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**FORMULARIO UNICO DE OPOSICION  
2000-12**

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**OPOSICION A:**

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| <input checked="" type="checkbox"/> Patente de Invención              | <input type="checkbox"/> Marca Colectiva        |
| <input type="checkbox"/> Patente de Modelo de Utilidad                | <input type="checkbox"/> Marca de Certificación |
| <input type="checkbox"/> Diseño Industrial                            | <input type="checkbox"/> Lema Comercial         |
| <input type="checkbox"/> Esquema de Trazado para Circuitos Integrados |                                                 |
| <input type="checkbox"/> Marcas de Productos o Servicios              |                                                 |

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**SOLICITUD  
PUBLICADA**

Número del expediente: 05-053-234

Solicitante: UCB FARCHIM S.A.

Apoderado: HÉCTOR GÓMEZ MEJÍA

Título de la nueva creación o denominación del signo:

**"USO DE LEVOCETIRICINA PARA EL TRATAMIENTO DE LA RINITIS  
ALÉRGICA PERSISTENTE."**

**GACETA No. 575 de 30 de Abril de 2007, N° de publicación: 1430**

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**OPOSICION PRESENTADA POR:**

**OPOSITOR**

Nombre: Lafranco S.A.

Dirección: Carrera 1 No. 46-84

Teléfono: (092) 449.30.51

Fax:

Domicilio: Cali - Valle

**IDENTIFICACION**

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Número: 890 301 463 -8

**REPRESENTANTE  
O APODERADO  
(74)**

Nombre: José Luis Reyes Villamizar

Dirección: Cra. 17 No. 88-23, Of. 205

Teléfono: 621.26.31

E-mail: info@reyes-abogados.com

Fax: 621.25.42

Domicilio: Bogotá, D.C.

**IDENTIFICACION**

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Número: 79'152.473 de Usaquén  
TP 44655

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**FUNDAMENTOS DE LA OPOSICION:**

**Causal:** Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16(las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 18 ( una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) 20-d (los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales) y 21.

**Justificación:** VER ANEXO

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Comprobante de pago No. 07-61-262 (Oposición) Fecha Julio 30 de 2007  
07-61-263 (Prórroga) Fecha Julio 30 de 2007

con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

## II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

## III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud en trámite 05-053-234, que reivindica el uso de la sal dihidrocloruro de levocetirizina en el tratamiento de la rinitis alérgica persistente, la rinorrea, la obstrucción nasal, la comezón nasal, el estornudo y el prurito ocular, con una dosis diaria de alrededor de 0.0005 mg a 2 mg de dicha sal por Kg de peso carece por completo de nivel inventivo, y aún de novedad, como se demuestra con los siguientes argumentos:

- Para cualquier persona medianamente versada en la materia es obvio que la formación de sales de los fármacos permite obtener cambios en la biodisponibilidad de los mismos, en especial en principios activos donde la previa disolución en fluidos acuosos (como en el caso del fluido gástrico) es un factor limitante en la posterior absorción de dicho fármaco. Así las cosas, no se puede pretender proteger mediante patente la formación de una sal como el dihidrocloruro de un fármaco, en este caso de la levocetirizina, pues como se mencionó anteriormente, la formación de sales de fármacos se encuentra reconocida con bastante anterioridad en el estado de la técnica, se emplea extendidamente en la industria farmacéutica y por lo tanto, no supone nivel inventivo de ninguna índole. (1)
- De otro lado, la solicitud en trámite pretende reivindicar de forma independiente (en distintas reivindicaciones) el empleo de la levocetirizina para tratar la rinitis alérgica, manifestada específicamente por la presencia de prurito, irritación nasal, estornudos, rinorrea, congestión nasal, picor en la garganta, ojos, oídos (2)

y edema alrededor de los ojos<sup>1</sup>. Con lo anterior en mente, es necesario anotar que el uso de antihistamínicos de segunda generación, grupo al que corresponde la levocetirizina, en el tratamiento de la sintomatología de la rinitis alérgica es conocido y ha sido ampliamente divulgado en la literatura científica, al igual que la característica distintiva del principio activo en cuestión, de no presentar los efectos adversos que en el sistema nervioso central pueden ocasionar los llamados fármacos de primera generación. De lo anterior dan cuenta las siguientes revelaciones bibliográficas:

- **EFFECT OF CETIRIZINE, LEVOCETIRIZINE, AND DEXTROCETIRIZINE ON HISTAMINE-INDUCED NASAL RESPONSE IN HEALTHY ADULT VOLUNTEERS<sup>2</sup>**

**Background:** Cetirizine, an effective H1-receptor antagonist, is a racemate mixture of two enantiomers: levocetirizine (R enantiomer) and dextrocetirizine (S enantiomer). **Methods:** To investigate the pharmacologic activity of the two enantiomers of cetirizine, we conducted a randomized, double-blind, four-way, crossover study to assess the effect of treatment with 5 mg levocetirizine, 5 mg dextrocetirizine, and 10 mg cetirizine and matched placebo, on histamine-induced changes in the nasal airways of 24 healthy volunteers. Four hours after a single oral intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold were calculated together with the absolute number of sneezes after each challenge. **Results:** Both levocetirizine and cetirizine significantly attenuated the histamine induced increase in nasal airway resistance by nearly 50% (from a median resistance of 2.51 Pa per cm<sup>3</sup>/s to 1.29 and 1.31 Pa per cm<sup>3</sup>/s, respectively) at the maximal concentration, and they concomitantly increased the histamine threshold by fourfold (from 8 to 32 mg/ml), compared with placebo. Sneezing was also attenuated by both levocetirizine and cetirizine. However, these antihistaminic effects were not seen with dextrocetirizine. **Conclusions:** This study shows a similar activity of levocetirizine and cetirizine on the inhibition of histamine-induced increase in nasal resistance, indicating that the antihistaminic properties of cetirizine are probably attributable to levocetirizine.

<sup>1</sup> Assessing and treating rhinitis. A practical guide for Canadian physicians. Can Med Assoc J 1994 151 (suppl):1-27 . <http://www.cma.ca/cpgs/rhinitis/>.

<sup>2</sup> Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. (eng; includes abstract) By Wang DY, Allergy [Allergy], 2001 Apr; Vol. 56 (4), pp. 339-43; PMID: 11284803

## • MANAGEMENT OF RHINITIS – THE SPECIALIST'S OPINION<sup>3</sup>.

### Summary

The aim of the guidelines in the International Consensus Report on the Diagnosis and Management of Rhinitis was to aid general practitioners (GPs) in the treatment of mild or moderate cases of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and non-allergic rhinitis. After the initial strategy of allergen avoidance, GPs have several medications at their disposal. For mild or occasional symptoms of SAR, an oral H<sub>1</sub>-antihistamine or topical antihistamines or chromones are advised. For moderate symptoms, a topical nasal steroid can be used with or without an oral H<sub>1</sub>-antihistamine supplemented if necessary with a topical antihistamine or chromone eyedrops. For PAR, patients should be advised on how to minimize their exposure to house-dust mite (HDM) allergens. For intermittent symptoms, an oral H<sub>1</sub>-antihistamine and an occasional oral decongestant can be used. For persistent symptoms, a topical nasal steroid is advised, possibly supplemented with an antihistamine. For non-allergic rhinitis, irritant factors should be identified and avoided if possible. Topical or oral decongestants can be used for intermittent symptoms. Topical ipratropium bromide is useful for drying up watery rhinorrhea. For moderate symptoms, either a topical nasal steroid or topical ipratropium bromide should be used. For all the conditions, if treatment proves ineffective and symptoms are severe, then a specialist referral is appropriate. Investigations are conducted to identify causative allergens. Further treatment options include immunotherapy and minimal invasive surgery. A large clinical study is ongoing to validate the guidelines and enable the development of simpler therapeutic options according to symptom severity. In the meantime, the current guidelines provide a valuable guide to both the GP and the specialist.

<sup>3</sup> Management of rhinitis—the specialist's opinion. By: Cauwenberge, P. Van. Clinical & Experimental Allergy, Dec98 Supplement 6, Vol. 28, p29, 5p; (AN 6103107)

• **DIAGNOSIS AND MANAGEMENT OF RHINITIS: COMPLETE GUIDELINES OF THE JOINT TASK FORCE ON PRACTICE PARAMETERS IN ALLERGY, ASTHMA AND IMMUNOLOGY<sup>4</sup>**

• This document contains complete guidelines for diagnosis and management of rhinitis developed by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council on Allergy, Asthma and Immunology. The guidelines are comprehensive and begin with statements on clinical characteristics and diagnosis of different forms of rhinitis (allergic, non-allergic, occupational rhinitis, hormonal rhinitis [pregnancy and hypothyroidism], drug-induced rhinitis, rhinitis from food ingestion), and other conditions that may be confused with rhinitis. Recommendations on patient evaluation discuss appropriate use of history, physical examination, and diagnostic testing, as well as unproven or inappropriate techniques that should not be used. Parameters on management include use of environmental control measures, pharmacologic therapy including recently introduced therapies and allergen immunotherapy. Because of the risks to patients and society from sedation and performance impairment caused by first generation antihistamines, second generation antihistamines that reduce or eliminate these side effects should usually be considered before first generation antihistamines for the treatment of allergic rhinitis. The document emphasizes the importance of rhinitis management for comorbid conditions (asthma, sinusitis, otitis media). Guidelines are also presented on special considerations in patients subsets (children, the elderly, pregnancy, athletes and patients with rhinitis medicamentosa); and when consultation with an allergist-immunologist should be considered.

Por si lo anterior no fuese suficiente para demostrar la carencia de Nivel Inventivo de la solicitud en curso, es necesario destacar el amplio conocimiento del uso de la levoceterizina en el tratamiento de la sintomatología de la rinitis alérgica, de conformidad con las revelaciones incluidas en los siguientes documentos:

- La publicación internacional WO 94/006429 publicada el 31 de Marzo de 1994 y titulada "COMPOSITIONS FOR TREATING ALLERGIC DISORDERS USING (-) CETIRIZINE." Revela:

<sup>4</sup> Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Mark S Dykewicz, MD,† Stanley Fineman, MD, MBA,§ Editors David P Skoner, MD, Chair, Workgroup on Rhinitis Richard Nicklas, MD; Rufus Lee, MD; Joann Blessing-Moore, MD; James T Li, MD, PhD\*; I Leonard Bernstein, MD††; William Berger, MD, MBA‡‡; Sheldon Spector, MD§§; and Diane Schuller, MD,\\ Associate Editors. Ann Allergy Asthma Immunol 1998;81:478-518.

## (57) Abstract

Methods and compositions are disclosed utilizing optically pure (-) cetirizine for the treatment of seasonal and perennial allergic rhinitis in humans while avoiding the concomitant liability of adverse effects associated with the racemic mixture of cetirizine. The optically pure (-) isomer is also useful for the treatment of allergic asthma and chronic and physical urticaria. (-) Cetirizine is an inhibitor of eosinophil chemotaxis and is therefore useful in the treatment of other conditions related to eosinophilia such as allergic asthma, seasonal allergic rhinitis, atopic dermatitis, some parasitic diseases, some chronic obstructive lung diseases and certain gastrointestinal and genitourinary disorders.

(...)

Racemic cetirizine dihydrochloride is an orally active, potent, long acting peripheral histamine  $H_1$  receptor antagonist. The compound is one of the second generation of  $H_1$  histamine receptor antagonists which generally offer some significant advantages beyond the first generation compounds. The advantages include (1) less sedation, (2) little anticholinergic activity and (3) longer duration, which improves patient compliance. In addition to being competitive inhibitors of histamine at the end organ site, second generation  $H_1$  histamine inhibitors appear to have other anti-allergic pharmacologic mechanisms which have led to their use in bronchial asthma, as well as in seasonal and perennial rhinitis and the chronic urticarias.

(...)

The present invention encompasses a method of treating the symptoms of seasonal and perennial allergic rhinitis in a human, which comprises administering to a human in need of such symptomatic relief therapy, an amount of (-) cetirizine, or a pharmaceutically acceptable salt thereof,

(...)

The term "treating the symptoms of seasonal and perennial rhinitis" as used herein means treating, alleviating or palliating such conditions, and thus providing relief from the symptoms of sneezing, rhinorrhea, nasal congestion, pruritus, conjunctivitis, pharyngitis, lacrimation, frontal headaches, irritability, anorexia, depression, insomnia, eustachian tube obstruction, and the like.

(...)

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like.

(...)

De la misma manera, en el capítulo reivindicatorio de la solicitud internacional en mención se describe:

1. A method of treating the symptoms of seasonal and perennial allergic rhinitis in a human which comprises administering to a human in need of such symptomatic relief therapy an amount of (-) cetirizine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate or palliate said allergic rhinitis.

5. The method of claim 4 wherein the amount administered is from about 2 mg to about 20 mg per day.

9. The method according to claim 2, wherein (-) cetirizine is administered as a hydrochloride salt.

11. An antirhinitis pharmaceutical composition for the treatment of a human in need of rhinitis therapy which comprises an amount of (-) cetirizine or a pharmaceutically acceptable salt

Como puede verse, la anterioridad en mención revela por lo menos desde 1994 absolutamente toda la materia que se reivindica en la solicitud colombiana en trámite, específicamente en lo referido al tratamiento de la sintomatología de la rinitis, formas farmacéuticas que contienen levocetirizina o (-) cetirizina o sus sales farmacéuticamente aceptables entre las que se prefiere la sal clorhidrato y el régimen de dosificación diario del medicamento, tal como se encuentra contenido en el capítulo reivindicatorio de la misma, circunstancia que demuestra la falta de nivel inventivo, y aún de novedad, de la solicitud 05-053-234.

- Por último, y si estuviéramos ante la ausencia de una revelación textual del uso de Levocetirizina en la rinitis alérgica persistente, es necesario resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso se encuentra dirigido al uso de una composición, lo cual es inaceptable a la luz de la Decisión 486.

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En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial.

Aunque a la ausencia de ellos nos hemos referido ya, cabe desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la *reproducción industrial* del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

#### IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18, 20-d y 21 (Requisitos de Patentabilidad e improcedencia de patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

#### V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

## Short communication

# Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers

**Background:** Cetirizine, an effective  $H_1$ -receptor antagonist, is a racemate mixture of two enantiomers: levocetirizine (*R* enantiomer) and dextrocetirizine (*S* enantiomer).

**Methods:** To investigate the pharmacologic activity of the two enantiomers of cetirizine, we conducted a randomized, double-blind, four-way, crossover study to assess the effect of treatment with 5 mg levocetirizine, 5 mg dextrocetirizine, and 10 mg cetirizine and matched placebo, on histamine-induced changes in the nasal airways of 24 healthy volunteers. Four hours after a single oral intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold were calculated together with the absolute number of sneezes after each challenge.

**Results:** Both levocetirizine and cetirizine significantly attenuated the histamine-induced increase in nasal airway resistance by nearly 50% (from a median resistance of 2.51 Pa per  $\text{cm}^3/\text{s}$  to 1.29 and 1.31 Pa per  $\text{cm}^3/\text{s}$ , respectively) at the maximal concentration, and they concomitantly increased the histamine threshold by fourfold (from 8 to 32 mg/ml), compared with placebo. Sneezing was also attenuated by both levocetirizine and cetirizine. However, these antihistaminic effects were not seen with dextrocetirizine.

**Conclusions:** This study shows a similar activity of levocetirizine and cetirizine on the inhibition of histamine-induced increase in nasal resistance, indicating that the antihistaminic properties of cetirizine are probably attributable to levocetirizine.

D. Y. Wang<sup>1</sup>, F. Hanotte<sup>2</sup>,  
C. De Vos<sup>2</sup>, P. Clement<sup>3</sup>

<sup>1</sup>National University of Singapore, Singapore; <sup>2</sup>UCB Pharma, Brussels, Belgium; <sup>3</sup>Academisch Ziekenhuis, ENT Department, Vrije Universiteit Brussel, Brussels, Belgium

Key words: cetirizine; dextrocetirizine; histamine threshold; levocetirizine; nasal resistance.

Christine De Vos, PhD  
UCB Pharma  
Allée de la Recherche 60  
B-1070 Brussels  
Belgium

Accepted for publication 23 November 2000

The role of histamine has been well documented in the pathophysiology of allergic airway diseases (1–3). An increased understanding, over the last few decades, of the pathogenic role of histamine in allergic diseases has been associated with the development of specific and highly efficacious  $H_1$ -receptor antagonists for symptomatic relief of allergic disease, particularly seasonal and perennial allergic rhinitis and urticaria (4–6). The  $H_1$ -receptor antagonists, generally called antihistamines, have broadly been classed into two categories, the first- and second-generation antihistamines. The first-generation antihistamines have been associated with central nervous system and anticholinergic side-effects, particularly sedation and impaired psychomotor activity (7), and are therefore not much used currently. In contrast, the newer second-generation antihistamines, such as cetirizine, loratadine, and fexofenadine, exhibit fewer sedative and anticholinergic effects and have a rapid onset of action, making them ideal for symptomatic relief of the allergic disease.

Controlled trials in patients with seasonal and perennial rhinitis have demonstrated that cetirizine is effective in attenuating nasal and/or ocular symptoms resulting from experimental or natural allergen exposure (8–11). However, cetirizine is a racemate mixture of two enantiomers: levocetirizine (*R* enantiomer) and dextrocetirizine (*S* enantiomer). The aim of this study was to investigate the activity of these two enantiomers on histamine-induced changes in nasal resistance and sneezing in healthy volunteers, and then to compare these effects with those of cetirizine and placebo.

## Material and methods

### Subjects

Twenty-eight healthy nonallergic volunteers were enrolled in this study. Of them, 24 subjects (nine males and 15 females) aged 20–38 years (mean age 29 years) completed the study. They were symptom-free and had normal findings on routine hematologic and biochemical blood test parameters. None of the volunteers smoked

more than five cigarettes a day or had a history of allergy or hypersensitivity to piperazines. They did not take any medication, except oral contraceptives during the 2 weeks preceding enrollment. All volunteers gave written informed consent prior to the study. This study was approved by the ethics committee of the university hospital, Free University of Brussels (Academisch Ziekenhuis, Vrije Universiteit Brussel), Belgium.

# Study design

This was a randomized, double-blind, placebo-controlled, four-way, crossover study. Each volunteer was entered into a randomized schedule to receive a single dose of 5 mg levocetirizine, 5 mg dextrocetirizine, 10 mg cetirizine, and matched placebo. Four hours after each intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal airway resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold (concentration that induces 100% increase in unilateral nasal resistance at the baseline) were calculated together with the absolute number of sneezes after each challenge.

To minimize the influence of the existing conditions of nasal obstruction and nasal hyperresponsiveness to the control solution, a standardized protocol for PAR and histamine challenge was maintained throughout all visits (12, 13). An inclusion criterion was applied to all volunteers who had a baseline nasal airway resistance of  $<2.8$  Pa per  $\text{cm}^3/\text{s}$  that did not increase by more than 30% from baseline value after application of the control solution. Nasal challenges with control solution and increasing doubling concentrations of histamine were then performed. Volunteers who demonstrated a 100% increase in nasal resistance at histamine concentrations of  $<8$  mg/ml were randomized to receive the study medication. In our experience, most healthy volunteers are eligible by this criterion. If the volunteers were disqualified by this criterion at any treatment visit, they were withdrawn from this study.

Volunteers were assessed for general well-being and any adverse

events before and after nasal provocation, and, all being well, they were given appointments to attend the clinic for the next visit after a washout period of 7–14 days.

# Measurement of nasal resistance

Nasal resistance was measured by PAR (Heyer, Bad Ems, Germany), as previously described (14). Briefly, a fixed airflow of  $250 \text{ cm}^3/\text{s}$  was blown through a nozzle into one nostril. The pressure induced by the nasal airway resistance to this airflow at a given level of the nozzle was measured. The measurements were expressed in Pa per  $\text{cm}^3/\text{s}$ , as recommended by the International Committee on Standardization of Rhinomanometry (15). In this study, nasal airway resistance was measured in each nostril 1 min and 5 min after each challenge, and the mean value of the two time measurements was calculated. The higher value of mean resistance from one of the nostrils was subsequently used in the final efficacy analysis.

# Histamine nasal provocation test

Histamine solutions of 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mg/ml were purchased (from HALAB Allergy Service, Brussels, Belgium) and equilibrated at  $30^\circ\text{C}$ . The control solution (diluent of histamine solution) was composed of  $\epsilon$ -aminocaproic acid (EACA; 13.1 mg), disodium phosphate (9.1 mg), sodium phosphate (1.2 mg), human serum albumin (HSA; 0.3 mg), and phenol (5 mg) in 1.0 ml water for injection.

Nasal provocation was carried out by nasal aerosol application with a Heyer nebulizer (Heyer, Bad Ems, Germany) (12, 13). The nebulizer contained the challenge solution and was aerosolized for introduction into the volunteer's nostrils through a nozzle. The nasal mucosa was consecutively provoked six times for 10 s (three times for each nostril alternately), with the study subject being in complete apnea after a full inspiration, in order to prevent the provocation solution from entering the bronchial tree. The same challenging procedures with increasing concentrations of histamine were

Table 1. Comparison of effect of treatment for 4 h with 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine compared with placebo on histamine-induced changes in nasal airway resistance (unit = Pa per  $\text{cm}^3/\text{s}$ ;  $n=24$  healthy volunteers)

| Histamine concentration (mg/ml) | Nasal airway resistance Pa per $\text{cm}^3/\text{s}$ |                     |                         |                           | Friedman test <sup>1</sup> <i>P</i> |
|---------------------------------|-------------------------------------------------------|---------------------|-------------------------|---------------------------|-------------------------------------|
|                                 | Placebo (median)                                      | Cetirizine (median) | Levocetirizine (median) | Dextrocetirizine (median) |                                     |
| 1                               | 0.78                                                  | 0.79                | 0.76                    | 0.84                      | 0.831                               |
| 2                               | 0.94                                                  | 0.83                | 0.83                    | 0.94                      | 0.099                               |
| 4                               | 1.12                                                  | 0.88                | 0.87                    | 1.12                      | 0.047                               |
|                                 | + <sup>(2)</sup>                                      |                     |                         |                           |                                     |
| 8                               | 1.44                                                  | 1.01                | 1.11                    | 1.26                      | 0.031                               |
|                                 | .                                                     |                     |                         |                           |                                     |
| 16                              | 1.82                                                  | 1.14                | 1.17                    | 1.36                      | 0.002                               |
|                                 | ***                                                   |                     |                         |                           |                                     |
|                                 | ..                                                    |                     |                         |                           |                                     |
|                                 | .                                                     |                     |                         |                           |                                     |
| 32                              | 2.51                                                  | 1.31                | 1.29                    | 2.06                      | 0.002                               |
|                                 | **                                                    |                     |                         |                           |                                     |
|                                 | ..                                                    |                     |                         |                           |                                     |
|                                 | .                                                     |                     |                         |                           |                                     |

<sup>1</sup>Global evaluation with Friedman test.

<sup>2</sup>When global evaluation was statistically significant ( $P<0.05$ ), two-by-two comparison of treatment was done. Only comparisons with  $P\leq 0.10$  are mentioned in tables.

\*  $0.05 < P < 0.10$

\*\*  $0.025 < P < 0.05$

\*\*\*  $0.01 < P < 0.025$

\*\*\*\*  $0.001 < P < 0.01$ .

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## Antihistaminic properties of levocetirizine

Table 2. Comparison of effect of treatment for 4 h with 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine compared with placebo on histamine threshold concentration, based on frequency of volunteers demonstrating 100% increase in mean nasal resistance ( $n=24$  healthy volunteers)

| Histamine threshold concentration (mg/ml)   | Number of volunteers |            |                |                  |
|---------------------------------------------|----------------------|------------|----------------|------------------|
|                                             | Placebo              | Cetirizine | Levocetirizine | Dextrocetirizine |
| 0.5                                         | 0                    | 1          | 0              | 1                |
| 1                                           | 1                    | 0          | 2              | 3                |
| 2                                           | 6                    | 1          | 0              | 2                |
| 4                                           | 4                    | 0          | 1              | 1                |
| 8                                           | 5                    | 5          | 2              | 6                |
| 16                                          | 1                    | 2          | 3              | 2                |
| 32                                          | 5                    | 5          | 5              | 5                |
| >32                                         | 2                    | 10         | 11             | 4                |
| Median of histamine threshold concentration | 8                    | 32         | 32             | 8                |

### Results of comparisons

Statistics were done on difference between logarithms (in base 2) of threshold concentration between each pair of treatments. For these calculations, threshold of >32 was replaced by 64 mg/ml.

### Friedman test

Global evaluation  $P=0.001$

### Two-by-two comparisons

Levocetirizine vs dextrocetirizine  $0.025 < P \leq 0.05$

Levocetirizine vs cetirizine  $P > 0.10$

Levocetirizine vs placebo  $0.01 < P \leq 0.025$

Dextrocetirizine vs cetirizine  $0.05 < P \leq 0.10$

Dextrocetirizine vs placebo  $P > 0.10$

Cetirizine vs placebo  $0.025 < P \leq 0.05$

performed, allowing an interval of 1 min after the last PAR measurement (which was 5 min after the beginning of the previous histamine administration).

### Statistical analysis

The sample size was estimated by a power calculation done on the basis of a previous study (data on file). On this basis, it was estimated that, after treatment with active drug, at least 24 volunteers were required to detect a significant doubling in histamine threshold at 90% power level with an alpha error of 5%; consequently, 28 eligible individuals were recruited into the study to allow for dropouts.

All data were expressed as median values, and the overall significance of changes in histamine threshold, nasal resistance, and the number of sneezes resulting from any treatment was assessed by the Friedman test. Multiple comparisons between all pair treatments were performed with the normal approximation of the multiple comparison procedure based on the Friedman rank sums test (16). All statistical tests were performed with the SAS® statistical package (Version 6.08) on an IBM-compatible microcomputer. Two-sided tests were used, and values of  $P < 0.05$  were regarded as significant.

### Results

Of the 28 volunteers recruited into the study, results for four subjects were not included in the overall efficacy analysis. One subject suffered from an episode of bronchitis after visit 4 and prior to receiving the last treatment at visit 5, and therefore did not complete the entire study protocol. The other three subjects, despite the fact that they were eligible, failed to react to histamine, showing a histamine threshold concentration of >32 mg/ml at every treatment visit. Their results were therefore considered to be not evaluable, and these volunteers were replaced.

### Effect of treatment on nasal resistance

Measurement of nasal airway resistance under placebo demonstrated that this was increased by histamine administration in a dose-dependent manner (Table 1). Treatment with both cetirizine and levocetirizine significantly attenuated the histamine-induced increases in nasal airway resistance at the maximal concentration of 32 mg/ml with almost 50% reduction over placebo (Table 1). Both cetirizine and levocetirizine were found to attenuate significantly the effects of histamine at concentrations of  $\geq 8$  and  $\geq 16$  mg/ml, respectively. In contrast, treatment with dextrocetirizine did not show any significant effect on histamine-induced increase in nasal airway resistance as compared to placebo.

### Effect of treatment on histamine threshold concentration

After treatment with placebo, 16/24 (67%) subjects demonstrated a histamine threshold concentration of  $\leq 8$  mg/ml. Treatment with cetirizine, levocetirizine, and dextrocetirizine decreased the number of subjects demonstrating a histamine threshold concentration of  $\leq 8$  mg/ml to 7/24 (29%), 5/24 (21%), and 13/24 (54%), respectively. The histamine threshold concentration was significantly increased fourfold from a median value of 8 mg/ml after treatment with placebo to a median value of 32 mg/ml after treatment with cetirizine ( $P < 0.05$ ) or levocetirizine ( $P < 0.025$ ) (Table 2). In contrast, dextrocetirizine was not found to alter significantly the histamine threshold concentration as compared to placebo, as the number of subjects with a threshold concentration below 8 mg/ml was 13 out of 24. Levocetirizine was found to be significantly

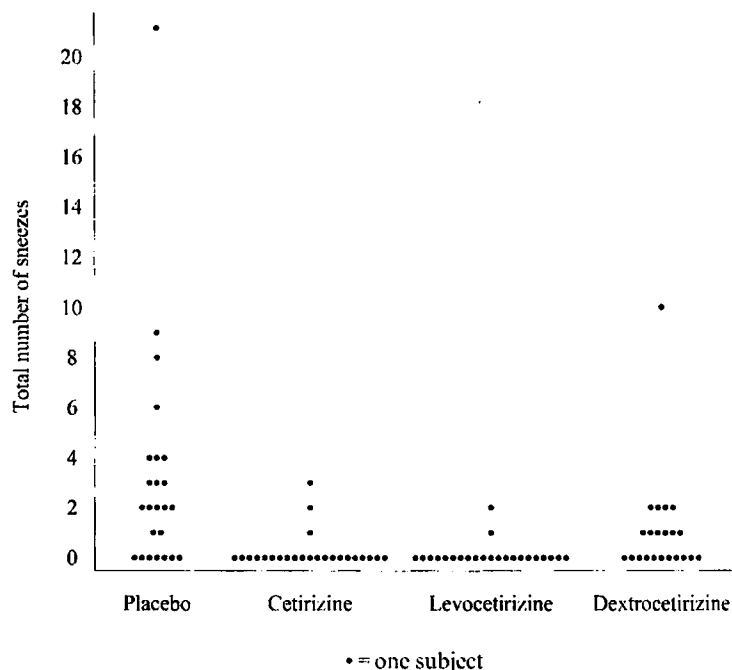


Figure 1. Effect of treatment for 4 h with placebo, 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine on histamine-induced sneezes.

( $P < 0.05$ ) more effective than dextrocetirizine in increasing the histamine threshold concentration. A comparison between cetirizine and levocetirizine, however, did not show a significant difference between them (Table 2).

#### Effect of treatment on sneezing

Fig. 1 shows the effect of individual treatment on the number of sneezes induced by histamine challenge. Treatment with either cetirizine or levocetirizine significantly ( $P < 0.01$ ) reduced histamine-induced sneezes, but not treatment with dextrocetirizine as compared to placebo ( $P > 0.10$ ).

#### Evaluation of safety

There was no special report on health-related problems or discomfort (i.e., drowsiness, fatigue, and dry mouth) caused by study medications among the volunteers. Only one subject reported an adverse event of bronchitis, which occurred 8 days after treatment with levocetirizine and was not judged to be a direct result of the study drug. However, this was a single-dose study, and the volunteers were interviewed 4 h after each intake of the study medication.

#### Discussion

In this study, levocetirizine 5 mg and cetirizine 10 mg appeared to be comparable in their antihistaminic activity. They significantly attenuated histamine-

induced increases in nasal airway resistance by almost 50% over placebo at the maximal concentration of 32 mg/ml. Concomitantly, the histamine threshold concentration was increased fourfold from 8 to 32 mg/ml. The number of sneezes induced by histamine nasal provocation was also significantly decreased by treatment with cetirizine or levocetirizine. In contrast, treatment with dextrocetirizine did not show a similar 'protective' effect as compared to placebo.

Our findings are in accordance with the findings of several studies investigating the effects of cetirizine in patients with seasonal and perennial allergic rhinitis. Frossard et al. have recently conducted two studies to investigate the effects of treatment with 10 mg cetirizine on changes in the nasal airway resistance of asymptomatic seasonal allergic rhinitis challenged with increasing doubling doses of histamine (17, 18). These authors showed that cetirizine significantly attenuated histamine-induced increases in nasal airway resistance (NAR) only 1.5 h after administration (17), and that these effects were prevalent even 24 h after treatment (18), when compared with placebo.

This is the first study to investigate the specific effects of each enantiomer of cetirizine on the histamine-induced nasal response. In view of the similarity of the antihistaminic effects observed for cetirizine and levocetirizine and the lack of any significant effects for dextrocetirizine in this study, it is likely that the effects of cetirizine in the management of allergic rhinitis are due to levocetirizine. Since cetirizine is composed of equal quantities of the two enantiomers, our study suggests that

preparations of levocetirizine at a dose of 5 mg may be useful in the management of seasonal and perennial allergic rhinitis in the future. In addition to its antihistaminic property, levocetirizine at the single dose of 5 mg was well tolerated by the volunteers, who did not suffer from any side-effects in this study.

In conclusion, this study demonstrates that the antihistaminic properties noted for cetirizine in the management of seasonal and perennial allergic rhinitis are probably due to the levocetirizine enantiomer.

Further studies are required to substantiate these findings in patients with ongoing seasonal and perennial allergic rhinitis.

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## Management of rhinitis – the specialist's opinion

P. VAN CAUWENBERGE

*Department of Otorhinolaryngology, University Hospital, Ghent, Belgium*

### Summary

The aim of the guidelines in the International Consensus Report on the Diagnosis and Management of Rhinitis was to aid general practitioners (GPs) in the treatment of mild or moderate cases of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and non-allergic rhinitis. After the initial strategy of allergen avoidance, GPs have several medications at their disposal. For mild or occasional symptoms of SAR, an oral  $H_1$ -antihistamine or topical antihistamines or cromones are advised. For moderate symptoms, a topical nasal steroid can be used with or without an oral  $H_1$ -antihistamine supplemented if necessary with a topical antihistamine or cromone eyedrops. For PAR, patients should be advised on how to minimize their exposure to house-dust mite (HDM) allergens. For intermittent symptoms, an oral  $H_1$ -antihistamine and an occasional oral decongestant can be used. For persistent symptoms, a topical nasal steroid is advised, possibly supplemented with an antihistamine. For non-allergic rhinitis, irritant factors should be identified and avoided if possible. Topical or oral decongestants can be used for intermittent symptoms. Topical ipratropium bromide is useful for drying up watery rhinorrhoea. For moderate symptoms, either a topical nasal steroid or topical ipratropium bromide should be used. For all the conditions, if treatment proves ineffective and symptoms are severe, then a specialist referral is appropriate. Investigations are conducted to identify causative allergens. Further treatment options include immunotherapy and minimal invasive surgery. A large clinical study is ongoing to validate the guidelines and enable the development of simpler therapeutic options according to symptom severity. In the meantime, the current guidelines provide a valuable guide to both the GP and the specialist.

**Keywords:** allergy, GPs, guidelines, rhinitis, specialist referral, symptom severity, treatment options.

### Introduction

The guidelines for the treatment of allergic rhinitis, published in the International Consensus Report on the Diagnosis and Management of Rhinitis [1], covered mild and moderate cases of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and perennial non-allergic rhinitis. The aim of the guidelines was to provide GPs with a simple and practical stepwise approach to the treatment of allergic and non-allergic rhinitis in patients not requiring a referral to a specialist. These guidelines were produced because the high prevalence of allergy in the population would make impractical the referral of all allergic patients to specialists. Also, instances of allergic and non-allergic rhinitis are

usually not severe and respond well to conventional medical treatment.

### Pharmacotherapy options

After the initial strategy of allergen avoidance, GPs have several medications at their disposal for the management of both allergic and non-allergic rhinitis: oral or topical antihistamines; cromones for the eye and nose; topical nasal steroids; topical and oral decongestants; and ipratropium bromide.

The guidelines present a logical approach to implementation of these different treatment regimens for mild or moderate cases of SAR, PAR and non-allergic rhinitis. If treatment proves ineffective, and the condition is considered severe, then specialist referral is appropriate – either to an ear, nose and throat (ENT) specialist or to an allergologist.

*Correspondence:* Professor P. van Cauwenberge, University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.

### Seasonal allergic rhinitis

All patients with SAR should be instructed to avoid exposure to pollen allergens on peak-pollen days; pollen forecasts should be monitored and high-pollen areas avoided. Staying inside with doors and windows closed may be necessary. If SAR causes only mild or occasional symptoms, an oral non-sedating  $H_1$  antihistamine with rapid onset can be taken as and when symptoms occur, or alternatively antihistamines or cromones may be topically applied to the nose and/or eyes (Fig. 1).

Moderate symptoms – especially those affecting predominantly the nose – should be treated with a topical nasal steroid, with the course of treatment starting early and continuing until the end of the pollen season. This treatment may be supplemented with antihistamines or cromones applied topically to the eyes as required. Moderate symptoms – affecting most prominently the eyes – may be treated with an oral non-sedating  $H_1$  antihistamine (as these are indicated for both the nose and eyes), or with a topical nasal steroid plus a topical antihistamine or cromone in the eyes if necessary. If these are unsuccessful and the condition is considered severe, then specialist referral is necessary.

Specialists may continue with the same treatment as for moderate symptoms, otherwise treatment may consist of short-term systemic steroids, specific immunotherapy, or symptomatic treatment with decongestants and analgesics.

Innumerable clinical trials have underpinned the use of these therapeutic regimens in SAR, however, some important recent trials should be mentioned as they

provide strong supportive evidence for the use of these regimens. Łozewicz *et al.* [2] investigated the effects of nedocromil sodium compared with placebo on the number of mast cells in the nasal mucosa after natural exposure to allergen during the pollen season from March to July. They showed that over this time period, mast cell numbers increased significantly in patients receiving placebo ( $P < 0.02$ ), while the nedocromil sodium group showed no change. At the end of the time period, mast cell numbers were significantly higher ( $P < 0.01$ ) in the placebo group compared with the nedocromil sodium group, showing the positive effect of nedocromil sodium.

One double-blind study compared a topical steroid, triamcinolone acetonide aqueous nasal spray 220 µg/day, with oral antihistamine, loratadine 10 mg/day, over a 4-week period [3]. Both treatments were active against SAR but the 'mean change in symptom score from baseline to endpoint' was significantly greater with triamcinolone acetonide for stuffiness and itching ( $P < 0.05$  for both); for sneezing ( $P < 0.01$ ); and for total nasal score ( $P < 0.01$ ). Triamcinolone acetonide was shown to be effective within 34 h and its efficacy increased over the following 4 days [4].

As well as their effects on clinical symptoms, topical steroids have also been shown to have an effect on antigen-presenting Langerhans' cells (CD1a<sup>+</sup> cells). When fluticasone propionate was given for 3 months, the number of CD1a<sup>+</sup> cells in the nasal mucosal epithelium decreased to almost zero, compared with the placebo group where cell numbers had increased [5].

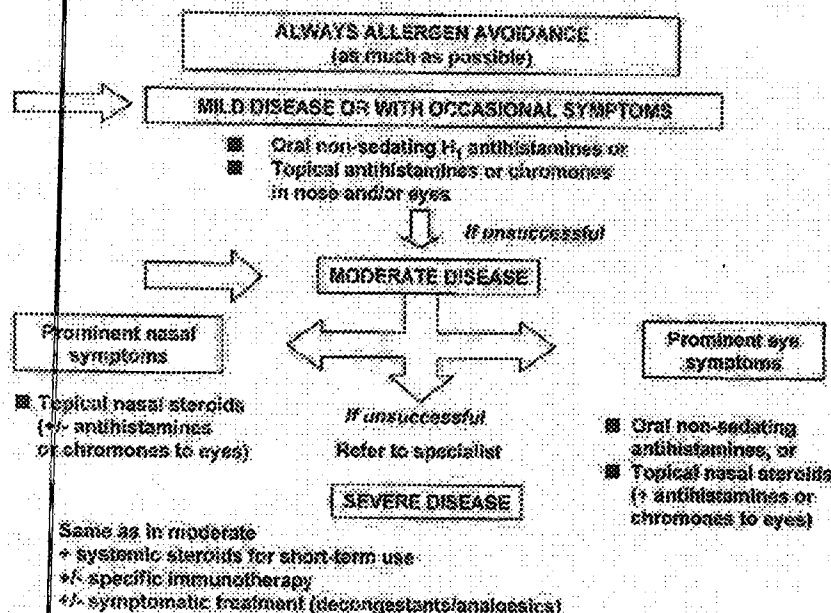


Fig. 1. Stepwise approach to the treatment of seasonal allergic rhinitis.

### Perennial allergic rhinitis in adults

The treatment of PAR commences with allergen avoidance (Fig. 2). The patient should be instructed in detail in house-dust mite (HDM) avoidance. Allergen-impermeable covers should be used on mattresses, duvets and pillows, and where possible, synthetic materials should be used in preference to down, wool or feathers. Attention must be paid to vacuuming items of bedding, carpets, soft furnishings and curtains and washing these items frequently where appropriate. Bedrooms should be damp-dusted weekly. It is usually helpful to provide patients with detailed written information; patient information leaflets are widely available for this purpose. Such guidance, in most instances, reduces the level of required pharmacological treatment.

If PAR causes only intermittent symptoms, an oral non-sedating  $H_1$  antihistamine can be used, augmented occasionally as necessary with an oral decongestant. If this is unsuccessful or if symptoms are persistent, then topical nasal steroids should be used, even where long-term use is anticipated. Steroids can be combined with an antihistamine if the combination proves more effective than steroid alone.

For children, daily topical nasal cromones or an oral non-sedating  $H_1$  antihistamine are prescribed initially – only if these are unsuccessful are topical nasal steroids used.

If these treatments fail, specialist referral is necessary. Specialist investigations should start by eliminating other factors and ensuring that the patient has PAR with no other accompanying conditions, such as polypsis, anatomical abnormalities, chronic sinusitis or tumours. Recourse to a short-term systemic steroid

may be made, or specific immunotherapy may be used. Symptomatic treatment with oral decongestants or topical application of ipratropium bromide (an anticholinergic) may also be useful.

If the condition fails to respond to these measures, then cautery, cryosurgery or partial resection of the nasal turbinates may be necessary.

### Perennial non-allergic rhinitis

Patients with perennial non-allergic rhinitis represent a heterogeneous group with many symptom-causing factors. Treatment should again start with the practical option of avoidance of the possible irritant factors if they can be identified. For conditions where symptoms are intermittent, topical decongestants can be used in the short term or oral decongestants may be given. Topical ipratropium bromide is useful where watery rhinorrhoea is occurring. Antihistamines do not appear effective.

In cases of moderate perennial non-allergic rhinitis, the predominant symptom will dictate treatment. For cases characterized mainly by nasal obstruction, but with little watery discharge, a topical nasal steroid should be prescribed, which – if effective – may be continued long-term. Where copious watery discharge predominates, then topical ipratropium bromide is recommended.

Severe symptoms require specialist treatment: short-term systemic steroids – followed by topical steroids – may be necessary to relieve nasal obstruction; oral decongestants may also be tried. Where watery rhinorrhoea predominates it is treated with increased doses of anticholinergics plus topical steroids. Again if these tactics do not control the condition it may be necessary

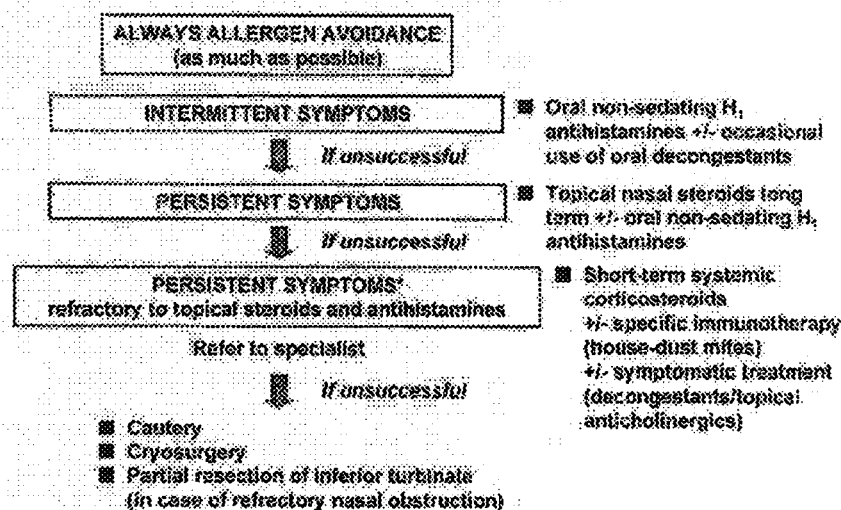


Fig. 2. Stepwise approach to the treatment of perennial rhinitis.

\*Look carefully for the presence of anatomical anomalies, chronic sinusitis, nasal polyps, tumours, etc

to consider cautery, cryosurgery or partial resection of the inferior turbinate to relieve nasal obstruction. Intractable watery rhinorrhoea may respond to cryosurgery or vidian neurectomy (a surgical procedure that interrupts the parasympathetic supply to the nose) to relieve symptoms; these procedures are usually reserved for extreme cases but are not always successful.

### Specialist investigations

When confronted with unsatisfactory clinical results, it is important that the specialist first verifies that the patient is indeed allergic, and if so, that the causative allergens are identified. A thorough history should first be taken, then skin-prick tests, RAST, and nasal provocation should be performed to identify the responsible allergen, which may lead to a change in the original diagnosis. Where these procedures confirm the veracity of the initial diagnosis, but the clinical response to treatment has been poor, the next step is often to try different drugs from the standard treatment choices of antihistamines, steroids and cromones, or to consider different combinations from those tried previously.

In very acute cases of allergic rhinitis, characterized by pronounced symptoms occurring on peak pollen days and/or complete obstruction of the nasal cavity, treatment with oral corticosteroids should be considered.

### Immunotherapy

SAR that does not respond to corticosteroids and/or antihistamines may be treated with immunotherapy, however, an accurate diagnosis is essential before immunotherapy is considered. The complexities, incon-

veniences and occasional side-effects associated with this treatment mean its use is reserved to specialist treatment of the more severe cases of allergic rhinitis. Immunotherapy has several modes of action (Fig. 3) amongst which is blocking the switching of uncommitted T lymphocytes to TH<sub>2</sub>-type cells, therefore decreasing production of IL-4 and IL-5, leading to subsequent decreased production of IgE.

Immunotherapy can also be considered in HDM-induced PAR, although the clinical results are not as strong (around 50% success) as in pollen allergy, where success rates are as high as 80%. Topical immunotherapy is now possible.

### Rhinitis medicamentosa

Rhinitis medicamentosa is caused by long-time abuse of topical nasal vasoconstrictors. It causes hypertrophy of the inferior turbinates and is very difficult to treat. Without prior treatment with oral corticosteroids – which do not even always work – topical corticosteroids are usually not sufficient. Minimally invasive surgery of the inferior turbinates (cryosurgery, electrocautery or partial resection of the turbinate) is sometimes necessary.

Cryotherapy (which consists of treating the inferior turbinates once or twice for about 90 s at -75 °C) may be effective, but the results can be short lived. Studies in perennial non-allergic rhinitis have shown effects to last for about 12 months. In allergic rhinitis the outcome is more short-lived, with the improvement starting to wane at 3 months and the original condition recurring by 12 months [6].

Patients with nasal polyps, anatomical anomalies or suspicion of malignancy (unilateral disease, blood-

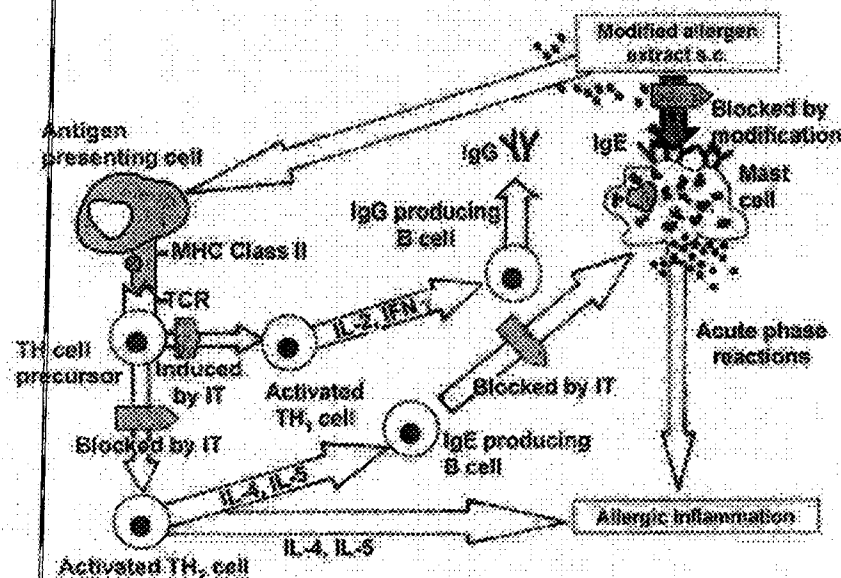


Fig. 3. Possible sites of action of immunotherapy (IT).

stained secretion, etc.) should be referred to the otorhinolaryngologist.

#### Rhinitis guidelines validation study

The guidelines discussed here have contributed greatly to the treatment of allergic rhinitis. It is now timely to extend these guidelines – to this end, a large study involving 300 centres and recruiting 600 patients is to be carried out during the pollen season of 1998 in Belgium, France and the UK. The aims of this study are to validate the usefulness of standardized therapeutic strategies and to produce simple definitions of mild, moderate and severe rhinitis. It is hoped that this will enable the development of simpler therapeutic options according to the severity of rhinitis symptoms. Study endpoints will be the patients' quality of life as measured using the Short Form-36 (SF-36) and Rhinitis Quality-of-Life Questionnaires (RQLQ). Comparisons will be made between patients receiving medication according to the treating physician's choice, and those receiving medication in accordance with the guidelines. The data from this study should be available in the spring of 1999.

#### Conclusion

The guidelines produced by the International Consensus Report on the Diagnosis and Management of Rhinitis provide an invaluable guide to help GPs in the treatment of common conditions such as SAR, PAR and perennial non-allergic rhinitis. Where initial treatment is unsatis-

factory, specialist referral may be necessary. The specialist can also benefit from these guidelines, and should be able to demonstrate knowledge through practical understanding of the detailed mechanisms of action of the various treatments, to ensure that the most appropriate treatment for each individual patient is prescribed. Finally, the specialist must always acknowledge that every patient with allergic or non-allergic rhinitis is unique.

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# Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology

Mark S Dykewicz, MD,<sup>‡</sup> Stanley Fineman, MD, MBA,<sup>§</sup> *Editors*

David P Skoner, MD,<sup>¶¶</sup> *Chair, Workgroup on Rhinitis*

Richard Nicklas, MD<sup>||</sup>; Rufus Lee, MD; Joann Blessing-Moore, MD<sup>¶</sup>; James T Li, MD, PhD<sup>\*\*</sup>; I Leonard Bernstein, MD<sup>††</sup>; William Berger, MD, MBA<sup>‡‡</sup>; Sheldon Spector, MD<sup>§§</sup>; and Diane Schuller, MD,<sup>|||</sup> *Associate Editors*

This document contains complete guidelines for diagnosis and management of rhinitis developed by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council on Allergy, Asthma and Immunology. The guidelines are comprehensive and begin with statements on clinical characteristics and diagnosis of different forms of rhinitis (allergic, non-allergic, occupational rhinitis, hormonal rhinitis [pregnancy and hypothyroidism], drug-induced rhinitis, rhinitis from food ingestion), and other conditions that may be confused with rhinitis. Recommendations on patient evaluation discuss appropriate use of history, physical examination, and diagnostic testing, as well as unproven or inappropriate techniques that should not be used. Parameters on management include use of environmental control measures, pharmacologic therapy including recently introduced therapies and allergen immunotherapy. Because of the risks to patients and society from sedation and performance impairment caused by first generation antihistamines, second generation antihistamines that reduce or eliminate these side effects should usually be considered before first generation antihistamines for the treatment of allergic rhinitis. The document emphasizes the importance of rhinitis management for comorbid conditions (asthma, sinusitis, otitis media). Guidelines are also presented on special considerations in patients subsets (children, the elderly, pregnancy, athletes and patients with rhinitis medicamentosa); and when consultation with an allergist-immunologist should be considered.

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**CONTRIBUTORS:** Donald W Aaronson, MD; Allen D Adinolfi, MD; James N Baraniuk, MD; Robert J Dockhorn, MD; William Dolen, MD; Howard M Druce, MD; Marianne Frieri, MD, PhD; Morton P Galina, MD; Leon Greco, MD; Alfredo A Jalowayski, PhD; Craig F La Force, MD; Eli O Meltzer, MD; Robert M Naclerio, MD; Keith M Phillips, MD; Gordon Raphael, MD; Michael Schatz, MD; Michael J Schumacher, MD; Howard J Schwartz, MD; Tommy C Sim, MD; Chester T Stafford, MD; William W Storms, MD; Michael J Tronolone, MD; Michael J Welch, MD; Chester C Wood, MD; and Robert S Zeiger, MD, PhD

**PRINCIPAL REVIEWERS:** Jean A Chapman, MD; Robert A Nathan, MD; John Santilli, Jr, MD; Michael Schatz, MD; and Betty B Wray, MD

This document was developed by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council on Allergy, Asthma and Immunology. The AAAAI and the ACAAI have jointly accepted responsibility for establishing these practice parameters. Because this docu-

ment incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official interpretation of this document by the AAAAI or ACAAI. Any request for information about or an interpretation of this document by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, ACAAI and the Joint Council on Allergy, Asthma and Immunology.

\* This parameter was developed with Dr. Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

<sup>‡</sup> Division of Allergy and Immunology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri; <sup>§</sup> Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; <sup>¶¶</sup> Departments of Pediatrics & Otolaryngology, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; <sup>||</sup> Department of Medicine, George Washington Medical Center, Washington, DC; <sup>¶</sup> Departments of Medicine & Pediatrics, Stanford University Medical Center, Palo Alto, California; <sup>\*\*</sup> Department of Medicine, Mayo Clinic & Medical School, Rochester, Minnesota; <sup>††</sup> Departments of Medicine & Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio; <sup>‡‡</sup> Department of Pediatrics, Division of Allergy and Immunology, University of California College of Medicine, Irvine, California; <sup>§§</sup> Department of Medicine, University of California-Los Angeles, Los Angeles, California; <sup>|||</sup> Department of Pediatrics, Pennsylvania State University, Milton S. Eisenhower Medical College, Hershey, Pennsylvania.

The Joint Task Force has made an intense effort to appropriately acknowledge all contributors to this parameter. If any contributors are inadvertently excluded, the Task Force will insure that appropriate recognition of such contributions is subsequently made.

reach high levels in poorly maintained homes and apartments. Eliminating cockroaches requires careful sanitation such as not allowing food to stand open or remain on unwashed dishes, promptly wiping up food spills and storing garbage in tightly closed containers. Use of "roach traps" has been advocated since these permit removal of the allergen-containing bodies of the insects. If the infestation is heavy, however, repeated applications of insecticide by a professional exterminator or changing homes may be required.

**Miscellaneous and non-allergic factors.** A host of other environmental factors may incite or worsen rhinitis. Agents producing occupational asthma by IgE-dependent mechanisms commonly trigger nasal and ocular symptoms. Because asthma may be more debilitating, occupational rhinoconjunctivitis is often ignored. Measures to control occupational asthma usually reduce occupational rhinitis and will not be discussed further. Rhinitis has also been attributed to irritants eg, tobacco smoke, formaldehyde, perfume and other strong odors, and newspaper ink. Some persons display increased "sensitivity" to environmental tobacco smoke.<sup>17</sup> The headache, nasal and chest symptoms do not appear to involve IgE. Avoidance of passive tobacco smoke is mandatory for such patients. The capacity of formaldehyde to cause stinging and burning of the eyes and nose, lacrimation, and decreased nasal mucous flow is well-established.<sup>18</sup> This appears to be irritant effect since even prolonged, high-level formaldehyde exposure only rarely results in IgE to formaldehyde-protein conjugates and this does not correlate with clinical symptoms.<sup>18,19</sup> Since respiratory symptoms generally occur at concentrations well above those at which the odor of formaldehyde is detectable, it is unlikely that formaldehyde would be an unsuspected cause of rhinitis. Perfume and newsprint are claimed to elicit symptoms in some rhinitis sufferers. The mechanism is uncertain but felt to be irritant.<sup>20</sup> If troublesome, avoidance is indicated.

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## Pharmacologic Therapy

32. Pharmacologic management should be considered in relation to the etiology and pathophysiology of the condition. If it is possible to anticipate the onset of symptoms, eg, seasonal rhinitis or rhinitis triggered by sporadic exposure, initiating prophylactic use of medications may lessen the impact of such exposure on the patient.

## Antihistamines

33. Oral antihistamines are effective in reducing symptoms of itching, sneezing, and rhinorrhea, and are first line therapy for treatment of allergic rhinitis. However, oral antihistamines have little objective effect on nasal congestion. Antihistamines reduce symptoms of allergic conjunctivitis, which are often associated with allergic rhinitis.

## Issues with sedation/performance impairment

34. Sedation and performance impairment are undesirable and potentially dangerous side effects of first generation antihistamines. Consequently, second generation antihistamines that are associated with less risk or no risk for these side effects should usually be considered before sedating antihistamines for the treatment of allergic rhinitis, and are even mandated in some segments of the transportation industry. Studies have demonstrated that many patients may not perceive performance impairment that is associated with first generation (classical) antihistamines. In the majority of states, patients taking sedating antihistamines are legally considered "under the influence of drugs."

## Adverse cardiac effects of some second generation antihistamines

35. Some older non-sedating antihistamines such as astemizole and terfenadine (the latter withdrawn from the US market in 1998) may cause prolongation of the QTc interval that may lead to the ventricular arrhythmia torsade de pointes especially with overdose, administration with certain concomitant medications (eg, some macrolide antibiotics, azole anti-fungal agents), and in the presence of severe liver disease.

Although many chemical mediators of inflammation play a role in producing the various symptoms and signs of allergic rhinitis, there is strong evidence that histamine is a mediator of major importance in this disorder. Once released from mast cells and basophils, histamine dilates blood vessels, increases vessel permeability, and stimulates sensory nerve endings and reflexes through the parasympathetic system that cause glandular secretion. Histamine given intranasally can reproduce all the symptoms of allergic rhinitis (sneezing, pruritus, rhinorrhea, blockage),<sup>1</sup> and therefore, H<sub>1</sub> histamine receptor antagonists (ie, H<sub>1</sub> antihistamines) are generally effective in controlling many of the symptoms of allergic rhinitis. Antihistamines are less efficacious (if at all) in other forms of rhinitis (eg, vasomotor, infectious), thereby making it important to establish a correct diagnosis before initiating therapy.

A major limitation of the use of the first generation (classical) antihistamines has been sedation. However, second generation antihistamines have been developed that in recommended doses significantly reduce or eliminate this problem. The availability of these second generation antihistamines has greatly improved the usefulness of antihistamines as pharmacotherapeutic agents since patients who otherwise would avoid antihistamine therapy due to sedation, can now utilize them and obtain significant benefit.

**Mechanism/pharmacokinetics.** Both first and second generation H<sub>1</sub> antihistamines are pharmacologic antagonists of histamine at the H<sub>1</sub>-receptor site and act by competitively binding to the H<sub>1</sub> receptor, thus blocking the H<sub>1</sub> response. Certain H<sub>1</sub>-receptor antagonists have metabolites that are active and as relevant, or even more relevant, than their parent compound (eg, loratadine, terfenadine, astemizole, hydroxyzine).<sup>2</sup> In addition to being antagonists of histamine, some of the second generation antihistamines may inhibit release of mast cell and basophil inflammatory mediators resulting in anti-allergic and anti-inflammatory effects.

Some of this action may be due to the ability of some, but not all, antihistamines to prevent release of histamine after antigen challenge.<sup>3</sup>

Oral antihistamines are readily absorbed, with peak serum concentrations usually occurring within 2 to 3 hours after a dose. The metabolism of all first generation and several second generation antihistamines is via the hepatic cytochrome P450 system. Clearance rates of H<sub>1</sub> antagonists are quite variable (2 hours to 10 days) but generally, serum elimination half-lives are shorter in children than in adults, longer in the elderly, but in all ages serum half-lives are less than their duration of bioactivity. In studies of the ability of antihistamines to suppress histamine- or antigen-induced wheal and flare reactions, peak suppression by antihistamines usually occurs 5 to 7 hours after an oral dose. Histamine suppressive effects can persist for up to 24 to 36 hours and longer (eg, hydroxyzine, cetirizine), even when serum concentrations of the parent compound have declined to their lowest limit of detection, probably secondary to the presence of active metabolites and/or high tissue drug concentrations.<sup>2</sup> Astemizole is unique in that it binds to peripheral H<sub>1</sub>-receptor sites with far greater affinity than do other H<sub>1</sub>-receptor antagonists. As a result, a single dose of astemizole produces serum and tissue levels that persist for days to weeks, with skin test suppression noted to last up to at least 6 weeks.<sup>4</sup>

**Clinical efficacy.** Oral antihistamines are capable of decreasing all the symptoms of allergic rhinitis (especially sneezing, itching, and nasal discharge) but are least effective in relieving nasal blockage. Numerous first generation antihistamines are available over-the-counter or by prescription. All first generation antihistamines belong to one of 6 different chemical classes based on their specific side chain substitution. There generally is little difference in clinical efficacy amongst these classes, although chlorpheniramine (alkylamine class) and hydroxyzine (piperazine class) have

**Assessing and treating rhinitis. A practical guide for Canadian physicians. Proceedings of the Canadian Rhinitis Symposium. Toronto, Ontario, Canada. January 14-15, 1994.**

[No authors listed]

**OBJECTIVES:** Rhinitis is an extremely common health problem in Canada and is a heterogeneous disorder, which may manifest with a variety of different clinical presentations and secondary complications. This document *Assessing and Treating Rhinitis: A Practical Guide for Canadian Physicians* has been developed to assist family physicians and specialists who assess and treat patients with rhinitis and its complications. **OPTIONS:** This guide provides an overview of the pathogenesis and key clinical features of the different types of rhinitis, as well as diagnostic tests that are available. Management strategies including patient information, pharmacotherapy, immunotherapy, and the role of surgical therapy in the treatment of rhinitis and its complications are reviewed. **OUTCOMES:** Symptoms of rhinitis have variable effects on our patients' health, ranging from minor irritation to significant morbidity with loss of time from work and school. Although the pathophysiology of many types of rhinitis is unknown, an accurate diagnosis is necessary, since not all types of rhinitis will respond to the same treatment measures. **EVIDENCE:** This guide is an edited review of presentations and discussions held by specialists in allergy, clinical immunology and otolaryngology who participated in the Canadian Rhinitis Symposium in Toronto, Ontario on January 14 and 15, 1994. **VALUES:** The value of a given diagnostic test or treatment option was determined based on the clinical experience and opinions of the specialists at the Symposium and a review of the literature. **BENEFITS, HARMS AND COSTS:** This document was designed to provide an overview of the most effective clinical approaches to the assessment and treatment of rhinitis. The clinical judgment of the practising clinician, however, must always be incorporated into any diagnostic or therapeutic decision. **RECOMMENDATIONS:** An accurate diagnosis of the type of rhinitis is necessary for treatment success. In treatment, all patients, regardless of the type of rhinitis, benefit from education concerning their condition. Each patient requires a customized approach to the management of their rhinitis, which may include pharmacotherapy, immunotherapy, and surgical therapy. **VALIDATION:** This guide was developed by the faculty and reviewed by the participants at the Canadian Rhinitis Symposium. As might be expected, these experts with different areas of interest and from different countries did not always have complete congruence of opinions. We believe, however, that this guide is a fair representation of the prevailing opinions expressed by the Symposium faculty and participants. **SPONSOR:** The Canadian Rhinitis Symposium, as well as technical support and assistance in manuscript preparation by the staff of Core Communications, were funded by an educational grant from Glaxo Canada Inc.

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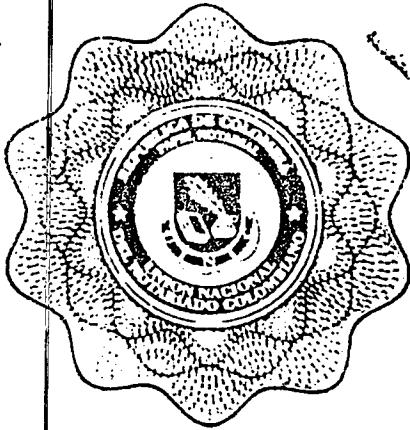
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| <b>(51) International Patent Classification <sup>5</sup> :</b><br><b>A61K 31/495</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 94/06429</b><br><b>(43) International Publication Date:</b> 31 March 1994 (31.03.94)                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>(21) International Application Number:</b> PCT/US93/08991<br><b>(22) International Filing Date:</b> 22 September 1993 (22.09.93)<br><b>(30) Priority data:</b><br>07/951,179 24 September 1992 (24.09.92) US<br><b>(71) Applicant:</b> SEPRACOR, INC. [US/US]; 33 Locke Drive, Marlborough, MA 01752 (US).<br><b>(72) Inventor:</b> GRAY, Nancy, M. ; 261 DeSimone Drive, Marlborough, MA 01752 (US).<br><b>(74) Agents:</b> HANSEN, Philip, E. et al.; Heslin & Rothenberg, 450 New Karner Road, P.O. Box 12695, Albany, NY 12212-2695 (US).                                                                                                                                                                                                                                                                                                                   |           | <b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| <b>(54) Title:</b> COMPOSITIONS FOR TREATING ALLERGIC DISORDERS USING (-) CETIRIZINE<br><br><b>(57) Abstract</b><br><br>Methods and compositions are disclosed utilizing optically pure (-) cetirizine for the treatment of seasonal and perennial allergic rhinitis in humans while avoiding the concomitant liability of adverse effects associated with the racemic mixture of cetirizine. The optically pure (-) isomer is also useful for the treatment of allergic asthma and chronic and physical urticaria. (-) Cetirizine is an inhibitor of eosinophil chemotaxis and is therefore useful in the treatment of other conditions related to eosinophilia such as allergic asthma, seasonal allergic rhinitis, atopic dermatitis, some parasitic diseases, some chronic obstructive lung diseases and certain gastrointestinal and genitourinary disorders. |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |



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a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá. - - - - -

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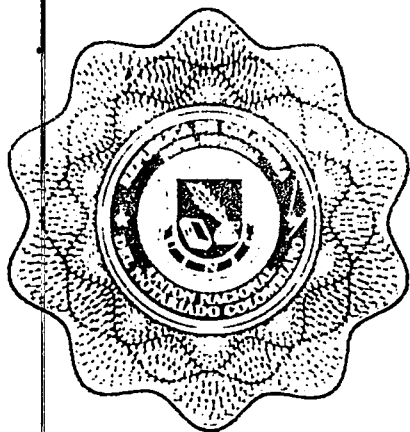
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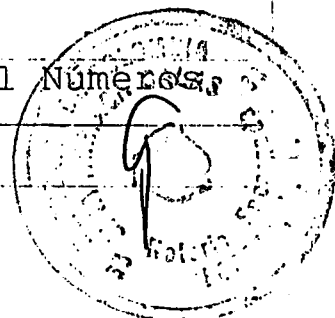
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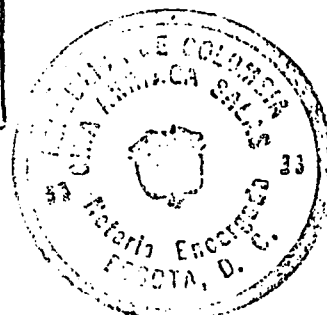
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| E.P. 5579  | 12/11/1973 | NOTARIA CUARTA DE CALI  | 28/11/1973 | 5995    | IX    |
| E.P. 4406  | 30/09/1974 | NOTARIA CUARTA DE CALI  | 28/11/1974 | 10887   | IX    |
| E.P. 192   | 03/02/1978 | NOTARIA CUARTA DE CALI  | 14/02/1978 | 25355   | IX    |
| E.P. 3479  | 07/09/1979 | NOTARIA CUARTA DE CALI  | 19/09/1979 | 34204   | IX    |
| E.P. 4274  | 12/12/1984 | NOTARIA NOVENA DE CALI  | 19/12/1984 | 73088   | IX    |
| E.P. 1155  | 21/05/1985 | NOTARIA SEPTIMA DE CALI | 03/06/1985 | 76917   | IX    |
| E.P. 1553  | 20/06/1986 | NOTARIA SEPTIMA DE CALI | 08/07/1986 | 85997   | IX    |
| E.P. 1458  | 09/06/1987 | NOTARIA SEPTIMA DE CALI | 24/12/1987 | 3508    | IX    |
| E.P. 7222  | 14/12/1988 | NOTARIA TERCERA DE CALI | 19/12/1988 | 13847   | IX    |
| E.P. 4530  | 04/09/1989 | NOTARIA TERCERA DE CALI | 07/09/1989 | 21508   | IX    |
| E.P. 3865  | 02/08/1990 | NOTARIA TERCERA DE CALI | 13/08/1990 | 31708   | IX    |
| E.P. 8305  | 13/12/1995 | NOTARIA TERCERA DE CALI | 23/01/1996 | 557     | IX    |
| E.P. 4559  | 16/11/1999 | NOTARIA TERCERA DE CALI | 26/11/1999 | 7911    | IX    |
| E.P. 6-004 | 02/12/2004 | NOTARIA TERCERA DE CALI | 14/12/2004 | 13371   | IX    |

## CERTIFICA

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

## CERTIFICA

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

## CERTIFICA

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL, TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTES: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTES: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMLMV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS. EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1. COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2. ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA, EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y

COMPROMISOS RESPECTIVOS HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

**CERTIFICA**

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002  
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS  
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

VICEPRESIDENTE  
ROBERTO S. VENTURA PAULY  
C.C.16697614

PRESIDENTE  
ESTHER ISABEL VENTURA DE RENDON  
C.C.38979831

GERENTE GENERAL Y REPRESENTANTE LEGAL  
JUAN MARIA RENDON GUTIERREZ  
C.C.17125100

PRIMER SUPLENTE DEL GERENTE  
ESTHER ISABEL VENTURA DE RENDON  
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE  
ROBERTO M. VENTURA CRISPINO  
C.C.9086003

**CERTIFICA**

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004  
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS  
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE  
JUAN PABLO REYES VILLAMIZAR  
C.C.80419709

**CERTIFICA**

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002  
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS  
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004  
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS  
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

## JUNTA DIRECTIVA

## PRINCIPALES

## PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON  
C.C. 38979831

## SEGUNDO RENGLON

ROSA VICTORIA VENTURA DE VISBAL  
C.C. 38992048

## TERCER RENGLON

JUAN PABLO REYES VILLAMIZAR  
C.C. 80419709

## SUPLENTES

## PRIMER RENGLON

JUAN MARIA RENDON GUTIERREZ  
C.C. 17125100

## SEGUNDO RENGLON

ROBERTO M. VENTURA CRISPINO  
C.C. 9086003

## TERCER RENGLON

ROBERTO S. VENTURA PAULY  
C.C. 16697614

CERTIFICA

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

## REVISOR FISCAL

ALFREDO LOPEZ & CIA. LIMITADA  
NIT. 800026893

**CAMARA  
DE COMERCIO  
DE CALI**

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 30 DE AGOSTO DE 2002

ORIGEN: ALFREDO LOPEZ &amp; CIA LTDA

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14678 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

## REVISOR FISCAL PRINCIPAL

ALFREDO LOPEZ CAMPO  
C.C. 8241912

## REVISOR FISCAL SUPLENTE

YAMILEC OSPINA MORALES  
C.C. 31996911

## CERTIFICA

CAPITAL AUTORIZADO: \$1,500,000,000  
 NUMERO DE ACCIONES: 150,000,000  
 VALOR NOMINAL: \$10  
 CAPITAL SUSCRITO: \$903,756,830  
 NUMERO DE ACCIONES: 90,375,683  
 VALOR NOMINAL: \$10  
 CAPITAL PAGADO: \$903,756,830  
 NUMERO DE ACCIONES: 90,375,683  
 VALOR NOMINAL: \$10

## CERTIFICA

QUE EL 03 DE MAYO DE 2004 BAJO LOS NROS. 4859, 4860 Y 4861 DEL LIBRO IX, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA ABRIL 30 DE 2004 RELATIVO A LA DECLARACION DE UN GRUPO EMPRESARIAL, EN EL CUAL CONSTA:

CONTROLANTE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: A) LA FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PUEDE LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD, DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

DE ACUERDO CON EL NUMERAL 3, ARTICULO 27 DE LA LEY 222 QUE SE TRANSCRIBE: CUANDO LA MATRIZ, DIRECTAMENTE O POR INTERMEDIO O CON EL CONCURSO DE LAS SUBORDINADAS, EN RAZON DE UN ACTO O NEGOCIO CON LA SOCIEDAD CONTROLADA O CON SUS SOCIOS, EJERZA INFLUENCIA DOMINANTE EN LAS DECISIONES DE LOS ORGANOS DE ADMINISTRACION DE LA SOCIEDAD.

SUBORDINADA: LABORATORIOS PAULY PHARMACEUTICAL S.A.

NIT: 800.097.402-6

DOMICILIO: CALI

ACTIVIDAD PRINCIPAL: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222.

SUBORDINADA: AMERICAN GENERICS S.A.

NIT: 800.223.214-9

DOMICILIO: CALI

ACTIVIDAD PRINCIPAL: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222.

SUBORDINADA: LAFRANCOL INTERNACIONAL S.A.

NIT: 815.003.912-2

DOMICILIO: ZONA FRANCA DEL PACIFICO BODEGA 6 PISO 2 KM 6 VIA YUMBO AEROPUERTO PALMIRA

ACTIVIDAD PRINCIPAL: REALIZACION DE ACTIVIDADES DESDE LA ZONA FRANCA, LAS CUALES CONSISTEN EN LA PRESTACION DE TODO TIPO DE SERVICIOS ASI COMO DISTRIBUIR, VENDER, COMPRAR, IMPORTAR, EXPORTAR Y ALMACENAR TODO TIPO DE MATERIAS PRIMAS, PRODUCTOS

TERMINADOS Y SEMITERMINADOS RELACIONADOS CON LA INDUSTRIA DE ALIMENTOS, COSMETICA, Y FARMACEUTICA.  
 PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 40% Y LABORATORIOS PAULY PHARMACEUTICAL S.A. POSEE EL 40% Y AMERICAN GENERICS S.A. POSEE EL 19.97%.

SUBORDINADA: LAFRANCOL PERU S.A.  
 REGISTRO UNICO DE CONTRIBUYENTE 20504784089  
 DOMICILIO: AVENIDA JAVIER PRADO OESTE 829 MAGDALENA, LIMA 17  
 ACTIVIDAD PRINCIPAL: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO.  
 PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 93.0%.

SUBORDINADA: LAFRANCOL (USA) CORP.  
 NUMERO DE DOCUMENTO: P 00000090126  
 DOMICILIO: 2121 PONCE DE LEON BLVD. STE 240 CORAL GABLES FL 33134  
 ACTIVIDAD PRINCIPAL: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO.  
 PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL POSEE EL 65.25%.

### CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO. 5234-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL  
 UBICADO EN: -K 1 46 84 DE CALI  
 RENOV: POR EL AÑO 2004

### CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO. 369809-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.  
 UBICADO EN: CRA. 1 NRO. 46A 70 DE CALI  
 FECHA MATRICULA: 29 DE ABRIL DE 1994  
 RENOV: POR EL AÑO 2004

### CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO. 369810-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.  
 UBICADO EN: -K 1 46 32 DE CALI  
 FECHA MATRICULA: 29 DE ABRIL DE 1994  
 RENOV: POR EL AÑO 2004

### CERTIFICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 25 DE MARZO DE 2004

### CERTIFICA

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABLES DESPUES DE LA FECHA DE SU PUBLICACION EN EL BOLETIN NOTICIAS DE INSCRIPCIONES, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

CCC11090814

DADO EN CALI A LOS 03 DIAS DEL MES DE MARZO DEL AÑO 2005 HORA: 11:04:33

EL SECRETARIO

*[Handwritten signature]*



Como Notario Veintiseis del Circuito de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C. - Colombia.

20 DIC 2005

GUSTAVO SAMPER RODRIGUEZ  
NOTARIO VEINTISEIS

**EN BLANCO**  
**NOTARIA VEINTISEIS**



**CAMARA  
DE COMERCIO  
DE CALI**

**EN BLANCO**  
**NOTARIA VEINTISEIS**