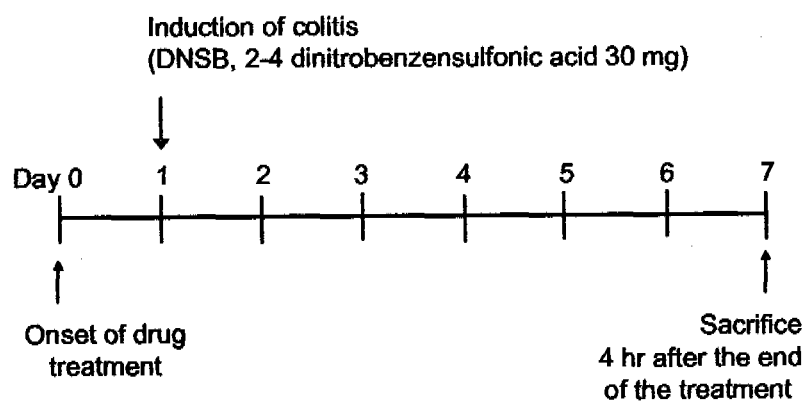
6. The use according to claim 5, wherein the compound of formula (IA) is (9S)-O5-[3-(1-oxoethyl)-methylamino-β-D-xylo-3,4,6-trideoxy-hexapyranosyl]-9-hydroxy-9-deoxy-erythronolide-A, or a pharmaceutically acceptable salt thereof.

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Figure 1

Scheme of drug treatment



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14. *La casa di un reame* (1993)

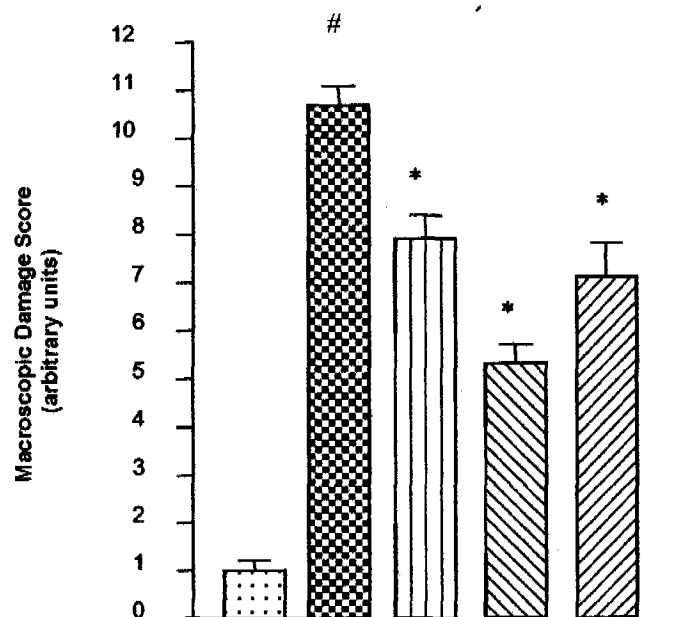
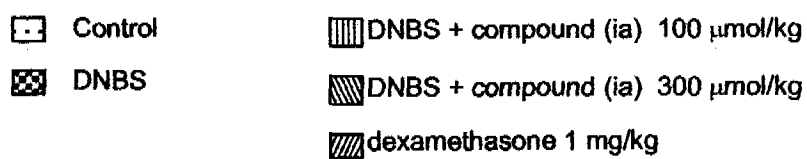
[illegible]

* Group can be easily subdivided into other tasks
* Several major processes in group related to the behavior

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Figure 3

Macroscopic damage score

* $p < 0.05$ vs DNBS# $p < 0.05$ vs control

15

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/060709

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/7048 A61P1/04 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/075494 A (ZAMBON GROUP S.P.A; MEREU, ANDREA; NAPOLETANO, MAURO; ORNAGHI, FERNAND) 18 August 2005 (2005-08-18) page 15, line 18 claims; examples	1-6
X	WO 2004/013153 A (ZAMBON GROUP S.P.A; NAPOLETANO, MAURO; MORIGGI, ERMANNO; MEREU, ANDREA) 12 February 2004 (2004-02-12) cited in the application Compound RN: 654076-73-0 (compound (ia)) page 28, lines 3-13 examples claim 31	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

Z document member of the same patent family

Date of the actual completion of the international search

19 July 2006

Date of mailing of the international search report

16/08/2006

Name and mailing address of the ISA/

European Patent Office, P.O. 5818 Patentlaan 2
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Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/060709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/198677 A1 (MERCEP MLANDEN ET AL) 7 October 2004 (2004-10-07) claims; examples claim 45	1-6
Y	"The Merck Manual" 1999, MERCK RESEARCH LABORATORIES, USA, XP002391025 pages 302-312	1-6
Y	US 5 712 253 A (LARTEY ET AL) 27 January 1998 (1998-01-27) column 2, lines 31-45 column 2, lines 60-67 claims	1-6
A	US 2002/035075 A1 (BORODY THOMAS JULIUS) 21 March 2002 (2002-03-21) See claim 3: clarithromycin paragraphs [0001], [0002]; examples 1,4-8	1-6
A	WO 00/42055 A (ZAMBON GROUP S.P.A; PELLACINI, FRANCO; BOTTA, DANIELA; ROMAGNANO, STEF) 20 July 2000 (2000-07-20) the whole document	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/060709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005075494	A	18-08-2005	NONE
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USO DE MACROLIDAS PARA TRATAR INFLAMACIÓN INTESTINAL 14

DESCRIPCIÓN

La presente invención se relaciona con métodos novedosos para tratar una respuesta inflamatoria en tejidos intestinales asociados con una enfermedad tal como enfermedad inflamatoria del intestino que involucra el intestino grueso y el intestino delgado. En particular la presente invención se relaciona con un nuevo uso de ciertas macrolidas para el tratamiento de la enfermedad inflamatoria del intestino.

La Enfermedad inflamatoria del intestino (IBD) es el término genérico para una enfermedad de causa desconocida que produce inflamación crónica o ulceración de la mucosa del intestino grueso y delgado. Esta enfermedad inflamatoria del intestino incluye tales enfermedades como colitis ulcerativa y Enfermedad de Crohn.

La Colitis ulcerativa es un IBD crónico, no específico que involucra una inflamación difusa en la mucosa del intestino grueso que origina lesiones ulcerativas del colón. La Enfermedad de Crohn, también conocida como enteritis regional o colitis granulomatosa, se ubica más frecuentemente en el intestino delgado (intestino delgado), especialmente en el íleo, pero este puede afectar cualquier parte del intestino, incluyendo el recto. En este último caso la diferenciación de la Enfermedad de Crohn de la colitis ulcerativa puede ocasionar problemas de diagnóstico. Generalmente, la inflamación se difiere de aquella

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de la colitis ulcerativa progresando a capas más profundas que la mucosa y afectando el epitelio en un menor grado. Ambas enfermedades han llegado a incrementarse frecuentemente especialmente en los países desarrollados. Por lo tanto, el tratamiento del IBD ha llegado a ser un problema importante de la medicina moderna.

Los tratamientos médicos actualmente disponibles para el IBD generalmente involucran terapia de droga dirigida hacia la supresión de la inflamación gastrointestinal. Los medicamentos más comúnmente utilizados para tratar IBD son drogas anti inflamatorias tales como los salicilatos. Las preparaciones de salicilato pueden ser efectivas en el tratamiento de enfermedades suaves a moderadas. Ejemplos de salicilatos incluyen sulfasalazina, olsalazina, y mesalamina. Todos estos medicamentos se dan oralmente en dosis altas para máximo beneficio terapéutico. Estas medicinas tienen efectos colaterales que incluyen ardor de estómago, náusea, vomito, diarrea, y jaqueca.

Personas con IBD más severos se pueden tratar con corticosteroides, tal como prednisona y hidrocortisona, que son más potentes y actúan más rápido que los salicilatos en el tratamiento de IBD, pero están dotados con potencialmente serios efectos colaterales.

En pacientes con IBD que no responden a los salicilatos o corticosteroides, se utilizan medicamentos que suprimen el sistema inmune. Sin embargo, los inmuno supresores originan riesgo incrementado de infección, falla renal, y pueden

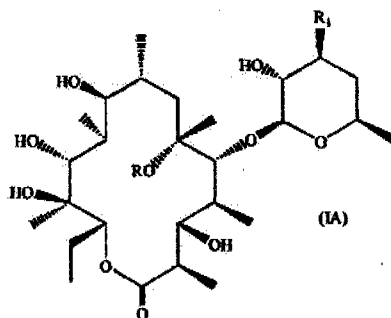
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incrementar la necesidad de hospitalización. En casos severos de la enfermedad, el paciente puede necesitar cirugía para remover el intestino afectado. Las drogas como anti diarreicos, laxantes, y aliviadores del dolor también se pueden suministrar para ayudar a aliviar los síntomas.

En razón a que todos los tratamientos médicos disponibles para el IBD son insatisfactorios y frecuentemente inefectivos, subsiste actualmente la necesidad para drogas novedosas capaces de tratar el IBD y evitar su recaída.

Hemos encontrado que algunas macrolidas, abarcadas por la Fórmula general (I), como se reporta en la solicitud de Patente Internacional WO 2004/013153 y dotado con actividad particularmente inflamatoria en la piel e inflamación de los pulmones, también es sorprendentemente efectivo en el tratamiento de la inflamación intestinal. Es por lo tanto un primer objeto de la presente invención utilizar un compuesto de la fórmula (IA)



En donde R es hidrógeno o metilo;

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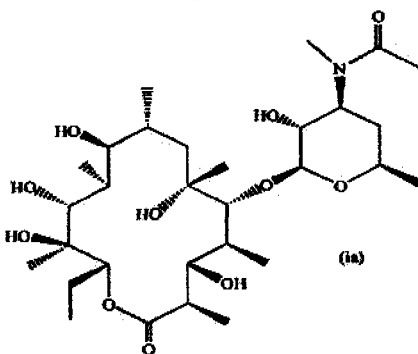
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R₁ es un grupo N-(C₁-C₄) acil-N-(C₁-C₃) alquilamino; o una sal farmacéuticamente aceptable de estos, en la preparación de un medicamento para tratar el IBD.

Ejemplos de sales farmacéuticamente aceptables de los compuestos de la fórmula (IA) son sales con ácidos minerales u orgánicos tales como cloruro de hidrógeno, bromuro de hidrógeno, yoduro de hidrógeno, ácido nítrico, ácido sulfúrico, ácido fosfórico, ácido acético, ácido tartárico, ácido cítrico, ácido benzoico, ácido succínico y ácido glutárico.

En particular, los compuestos de la fórmula (IA) o una sal farmacéuticamente aceptable de esta se puede utilizar para tratar colitis ulcerativa o Enfermedad de Crohn.

Los compuestos particularmente preferidos de la fórmula (IA) de acuerdo con la invención es el compuesto de fórmula (ia)



A saber, (9S)-O5-[3-(1-oxoetil)-metilamino-β-D-xilo-3, 4,6-trideoxi-hexapiranosil]-9- hidroxí-9-deoxo-eritronolida-A, o una sal farmacéuticamente aceptable de esta.

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A menos que se especifica otra cosa, el término "tratamiento" como se utiliza aquí se relaciona con el tratamiento con el fin de curar o aliviar una enfermedad o una condición, y para el tratamiento con el fin de evitar el desarrollo o recaída de una enfermedad o una condición.

El término "paciente", como se utiliza aquí, se relaciona con cualquier humano o mamífero no humano en necesidad del tratamiento de acuerdo con la invención.

En IBD, el proceso constante de lesión inflamatoria y reparar el recubrimiento del colón (mucosa colónica) se considera que hace al individuo más susceptible al cáncer. El cáncer de Colón no distingue entre enfermedad activa y remisión. Los Pacientes cuya enfermedad se ha sosegado tienen el mismo riesgo como aquellos que tienen la enfermedad más activa.

Por ejemplo, los pacientes con colitis ulcerativa prolongada son están en alto riesgo de desarrollar cáncer de colón. El riesgo de cáncer se incrementa con la duración y el alcance de involucramiento de la mucosa colónica. Por ejemplo, si solo están involucrados el recto y el colón descendente, el riesgo de cáncer no es mayor de lo normal. Sin embargo, si el todo el colón está involucrado, el riesgo de cáncer puede ser mayor.

Es por lo tanto un objeto adicional de la presente invención el uso de un compuesto de la fórmula (IA) como se definió anteriormente o una sal farmacéuticamente aceptable de esta para la preparación de un medicamento para evitar el cáncer de colón.

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En un aspecto adicional, la presente invención se relaciona con un método para tratar el IBD, que comprende administrar a un paciente en necesidad de este una cantidad terapéuticamente efectiva de un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable de esta.

En un aspecto aún adicional la presente invención se relaciona con un método para evitar el cáncer de colón, que comprende administrar a un paciente en necesidad de este una cantidad terapéuticamente efectiva de un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable de esta. La actividad farmacológica del compuesto de la fórmula (ia), como un compuesto representativo de los compuestos de la presente invención, se evalúa en modelos in vivo de inflamación intestinal, como se ilustra en la siguiente PARTE EXPERIMENTAL.

Breve descripción de los dibujos

En la parte experimental adelante se hace referencia a los dibujos adjuntos en los cuales:

La Figura 1 muestra el esquema de tratamientos de droga. Las drogas orales se suspenden en 1% metocel y se dan en un volumen de 0.5 ml.

La Figura 2 muestra el criterio de clasificación de daño macroscópico. La clasificación final se obtiene por la suma de todos los valores.

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La Figura 3 muestra valores de clasificación de daño macroscópico que indica la severidad de la colitis inducida por DNBS en ratas. Cada columna indica el valor medio obtenido de de 6-8 animales $\pm$ E.E.M. (líneas verticales). Diferencia significativa de valores de control * $P < 0.05$ (ANOVA de una vía seguido por ensayo Student-Newman-Keuls).

PARTE EXPERIMENTAL

Métodos

Inducción de colitis

Ratas Sprague-Dawley macho Albinas, de peso corporal 200-250 g, se tratan con DNBS intrarectal ácido 2,4-dinitrobenzenosulfónico, 30 mg en 0.25 ml de 50% etanol) bajo una anestesia suave con dietil éter. En experimentos de control, los animales reciben 0.25 ml de solución salina (NaCl 0.9%). Los Animales se someten a procedimientos experimentales posteriores 6 días después de la inducción de la colitis con DNBS (Blandizzi et al., la modulación preunión alterada de las rutas colinérgicas y no adrenérgicas intestinales por los alfa-2-adrenoceptores en la presencia de colitis experimental. Br J Pharmacol 139, 309-320, 2003).

Diseño Experimental

El compuesto de fórmula (ia), de ahora en adelante la macrolida, se suspende en 1% metocel y se administra a los animales mediante alimentación forzosa intra gástrica en un volumen de 0.5 ml en las dosis de 100 o 300 $\mu\text{mol/kg/día}$ durante 7 días consecutivos. La inducción de la colitis se desarrolla en el día 2 como se

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reportó anteriormente. Los Animales se someten a procedimientos experimentales posteriores en el día 7, cuatro horas después de administración de la última dosis de la macrolida o su vehículo (Figura 1). Cada serie experimental incluye los siguientes grupos de tratamiento:

- 1) Controles (vehículo de droga intra gástrico durante 7 días más solución salina intra colónica en el día 2);
- 2) Macrolida intra gástrica durante 7 días más solución salina intra colónica en el día 2;
- 3) Vehículo de droga intra gástrica durante 7 días más DNBS intra colónico en el día 2;
- 4) Macrolida intra gástrica durante 7 días más DNBS intra colónico en el día 2.

Cada punto de datos representa el valor medio de los resultados obtenidos de al menos 6-8 animales. El efecto de la macrolida se compara con aquella de la dexametasona (1 mg/kg/día, mediante ruta oral), conocida por ejercer una buena acción anti inflamatoria en el modelo de rata de colitis inducida por TNBS (Bobin-Dubigeon et al., Effects of tumor necrosis factor- α synthesis inhibitors on rat trinitrobenzene sulfonic acid-induced chronic colitis. Eur J Pharmacol 431, 103-110, 2001).

La Dexametasona se administra una vez al día luego del mismo tiempo de programación adoptado para la macrolida.

Evaluación histológica y macroscópica de la inflamación intestinal

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Al final de los tratamientos, se sacrifican los animales y se evalúa la severidad de la inflamación colónica microscópicamente de acuerdo con el criterio reportado previamente por Wallace and Keenan (Wallace JL y Keenan CM, An orally active inhibitor of leukotriene synthesis accelerates healing in a rat model de colitis. Am J Physiol, 258, G527-G534, 1990) con menores modificaciones (Blandizzi et al., 2003). En resumen, la evaluación macroscópica se basa en el siguiente criterio: presencia de adhesiones entre el colón y otros órganos intra abdominales; consistencia de materia fecal colónica (como un marcador indirecto de diarrea); adhesión de la pared colónica; presencia y extensión de hiperemia y daño macroscópico de la mucosa (evaluado con la ayuda de una regla) (Figura 2). Todos los parámetros de daño macroscópico se registran y se clasifican para cada rata mediante dos observadores independientes segados al tratamiento.

Resultados

Los resultados obtenidos se ilustran en La Figura 3. Las ratas de Control exhiben una clasificación de daño macroscópico insignificante, que cuenta para 1.0 ± 0.2 . Los animales tratados con DNBS, el alcance de las lesiones inflamatorias fue significativamente mayor que el observado en las ratas de control (10.7 ± 0.4), que indica la ocurrencia de colitis. La macrolida ejerce efectos anti inflamatorios significativos en 100 y 300 $\mu\text{mol/kg}$ (-24% y -51%, respectivamente). La Dexametasona induce similar efecto anti inflamatorio a aquel observado con la macrolida 100 $\mu\text{mol/kg}$.

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Conclusiones

Los datos obtenidos del presente estudio indican un buen patrón de actividad anti inflamatoria de la macrolida contra la colitis experimental. En este aspecto, la eficacia de la macrolida parece ser comparable con aquella de la dexametasona, una droga anti inflamatoria bien conocida. Es así claro a partir de la evidencia experimental reportada anteriormente que un compuesto de fórmula (IA), especialmente el compuesto de fórmula (ia) o una sal farmacéuticamente aceptable de esta, puede ser utilizado efectivamente en el tratamiento de IBD y en la prevención de cáncer de colón. Las cantidades terapéuticamente efectivas de un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable de esta dependerá de la edad y el estado fisiológico general del paciente, la ruta de administración y la formulación farmacéutica utilizada; las dosis terapéuticas estarán generalmente entre aproximadamente 10 y 2000 mg/día y preferiblemente entre aproximadamente 30 y 1500 mg/día. Los compuestos de la presente invención para uso en el tratamiento y/o profilaxis de las enfermedades mencionadas anteriormente se utilizarán preferiblemente en una forma farmacéutica que es adecuada para administración oral, rectal, sublingual, parenteral, tópica, transdérmica y por inhalación.

Es por lo tanto un objeto adicional de la presente invención suministrar formulaciones farmacéuticas que contienen una cantidad terapéuticamente efectiva de un compuesto de fórmula

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(IA) o una sal farmacéuticamente aceptable de esta junto con un vehículo farmacéuticamente aceptable.

Las formulaciones farmacéuticas de la presente invención pueden ser líquidas, adecuadas para administración oral y/o parenteral, por ejemplo gotas, jarabes, soluciones, soluciones inyectables listas para uso o preparadas por dilución de un liofilizado, pero preferiblemente sólidas, por ejemplo comprimidos. Cápsulas, gránulos, polvos, glóbulos, pessaries, supositorios, cremas, pomadas, geles o ungüentos; o alternativamente soluciones, suspensiones, emulsiones, u otras formas adecuadas para inhalación y administración transdérmica.

Dependiendo del tipo de formulación, estas formulaciones contendrán, a pesar de una cantidad de efecto terapéutico de un compuesto de fórmula (IA) o una sal farmacéuticamente aceptable de esta, excipientes sólidos o líquidos o diluentes para uso farmacéutico y opcionalmente otros aditivos utilizados normalmente en la preparación de formulaciones farmacéuticas por ejemplo espesantes, agentes de agregación, lubricantes, desintegrantes, saborizantes y colorantes.

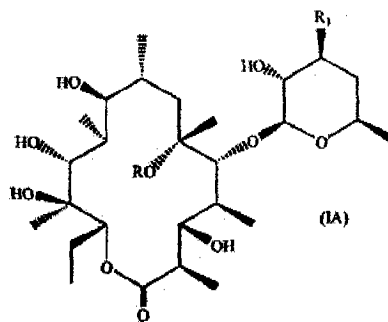
Las formulaciones farmacéuticas de acuerdo con la invención, se pueden producir de acuerdo con técnicas convencionales. Como un ejemplo, las cápsulas de gelatina dura para administración oral que comprenden de 100 mg a 300 mg de la macrolida y un vehículo farmacéuticamente aceptable se pueden preparar al ser administradas a un paciente en necesidad de esta.

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REIVINDICACIONES

1. El uso de un compuesto de fórmula (IA)



En donde R es hidrógeno o metilo;

R₁ es un grupo N-(C₁-C₄) acil-N-(C₁-C₃) alquilamino;

o una sal farmacéuticamente aceptable de esta, en la preparación de un medicamento para el tratamiento de enfermedades inflamatorias del intestino.

2. El uso de acuerdo con la reivindicación 1, en donde el compuesto de fórmula (IA) es (9S)-O5-[3-(1-oxoetil)-metiloamino-β-D-xilo-3, 4,6-trideoxi-hexapiranosil]-9-hidroxi-9-deoxo-eritronolida-A, o una sal farmacéuticamente aceptable de esta.
3. El uso de acuerdo con la reivindicación 1 o 2, en donde la enfermedad inflamatoria del intestino es colitis ulcerativa.

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4. El uso de acuerdo con la reivindicación 1 o 2, en donde la enfermedad inflamatoria del intestino es la Enfermedad de Crohn.
5. El uso de un compuesto de fórmula (IA) como se definió en la reivindicación 1, para la prevención del de cáncer de colón.
6. El uso de acuerdo con la reivindicación 5, en donde el compuesto de fórmula (IA) es (9S)-O5-[3-(1- oxoetil)-metiloamino- β -D-xilo-3, 4,6-trideoxi-hexapiranosil]-9-hidroxi-9-deoxo- eritronolida-A, o una sal farmacéuticamente aceptable de esta.

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Figura 1

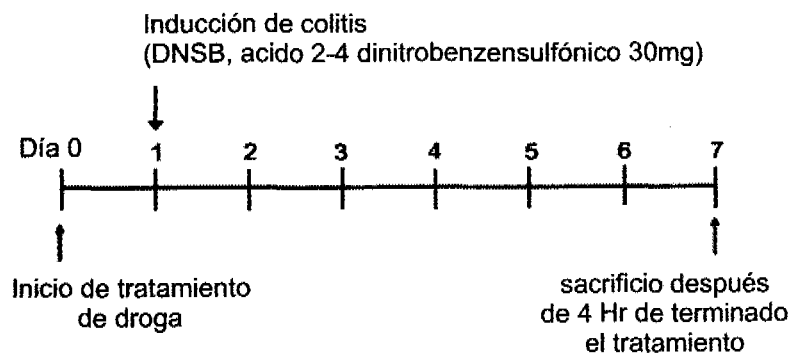
Esquema de tratamiento de droga

Figura 2

criterio de clasificación de daño Microscópico

Adicciones			Consistencia de las heces			Ulceración							Grosor del intestino	clasificación final

* el colon pude separarse fácilmente de otros tejidos

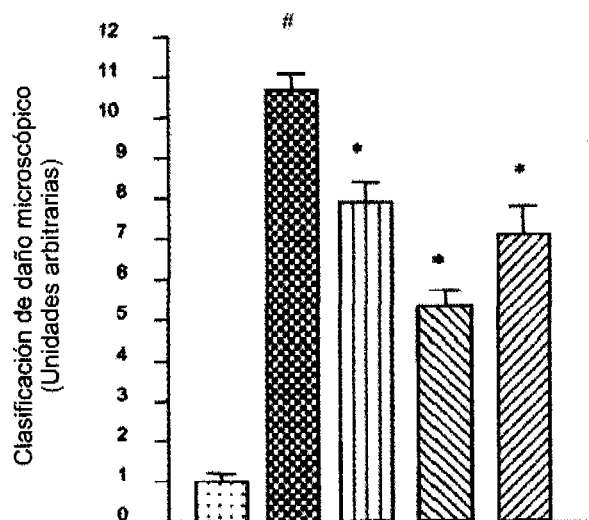
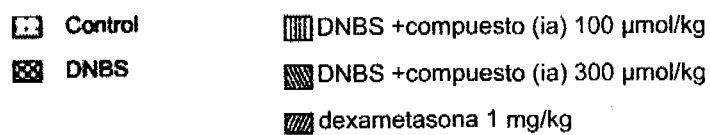
espesor máximo de intestino en mm se agrega a la clasificación final

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Clasificación de daño microscópico



* $p < 0.05$ vs DNBS

$p < 0.05$ vs control

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From the INTERNATIONAL BUREAU

PCT**NOTIFICATION OF THE RECORDING
OF A CHANGE**(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

LONGONI, Alessandra
Zambon S.p.A.
Patent Office
Via Lillo del Duca, 10
I-20091 Bresso
ITALIE

Date of mailing (day/month/year) 06 June 2007 (06.06.2007)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference F-410	
International application No. PCT/EP2006/060709	International filing date (day/month/year) 14 March 2006 (14.03.2006)

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address ZAMBON GROUP S.P.A. Via Della Chimica, 9 I-36100 Vicenza Italy	State of Nationality IT	State of Residence IT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person
 ☐ the name
 ☐ the address
 ☐ the nationality
 ☐ the residence

Name and Address ZAMBON S.P.A. Via Lillo del Duca, 10 I-20091 Bresso Italy	State of Nationality IT	State of Residence IT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The above change is to be recorded also in respect of the agent, as indicated in the addressee box at the top of this form.

4. A copy of this notification has been sent to:

☒ the receiving Office	☒ the designated Offices concerned
☐ the International Searching Authority	☐ the elected Offices concerned
☐ the International Preliminary Examining Authority	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Blanc Veronique
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	Telephone No. +41 22 338 96 66

36

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

LONGONI, Alessandra
ZAMBON GROUP S.P.A.
Intellectual Property Dept.
Via Lillo Del Duca, 10
I-20091 Bresso (MI)
ITALIE

Date of mailing (day/month/year) 29 June 2006 (29.06.2006)	
Applicant's or agent's file reference F-410	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/060709	International filing date (day/month/year) 14 March 2006 (14.03.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 21 March 2005 (21.03.2005)
Applicant ZAMBON GROUP S.P.A. et al	

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

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
21 March 2005 (21.03.2005)	05102244.0	EP	15 June 2006 (15.06.2006)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P-410	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2006/060709	International filing date (day/month/year) 14/03/2006	(Earliest) Priority Date (day/month/year) 21/03/2005
Applicant ZAMBON GROUP S.P.A.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060709

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/7048 A61P1/04 A61P35/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/075494 A (ZAMBON GROUP S.P.A; MEREU, ANDREA; NAPOLETANO, MAURO; ORNAGHI, FERNAND) 18 August 2005 (2005-08-18) page 15, line 18 claims; examples	1-6
X	WO 2004/013153 A (ZAMBON GROUP S.P.A; NAPOLETANO, MAURO; MORIGGI, ERMANNO; MEREU, ANDREA) 12 February 2004 (2004-02-12) cited in the application Compound RN: 654076-73-0 (compound (1a)) page 28, lines 3-13 examples claim 31	1-6
-/-		
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 19 July 2006		Date of mailing of the international search report 16/08/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Veronese, A

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/060709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/198677 A1 (MERCEP MLANDEN ET AL) 7 October 2004 (2004-10-07) claims; examples claim 45	1-6
Y	"The Merck Manual" 1999, MERCK RESEARCH LABORATORIES, USA, XP002391025 pages 302-312	1-6
Y	US 5 712 253 A (LARTEY ET AL) 27 January 1998 (1998-01-27) column 2, lines 31-45 column 2, lines 60-67 claims	1-6
A	US 2002/035075 A1 (BORODY THOMAS JULIUS) 21 March 2002 (2002-03-21) See claim 3: clarithromycin paragraphs [0001], [0002]; examples 1,4-8	1-6
A	WO 00/42055 A (ZAMBON GROUP S.P.A; PELLACINI, FRANCO; BOTTA, DANIELA; ROMAGNANO, STEF) 20 July 2000 (2000-07-20) the whole document	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/060709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005075494 A	18-08-2005	NONE	
WO 2004013153 A	12-02-2004	AU 2003269861 A1	23-02-2004
		BR 0313162 A	05-07-2005
		CA 2493995 A1	12-02-2004
		CN 1678620 A	05-10-2005
		EP 1529053 A2	11-05-2005
		HR 20050195 A2	31-12-2005
		JP 2005538998 T	22-12-2005
		US 2006058246 A1	16-03-2006
US 2004198677 A1	07-10-2004	BG 108073 A	31-05-2005
		BR 0206347 A	10-02-2004
		CA 2434009 A1	18-07-2002
		CN 1491230 A	21-04-2004
		CZ 20031825 A3	12-11-2003
		EE 200300293 A	15-10-2003
		EP 1351973 A1	15-10-2003
		WO 02055531 A1	18-07-2002
		HR 20010018 A2	31-12-2002
		JP 2004518670 T	24-06-2004
		PL 363478 A1	15-11-2004
		SK 9792003 A3	08-01-2004
US 5712253 A	27-01-1998	AT 236185 T	15-04-2003
		CA 2257361 A1	24-12-1997
		DE 69720551 D1	08-05-2003
		DE 69720551 T2	26-02-2004
		DK 1021456 T3	18-08-2003
		EP 1021456 A1	26-07-2000
		ES 2196331 T3	16-12-2003
		JP 2000512653 T	26-09-2000
		PT 1021456 T	29-08-2003
		WO 9748713 A1	24-12-1997
US 2002035075 A1	21-03-2002	NONE	
WO 0042055 A	20-07-2000	AT 308552 T	15-11-2005
		AU 769006 B2	15-01-2004
		AU 2663600 A	01-08-2000
		BR 0007514 A	20-11-2001
		CA 2368400 A1	20-07-2000
		CN 1336932 A	20-02-2002
		DE 60023647 D1	08-12-2005
		EP 1144427 A2	17-10-2001
		ES 2251966 T3	16-05-2006
		HU 0105105 A2	29-04-2002
		IT MI990061 A1	17-07-2000
		JP 2002534531 T	15-10-2002
		MX PA01007164 A	27-03-2002
		NO 20013517 A	16-07-2001
		RU 2243230 C2	27-12-2004
		SK 9812001 A3	07-01-2002
		US 6455576 B1	24-09-2002
		ZA 200105748 A	14-10-2002

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/060700

International filing date (day/month/year)
14.03.2006

Priority date (day/month/year)
21.03.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/7048 A61P1/04 A61P35/00

Applicant
ZAMBON GROUP S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 68.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Veronese, A

Telephone No. +49 89 2399-7824



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/060709

Rule No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.9(a) and 23.1 (b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/060709

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-6
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-6
Industrial applicability (IA)	Yes: Claims	1-6
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and/or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/060709

Re Item V

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

The documents listed below have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

- D1: WO 2005/075494 A (ZAMBON GROUP S.P.A) 18 August 2005
- D2: WO 2004/013153 A (ZAMBON GROUP S.P.A) 12 February 2004 cited in the application
- D3: US 2004/198677 A1 (MERCEP MLANDEN ET AL) 7 October 2004
- D4: "The Merck Manual" 1999, MERCK RESEARCH LABORATORIES, USA, XP002391025
- D5: US-A-5 712 253 (LARTEY ET AL) 27 January 1998
- D6: US 2002/035075 A1 (BORODY THOMAS JULIUS) 21 March 2002
- D7: WO 00/42055 A (ZAMBON GROUP S.P.A) 20 July 2000

Novelty

None of the documents retrieved in the search discloses the use of the claimed macrolide derivatives for the treatment of the diseases listed in the claims. In view of the prior art available, the claimed subject matter is new.

Note, the ISA has not considered D1 as prior art relevant for the establishment of novelty and inventive step, because the claimed subject matter validly claims priority from the earlier application N. EP05102244.

Inventive step

D2 is considered the closest prior art. This document discloses the relevant macrolide derivatives, their antiinflammatory activity, and their use for the treatment of inflammatory disorders. The specific diseases listed in claims 1-5 are however not explicitly mentioned. In view of this prior art, the problem underlying the present application can be seen as the provision of new therapeutic applications for the claimed macrolides.

As the applicant states in the description, the most commonly used medicaments for the

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/060709

treatment for inflammatory bowel disease are antiinflammatory agents (this is confirmed by D4, "The Merck Manual"). It is also known that patients affected by inflammatory diseases often develop colon cancer.

It would therefore be straightforward for a skilled person confronted with the underlying problem, to test the claimed macrolide derivatives as medicaments to treat the inflammatory disorders mentioned in the claims.

D3 and D5, which teach to use some macrolide derivatives related to the claimed ones to treat Crohn's disease and ulcerative colitis, provide additional pieces of information which would have prompted a skilled person to arrive at the claimed invention without the need of an inventive step.

For this reason, in the absence of any evidence that the claimed compounds produce a new unexpected technical effect the claimed subject matter may not be considered to involve an inventive step.

Re Item VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2005075494	18 August 2005	25 January 2005	29 January 2004

Re Item VII

It appears that figure 2 is not complete. (the table contains no data).

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PATENT COOPERATION TREATY

WO 2006/100195
PCT/EP2006/060709

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

LONGONI, Alessandra
Zambon S.p.A.
Patent Office
Via Lillo del Duca, 10
I-20091 Bresso
ITALIE

02 AGO. 2007

Date of mailing (day/month/year) 26 July 2007 (26.07.2007)		IMPORTANT NOTICE	
Applicant's or agent's file reference F-410			
International application No. PCT/EP2006/060709	International filing date (day/month/year) 14 March 2006 (14.03.2006)	Priority date (day/month/year) 21 March 2005 (21.03.2005)	
Applicant ZAMBON S.P.A. et al			

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
28 September 2006 (28.09.2006)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, SY, TM, US

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

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

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

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 24, SWITZERLAND	Authorized officer Ellen Moyse
Facsimile No. +41 22 338 82 70	e-mail: pt05.pct@wipo.int

Form PCT/IB/308(Second and Supplementary Notice) (January 2004)

PATENT COOPERATION TREATY

WO 2006/100195
PCT/EP2006/060709

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From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

LONGONI, Alessandra
ZAMBON GROUP S.P.A.
Intellectual Property Dept.
Via Lillo Del Duca, 10
I 20091 Drosco (MI)
ITALIE

- 6 NOV. 2006

mm

Date of mailing (day/month/year) 26 October 2006 (26.10.2006)		
Applicant's or agent's file reference F-410		IMPORTANT NOTICE
International application No. PCT/EP2006/060709	International filing date (day/month/year) 14 March 2006 (14.03.2006)	Priority date (day/month/year) 21 March 2005 (21.03.2005)
Applicant ZAMBON GROUP S P A et al		

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
28 September 2006 (28.09.2006)

CH

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

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, SE, TZ, UG, ZM

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse
Facsimile No. +41 22 338 82 70	e-mail: pt05@wipo.int

Form PCT/IB/308(First Notice) (January 2004)

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P. 908
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TRADUCCIÓN OFICIAL DEL ITALIANO AL ESPAÑOL DE LEGALIZACIÓN DE
FIRMAS Y APOSTILLE DE PODER DE "ZAMBON S.p.A." A DILIA MARIA
RODRÍGUEZ D'ALEMAN y CLAUDIA LUCIA CARO RAMÍREZ

PRIMERA DE CINCO PÁGINAS DEL DOCUMENTO:

- Dos columnas de texto, a la izquierda en español, a la derecha en inglés, sobre el poder en mención firmado.
- Sello circular de De Simona Daniela Di Silvano, Notaria en Bresso. Firma ilegible.

SEGUNDA DE CINCO PÁGINAS DEL DOCUMENTO, TEXTO EN ITALIANO:

REPERTORIO No. 23.058

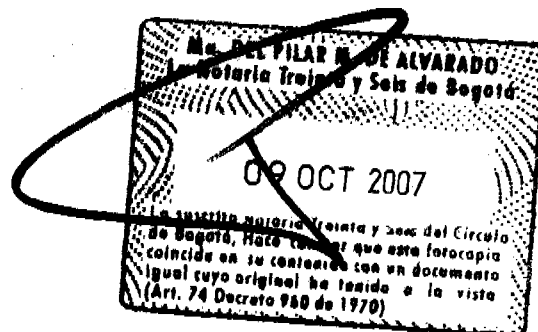
REPUBBLICA ITALIANA
AUTENTICACIÓN DE FIRMA

El veinte de junio de dos mil siete, en Bresso, en mi oficina,, yo, la suscrita
DANIELA DE SIMONE, Notaria inscrita en el registro de los Distritos Notariales
reunidos de Milán, Busto Arsizio, Lodi, Monza y Varese; residente en Bresso y
con oficina en la Via Vittorio Veneto N. 28,

CERTIFICO

Que se registró en mi presencia la anterior firma de:

Bandra Patricia Cardona Mejia
BANDRA PATRICIA CARDONA MEJIA
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0368 MINJUSTICIA 1997



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50

- PAOLA LUCIA CORNA PELLEGRINI SPANDRE, nacida en Brescia el 9 de octubre de 1958, en calidad de Directora General de la ZAMBON S.p.A., con sede en Bresso (Mi), en la Via Lillo del Duca No.10, domiciliada por su encargo en la sede social

De cuya identidad personal, calificación y poderes de firma yo notaria doy fe.

Firma ilegible y sello circular de: DE SIMONE DANIELA DI SILVANO - Notaria en Bresso.

- Estampilla oficial de €14,62

TERCERA DE CINCO PÁGINAS DEL DOCUMENTO:

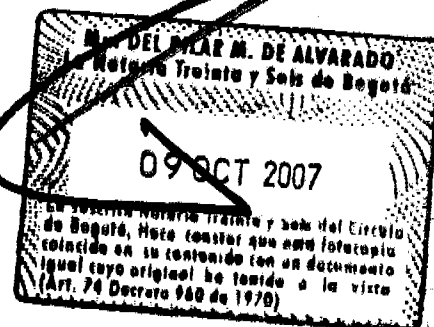
- Texto en Italiano del acta de cesión.
- Sello circular de De Simona Daniela Di Silvano, Notaria en Bresso. Firma ilegible.

CUARTA DE CINCO PÁGINAS DEL DOCUMENTO:

- Dos columnas de texto, a la izquierda en español, a la derecha en inglés, de certificado notarial.
- Sello circular de De Simona Daniela Di Silvano, Notaria en Bresso. Firma ilegible.

QUINTA DE CINCO PÁGINAS DEL DOCUMENTO, TEXTO EN ITALIANO:

Sandra Cardona
SANDRA PATRICIA CARDONA MEJIA
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0308 MINJUSTICIA 1997



50

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"APOSTILLE"

(Convención de la Haya del 5 de octubre de 1961)

1. PAIS: ITALIA

El presente acto público

2. Fue suscrito por: D. DE SIMONE

3. Agente en calidad de: NOTARIA EN BRESSO

4. Tiene el sello /timbre de: SELLO NOTARIAL

CERTIFICADO

5. En MILÁN 6. El: 8 de julio de 2007

7. Por la Oficina del Ministerio Publico

8. Bajo el número: 8600 AP

9. Sello /timbre: Sello de estado.

10. Firma: El Procurador Sustituto de la Republica, Dr. Isodoro Palma. Firma ilegible.

Sello circular: Procuraduría de la Republica – Tribunal Ordinario de Milán.

FIN DEL DOCUMENTO

Laudra Cordoba
SARDNA MARIA CORDONA MEJIA
TRADUCCION
PRETE OFICIAL
RESOLUCION 11000-1992

MINISTERIO DE
RELACIONES EXTERIORES
2007 AGO - 1 A 11:02
RECIBIDO

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO
879367
Sardna Cordoba

Ms. DEL PILAR M. DE ALVARADO
La Notaria Treinta y Seis del Circulo
de Bogotá, Hace constar que esta fotocopia
coincide en su contenido con un documento
igual cuyo original ha tenido a la vista
(Art. 74 Decreto 968 de 1970)
09 OCT 2007

57

P. 900 52

COLOMBIA
THE OFFICIAL
NOTARY

COLOMBIA

Carrera 11 N° 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 Fax: (57 1) 6350824 Email: info@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de
ZAMBON S.p.A.

una sociedad organizada y existente de acuerdo con las leyes de **Italia**

y en actual cumplimiento de su objeto social, con domicilio en
Via Lillo del Duca, 10 - 20091 BRESSO (Milano) - Italia

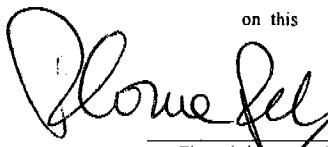
por el presente instrumento confiero (conferimos) poder especial a favor de **DILIA MARIA RODRIGUEZ D'ALEMAN**, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y **CLAUDIA LUCIA CARO RAMIREZ**, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos: **"Aparato para aerosol, en particular para niños"**

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
- 5) Registrar nombres de dominio ante la entidad competente.
- 6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.
- 7) Ratificar o no la agencia oficiosa.
- 8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los

días de


Firma / signature
ZAMBON S.p.A.

POWER OF ATTORNEY

I (we), the undersigned

legal representative(s) of
ZAMBON S.p.A.

an organization existing under the laws of **Italy**

and in present execution of its business activity, domiciled at
Via Lillo del Duca, 10 - 20091 BRESSO (Milan) - Italy

do hereby grant POWER OF ATTORNEY to **DILIA MARIA RODRIGUEZ D'ALEMAN**, identification card No. 41.654.882 of Bogotá, and tp. 20824 and **CLAUDIA LUCIA CARO RAMIREZ**, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

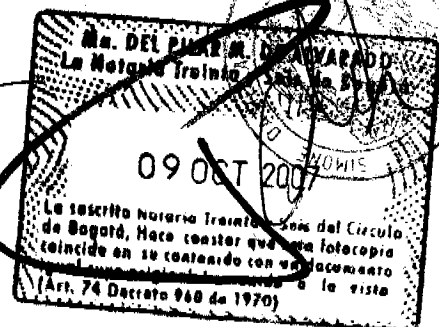
"Aerosol apparatus, in particular for children"

- 1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.
- 2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
- 3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.
- 4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above-mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
- 5) To register domain names before the competent entity.
- 6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.
- 7) To ratify or not the officious agency.
- 8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed at

on this

day of



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Repertorio n. 23.058

REPUBBLICA ITALIANA

Autentica di firma

Il ventuno giugno duemilasette, in Bresso e nel mio studio.

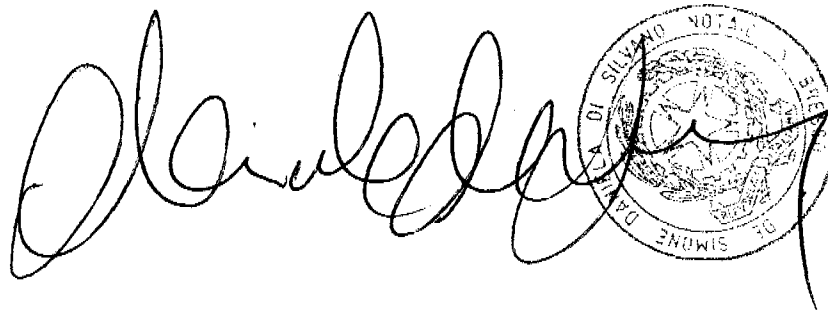
Io sottoscritta **DANIELA DE SIMONE**, notaio iscritto nel ruolo dei distretti notarili riuniti di Milano, Busto Arsizio, Lodi, Monza e Varese e residente in Bresso con studio alla Via Vittorio Veneto n.28,

certifico

che è stata apposta in mia presenza la precedente firma da:

- **Paola Lucia CORNA PELLEGRINI SPANDRE**, nata a Brescia il 9 ottobre 1958, in qualità di direttore generale della **ZAMBON S.p.A.**, con sede in Bresso (MI) alla Via Lillo Del Duca n.10, domiciliata per la carica presso la sede sociale.

Della identità personale qualifica e poteri della firmataria io notaio sono certo.



A large, stylized handwritten signature in black ink, likely belonging to Daniela De Simone, the notary.



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COLOMBIA

Carrera 11 N. 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 -- Fax (57 1) 6350824 -- Email: info@clarkemodex.com.co

PROCURA

Io (noi), sottoscritto/i

legale/i rappresentante/i di **ZAMBON S.p.A.**

una società organizzata ed esistente ai sensi della legge Italiana

e in presente esecuzione del suo oggetto sociale, con sede in

Via Lillo del Duca, 10 – 20091 BRESCO (Milano) – Italia

con il presente documento concedo/concediamo MANDATO a DILIA MARIA RODRIGUEZ D'ALEMAN, carta d'identità n. 41.654.882 di Bogotá, tp 20824, e CLAUDIA LUCIA CARO RAMIREZ, carta d'identità n. 40.017.374 di Tunja, tp 36448, residenti a Bogotá, Colombia, per rappresentare il concedente dinnanzi a qualsiasi autorità e/o persona fisica o giuridica, in particolare dinnanzi alle autorità amministrative, amministrative in materia di contenzioso, autorità giudiziarie, tribunali dell'arbitrato e/o qualsiasi altra autorità, in relazione a quanto segue:

"Apparecchiatura per aerosol, in particolare per bambini"

1) e a depositare, continuare, ottenere e/o registrare qualsiasi tipo di privativa, vale a dire: brevetti d'invenzione, modelli d'utilità, disegni industriali, varietà vegetali, marchi, slogan, nomi e insegne commerciali, emblemi e denominazioni d'origine nonché i rispettivi rinnovi, cessioni, cambi di nome e/o di domicilio, accordi e licenze.

2) e a depositare, continuare, ottenere e/o registrare diritti d'autore di qualsiasi tipo nonché la protezione di segreti industriali o know-how.

3) e a depositare, continuare, ottenere e/o registrare registrazioni sanitarie, autorizzazioni e/o licenze operative nonché i rispettivi rinnovi o cessioni, cambi di nome, e/o di domicilio, accordi e licenze.

4) e a presentare atti di opposizione, osservazioni, rilievi, reconsiderazioni, appelli, cancellazioni, azioni di nullità, per la difesa del consumatore, licenze, azioni per la protezione di segreti industriali e altre azioni ad esse collegate e contro la concorrenza sleale, azioni derivate dall'ottenimento o dallo sfruttamento di licenze, azioni per ottenere indennizzi. I mandatarî di cui sopra potranno altresì prendere parte a e intervenire in procedimenti di natura civile, penale, commerciale o contenzioso-amministrativo, in azioni di tutela, di polizia, cause o azioni legali promosse o subite dal concedente il presente mandato.

5) e a registrare nomi a dominio dinnanzi alle autorità competenti.

6) Ai sensi del presente mandato, i mandatarî sopra citati vengono investiti del potere di conciliare, cancellare, risolvere, sottoporre ad arbitrato, ritirare, ricevere e prendere possesso di ciò che funge da oggetto della controversia e di rinunciare ai diritti concessi o in corso di concessione, ammettere prove agli atti.

7) e a ratificare o non ratificare provvedimenti non ufficiali.

8) Io (noi) con la presente nomino/nominiamo i mandatarî sopra citati con potere di ricevere notificazioni e nominare legali per provvedimenti giudiziali e extragiudiziali, sostituire questo mandato e revocarne la sostituzione.

Redatto e firmato a

il

2007

Firma

ZAMBON S.p.A.

[Handwritten signature]

[Circular stamp: NOTARÍA TREINTA, BOGOTÁ]

09 OCT 2007

M. DEL ROSARIO DEL VALVARADO
La Notaría Treinta, Bogotá

El presente documento es copia de la original que se contiene con un documento igual que original ha tenido a la vista (Art. 74 Decreto 960 de 1970)

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CERTIFICADO NOTARIAL

(Cuando el solicitante es SOCIEDAD)

(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
firmó de su puño
y letra el documento que antecede.

2. Conoce al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.

3. El otorgante ha firmado el referido documento en su carácter de _____
de la persona jurídica _____

4. La citada persona jurídica con sede en _____ está legalmente constituida, que tiene actualmente existencia legal y que el acto para el cual se ha otorgado este poder está comprendido entre los que constituyen su objeto social.
5. El otorgante tiene efectivamente la representación que ostenta, que esta es legítima y que está facultado para otorgar este poder.
6. las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque he tenido a la vista los documentos auténticos.

Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

CERTIFICADO NOTARIAL (Cuando el solicitante es INDIVIDUO)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
firmó en su presencia
el documento que antecede, conoce al otorgante y que este está legalmente capacitado para el otorgamiento.

Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante quien se otorgue, debe expedir una certificación dejando constancia 1) de la existencia legal de la sociedad, 2) de que esta ejerce actualmente su objeto social, y 3) de que la persona o personas que otorgan el poder están facultadas para hacerlo, dejando constancia así mismo de que tuvo a la vista las pruebas que acrediten tales circunstancias.

LEGALIZACIÓN POR EL CONSUL DE COLOMBIA
O POR APOSTILLA

NOTARIAL CERTIFICATE

(When the applicant is a CORPORATION)

(Powers of attorney granted in: El Salvador, Mexico, U.S.A. and Venezuela)

This _____ day of _____
the undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the power of attorney)

of _____ legal _____ age _____ and _____ domiciled
in _____ set his hand on
the foregoing document.

2. The grantor is to him personally known and that he/she has legal capacity to execute the document.

3. The grantor has executed the foregoing document in his capacity of _____
of the juridical person _____

4. The mentioned juridical person with place of business in _____ is duly organized, has actual legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. The grantor has in fact the referred quality and that his/her representation is legal and that he/she is empowered to grant this power of attorney.

6. I have based the above certifications 3, 4 and 5, on the authentic documents which for such purpose were exhibited to me.

Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

NOTARIAL CERTIFICATE (When the applicant is an INDIVIDUALS)

On this _____ day of _____
the undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the Power of Attorney)

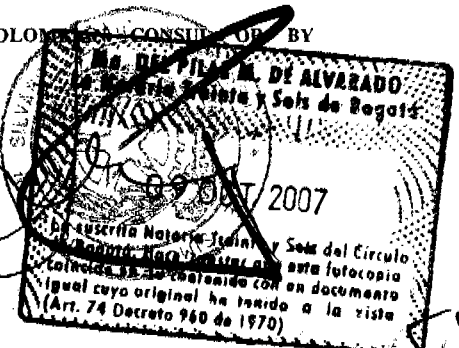
of legal age and domiciled at _____
signed in his presence the foregoing
document, the grantor is to him personally known and that he/she has legal capacity to execute the document.

Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

For all other countries the Colombian Consul or before who it is granted must issue a certification stating 1) the legal existence of the corporation, 2) that the corporate purposes are actually being accomplished, 3) that the person or persons who grant this Power of Attorney are empowered to do it. The Consul will certify also that the documents evidencing those circumstances were exhibited to him.

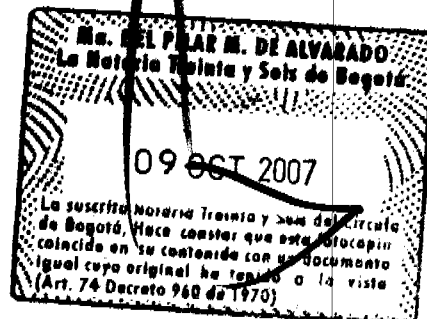
LEGALIZATION BY THE COLOMBIAN CONSUL OR BY
APOSTILLE.



8600 Af

D. De Simone
Notario en Bogotá
hij. de usario

8600 Af
hij. de 1. de f. b.



56
56

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-105847- -00000-0000

Fecha: 2007-10-09 16:10:28 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 55



Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐


Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia