

100

Señor

**SUPERINTENDENTE DE INDUSTRIA Y COMERCIO**

**E. S. D.**

---

**REF: EXPEDIENTE 04-07561**

**TÍTULO SOLICITADO: "FORMULACIONES ANTIHISTAMÍNICAS PARA FORMAS DE DOSIFICACIÓN DE CÁPSULA BLANDA"**

**PUBLICACIÓN: Gaceta 555 de 31-08-2005, número de publicación 418**

**PRIORIDAD: US 09/909,313 de 20/07/2001**

**SOLICITANTE: R.P. SCHERER TECHNOLOGIES INC.**

**APODERADO: LUIS FELIPE CASTILLO GIBSON**

**TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN**

**JOSÉ LUIS REYES VILLAMIZAR**, identificado como aparece al pie de mi firma, reconocido apoderado de los opositores en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito ratifico mi petición en el sentido de que se niegue el beneficio patentario a la solicitud contenida en el expediente **04-007-561** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

## **I. LEGÍTIMO INTERÉS**

Reitero que asiste a las sociedades opositoras, en particular, para efectos de esta prórroga, a **TECNOQUÍMICAS 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.

## **II. COMPLEMENTO DE INFORMACIÓN**

La solicitud colombiana 04-007-561 en trámite, revela formulaciones antihistamínicas para uso en formas de dosificación de cápsula blanda que comprende a) Loratadina y derivados de la misma y b) un sistema de solvente que comprende una mezcla de ácidos grasos de cadena media.

### **2.1 Las reivindicaciones de la solicitud colombiana en curso, carecen de Nivel Inventivo.**

Ruego al Despacho se sirva tener en cuenta lo consignado a continuación:

**A.** La patente americana US 4,863,720 de título "PHARMACEUTICAL PREPARATION AND METHODS FOR ITS PRODUCTION", publicada el 5 de septiembre de 1989, revela una preparación farmacéutica con Benzodiazepinas como ingredientes activos, y que comprende una solución del principio activo en un primer solvente seleccionado del grupo que consiste de Polialquenglicerol, ésteres de ácidos grasos de Glicerina-polioxietilenglicol, ésteres parciales de ácidos grasos de sorbitol, ésteres parciales de polihidroxietilen-sorbitol, polivinil pirrolidonas, polivinil alcoholes, éteres de alcoholes grasos de polihidroxietileno, entre otros, y un segundo solvente el cual es etanol y que puede ser reemplazado parcialmente por un compuesto seleccionado de del grupo que consiste de diglicéridos de ácidos grasos de cadena media y triglicéridos de ácidos grasos de cadena media, y un propelente farmacológicamente inerte, y cuya preparación será llenada en un container de aerosol y será rociado "sprayable" como un aerosol medidor de dosis.

Si bien es cierto la anterioridad mencionada no se refiere a cápsulas de gelatina blanda de Loratadina o sus derivados, es bien claro que describe una composición que además de contener un principio activo, tiene un sistema solvente conformado por ácidos grasos de cadena media y cuenta con la presencia de polivinilpirrolidona (Povidona) o de polioxietilen-sorbitol entre otros, muy probablemente como dispersantes tal como lo sugiere la solicitud colombiana en trámite, de tal forma que nos encontramos frente a formulaciones similares como se podrá observar en el cuadro comparativo:

| CO 04-007-881                                                                                                                                                                                                                                                                                                                                                    | US 4,663,720                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>* Principio activo (Loratadina o Descarboetoxiloratadina)</li><li>* Sistema solvente: mezcla de mono y diglicéridos de ácidos grasos de cadena media,</li><li>* Dispersante: Povidona (Pirrolidinpirrolidona) y Polysorbate™ 80 (Monooleato de sorbitol polioxietilenado).</li><li>* Cápsulas de gelatina blanda</li></ul> | <ul style="list-style-type: none"><li>* Principio activo (Benzodiazepinas)</li><li>* Sistema Solvente: Primer solvente Polivinilpirrolidona, Ésteres parciales de ácidos grasos de Sorbitol, ó ésteres parciales de polihidroxi-etilen-sorbitol, entre otros, y Segundo solvente Di y Triglicéridos de ácidos grasos de cadena media</li><li>* Aerosol</li></ul> |

B. La patente americana US 5,352,704 de título "GUANIDINOBENZENE DERIVATIVES", publicada el 4 de octubre de 1994, revela derivados de guanidinobenceno con actividad antiviral y composiciones para administración oral que los contienen, los cuales preferiblemente son formulados en formas de unidad de dosis tales como tabletas, polvos, grageas, partículas o cápsulas, y en donde las cápsulas blandas pueden contener un vehículo convencional tal como aceites de plantas, polietilenglicol o glicerol, o un agente de suspensión oleoso, una solución o un agente humectante tal como un surfactante.

Dentro de los agentes de suspensión descritos en la patente US 5,352,704, se encuentran metilcelulosa, CMC Na+, HPC, HPMC, polivinilpirrolidona, polivinilalcohol, goma tragacanto, gelatina o alginato de sodio, y como agentes humectantes se encuentran ésteres de ácidos grasos de polioxietilen sorbitan, ésteres de ácidos grasos de polioxietileno, aceite de

ricino hidrogenado, aceite de sésamo, aceite de soya, propilenglicol, polietilenglicol, o etilalcohol.

De la simple lectura de lo consignado anteriormente, podemos ver que se refiere a una composición que puede estar en forma de cápsulas blandas conformada por un principio activo (antiviral) y un sistema solvente convencional como es un aceite vegetal o un agente de suspensión como Polivinilpirrolidona, o un agente humectante como ésteres de ácidos grasos de polioxietilensorbitan o ésteres de ácidos grasos de polioxietileno; así las cosas, lo revelado en la solicitud colombiana en trámite ya había sido anticipado puesto que tanto el sistema solvente como la forma de dosificación unitaria en forma de cápsulas de gelatina blanda ya habían sido revelados, con la única excepción de que se refieren a principios activos distintos.

- C. La patente americana US 5,595,997 de título "METHODS AND COMPOSITIONS FOR TREATING ALLERGIC RHINITIS AND OTHER DISORDERS USING DESCARBOETHOXYLORATADINE", publicada el 21 de enero de 1997, revela un método de tratamiento de la rinitis alérgica en humanos que comprende la administración a dicho humano de una cantidad terapéuticamente efectiva de Descarboetoxiloratadina o una sal del mismo junto con un vehículo farmacéuticamente aceptable.

Los ejemplos 7 y 8 por su parte, se refieren a cápsulas y cápsulas de gelatina blanda respectivamente, siendo más adecuado para efectos de comparación el ejemplo 8, en el cual se describe que la mezcla del principio activo en un aceite digestible tal como aceite de soya, lecitina, aceite de semillas de algodón o aceite de oliva es preparada y luego inyectada por medio de bomba de desplazamiento positivo dentro de la gelatina para formar cápsulas de gelatina blanda que contienen 0.1 a 10 mg del ingrediente activo y que posteriormente son lavadas y secadas.

En este punto es importante resaltar que la anterioridad describe cápsulas de gelatina blanda de Descarboetoxiloratadina cuyo sistema solvente es un sistema convencional basado en aceites vegetales ampliamente utilizados en la fabricación de este tipo de formas farmacéuticas.

Ahora bien, si unimos los conocimientos proporcionados en los documentos descritos en los literales A, B y C, vemos que su combinación permite deducir lo que pretende la invención objeto de protección. El nivel de obviedad, sin lugar a dudas puede estar basado en la existencia de composiciones farmacéuticas cuyos sistemas solventes pueden estar conformados por mezclas de ácidos grasos de cadena media, ya sea o no en forma de cápsulas de gelatina blanda de principios activos distintos a Loratadina, y de cápsulas de gelatina blanda de Descarboetoxiloratadina con sistemas solventes oleosos convencionales, de tal manera que una persona versada en la materia podría sugerir la formulación de Loratadina o sus derivados con variaciones en el sistema solvente haciendo por ejemplo inclusión de ácidos grasos de cadena media, inclusión o no de agentes de suspensión o humectantes o dispersantes, estos cambios en la formulación estarán encaminados al mejoramiento de algunas características de la misma, como por ejemplo la solubilidad del activo, la biodisponibilidad o la estabilidad de la formulación, entre otros factores.

En consecuencia, la solicitud objeto de patentabilidad, carece de Nivel inventivo teniendo en cuenta lo revelado en los documentos de los literales A, B, y C, puesto que una persona versada en la materia puede derivar la formulación de compuestos como Desloratadina (Descarboetoxiloratadina) en cápsulas de gelatina blanda con un sistema solvente basado en ácidos grasos de cadena media y dispersantes.

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.

### **III. PRUEBAS**

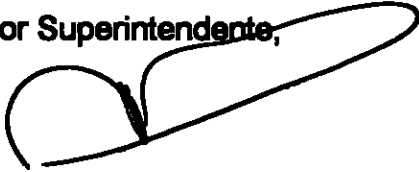
Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, las siguientes:

- Copia de la portada y del capítulo reivindicatorio de la patente americana US 4,863,720.

105 ✓

- Copia de la portada y de las columnas 5 y 6 de la patente americana US 5,352,704.
- Copia de la portada, de los ejemplos 7 y 8 y del capítulo reivindicatorio de la patente US 5,595,997.

Señor Superintendente,



**JOSÉ LUIS REYES VILLAMIZAR**

C.C. 79.152.473 de Usaquén  
T.P.A. 44.655 de C.S.J.

United States Patent [19]  
Burghart et al.

[11] Patent Number: 4,863,720  
[45] Date of Patent: Sep. 5, 1989

[34] PHARMACEUTICAL PREPARATION AND  
METHODS FOR ITS PRODUCTION

[76] Inventors: Walter Burghart, A-1030 Vienna,  
Salimgasse 4, Vienna, Austria; Kurt  
Burghart, D-22117 Roodorf,  
Seegberg 2, Roodorf, Fed. Rep. of  
Germany

[21] Appl. No.: 127,293

[22] PCT Filed: Mar. 10, 1987

[86] PCT No.: PCT/AT87/00018

§ 371 Date: Nov. 10, 1987

§ 102(e) Date: Nov. 10, 1987

[87] PCT Pub. No.: WO87/05210

PCT Pub. Date: Sep. 11, 1987

[30] Foreign Application Priority Data

Mar. 10, 1986 [AT] Austria ..... A621/86

[51] Int. Cl. .... A61L 9/04

[52] U.S. Cl. .... 424/45; 424/78;

424/81; 424/923

[58] Field of Search ..... 424/45, 78, 81, 923

[36] References Cited

FOREIGN PATENT DOCUMENTS

154632 4/1977 Belgium .  
0834632 10/1977 Belgium .  
2130044 1/1979 Fed. Rep. of Germany .  
2394347 3/1979 France .  
81/01421 3/1981 PCT Int'l Appl. .

Primary Examiner—Thurman K. Page

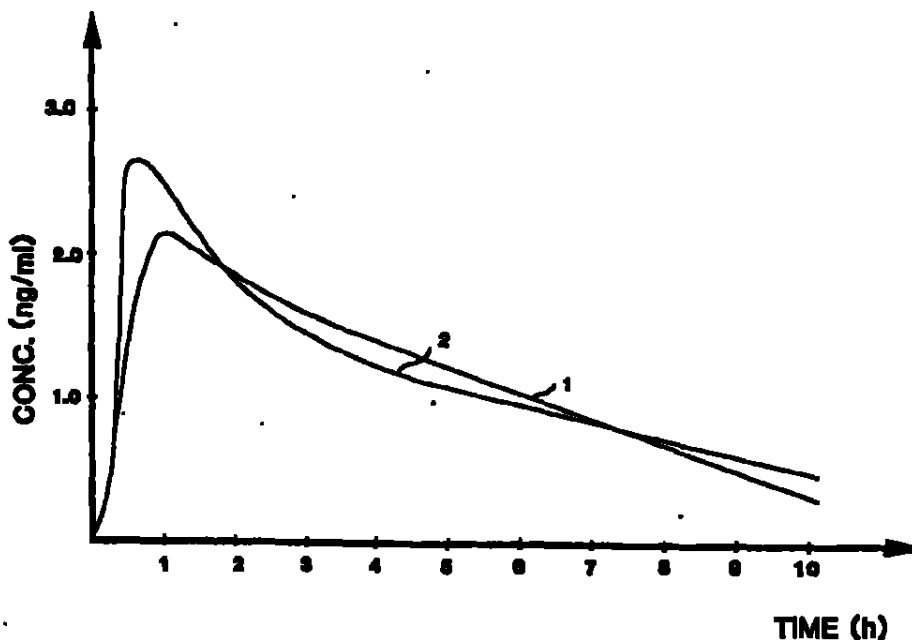
Assistant Examiner—P. L. Prater

Attorney, Agent, or Firm—Nixon & Vanderhye

[57] ABSTRACT

A sprayable pharmaceutical preparation available in doses in aerosol containers comprises an active ingredient dissolved in polyalkylene glycol, and/or polyethylene glycol, and/or fatty glycolic acid ester of glycerine-polyalkylene glycol, and/or glycerine-polyethyleneglycol oxylate and/or glycerine-polyethyleneglycol oxylate, and/or partial fatty acid esters of sorbitol or polyhydroxyethylene sorbitol and/or polyvinylpyrrolidone, and/or polyvinyl alcohols, and/or fatty alcohol ethers of polyhydroxyethylene, or fatty acid esters of polyhydroxyethylene and/or condensates of polyhydroxyethylene-polyhydroxypropylene and/or propylene carbonate, mixed with ethanol, substituted if necessary at least partially with middle chain diglyceride and/or triglyceride of fatty acids, and with a pharmacologically acceptable propellant, in particular halogenated hydrocarbons.

16 Claims, 1 Drawing Sheet



-continued

|                  |            |
|------------------|------------|
| Glycerine        | 8,300 mg   |
| Sodium ascorbate | 8,125 mg   |
| Propellant       | 79,300 mg  |
|                  | 100,000 mg |

The mixture resulted in a complete, stable solution which could be sprayed in accurate doses without problems. Spray jets of each 110 mg aerosol proved to be particularly effective.

The dosage weight of 110 mg could be reproduced at any time using the spraying device mentioned in Example 3.

## EXAMPLE 6

A solution was prepared containing specified quantities of the following components per 100 mg aerosol:

|                         |            |
|-------------------------|------------|
| Triazolam               | 0.125 mg   |
| Polyethylene glycol 400 | 7,800 mg   |
| Ethanol                 | 25,000 mg  |
| Ethyl vanillin          | 0.150 mg   |
| Glycerine               | 8,300 mg   |
| Sodium ascorbate        | 8,125 mg   |
| Propellant              | 67,300 mg  |
|                         | 100,000 mg |

The mixture resulted in a complete, stable solution which could be sprayed in accurate doses without problems. Spray jets of each 100 mg aerosol proved to be particularly effective.

The dosage weight of 100 mg could be reproduced at any time.

## BRIEF DESCRIPTION OF THE DRAWING

The relative bioavailability of the formulation stated in the example was examined and is shown in the figure. Each curve represents the evaluated mean value.

The measured values (ng/ml) are indicated on the ordinate versus the time (h) on the abscissa. It is evident from the figure, that the bioavailability after administration of two spray jets (curve 1) is somewhat lower than that obtained after administration of a tablet with 0.5 mg Triazolam (curve 2). However, the two spray jets contained a dose of only 0.25 mg Triazolam.

7 hours after administration the areas under both curves are approximately identical, although the dosage after administration of two spray jets was only half of that after administration of the tablet, g. 16

## EXAMPLE 7

In order to evaluate how much the content of the solubilizing agent Polyethylene glycol 400 may be reduced to gain still a complete solution of Triazolam, an aerosol was prepared containing specified quantities of the following components:

|                         |           |
|-------------------------|-----------|
| Triazolam               | 0.50 mg   |
| Polyethylene glycol 400 | 6.00 mg   |
| Ethanol                 | 32.80 mg  |
| Ethyl vanillin          | 0.10 mg   |
| Glycerine               | 1.00 mg   |
| Sodium ascorbate        | 0.20 mg   |
| Propellant              | 60.00 mg  |
|                         | 100.00 mg |

It was not possible to dissolve the specified quantity of Triazolam in this formulation.

We claim:

1. A pharmaceutical preparation with benzodiazepines as active ingredients, said preparation comprising a solution of the active ingredient in a first solvent selected from the group consisting of a polyalkylene glycol, glycerine-polyethylene glycol or fatty acid esters, partial fatty acid esters of sorbitol, partial fatty acid esters of polyhydroxyethylene-sorbitol, 2,2,2-trifluoroethylololones, polyvinyl alcohols, polyhydroxyethylene fatty alcohol ethers, polyhydroxyethylene fatty acid esters, polyhydroxyethylene-polyhydroxypropylene condensates and propylene carbonate, and a second solvent which is ethanol which may be at least partly replaced by a compound selected from the group consisting of a medium-chain fatty acid diglyceride and a medium-chain fatty acid triglyceride, and a pharmacologically inert propellant, said preparation being filled in an aerosol container and being sprayable as a metered dose aerosol.

2. A pharmaceutical preparation according to claim 1, wherein said first solvent is polyethylene glycol.

3. A pharmaceutical preparation according to claim 1, wherein said glycerine-polyethylene glycol or fatty acid esters are selected from the group consisting of glycerine-polyethylene-glycol or oxyolates and glycerine-polyethylene glycol or stearate.

4. A pharmaceutical preparation according to claim 1, wherein said pharmacologically inert propellant is a halogenated hydrocarbon.

5. A pharmaceutical preparation according to claim 1, wherein relative to a volume of 100  $\mu$ l a spray jet contains 0.1-5 mg of active ingredient 3-30 mg of said first solvent selected from the group consisting of polyethylene glycol, glycerine-polyethylene-glycol or oxyolates, partial fatty acid esters of sorbitol, partial fatty acid esters of polyhydroxyethylene-sorbitol, polyvinylpyrrolidone, polyvinyl alcohols, polyhydroxyethylene fatty alcohol ethers and polyhydroxyethylene fatty alcohol esters respectively and polyhydroxyethylene-polyhydroxypropylene condensates, 10-40 mg of ethanol, and the remaining part propellant and a pharmaceutically acceptable adjuvant or flavor.

6. A pharmaceutical preparation according to claim 5, wherein said first solvent is present in an amount of 5-25 mg.

7. A pharmaceutical preparation according to claim 5, wherein said ethanol is present in an amount of 15-30 mg.

8. A pharmaceutical preparation according to claim 1, wherein when said active ingredient is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-a]-[1,4] benzodiazepine, each 100 mg solution or each spray jet contains 0.05-0.3 mg of that active ingredient.

9. A pharmaceutical preparation according to claim 1, wherein benzodiazepines and polyethylene glycol are present in a weight ratio between 1:20 and 1:60.

10. A pharmaceutical preparation according to claim 9, wherein said benzodiazepine is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-a]-[1,4] benzodiazepine.

11. A pharmaceutical preparation according to claim 9, wherein said benzodiazepine and acid polyethylene glycol are present in a weight ratio between 1:25 and 1:35.

12. A pharmaceutical preparation according to claim 1, wherein benzodiazepine and a first solvent selected

108

7

from the group consisting of propylene carbonate, glycerine-poly-ethyleneglycol oxystearate and medium-chain fatty di- and - triglycerides are present in a weight ratio between 1:10 and 1:20.

13. A pharmaceutical preparation according to claim 12, wherein said benzodiazepine is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one.

14. A process for preparing a pharmaceutical preparation with benzodiazepines as the active ingredients, and process comprising the steps of:

dissolving 0.1 to 5 parts by weight of a benzodiazepine in 3 to 50 parts by weight of a first solvent selected from the group consisting of a polyalkylene glycol, glycerine-polyethylene glycol oxy fatty acid esters, partial fatty acid esters of sorbitol, partial fatty acid esters of polyhydroxyethylene-sorbitol, polyvinyl pyrrolidones, polyvinyl alcohols, polyhydroxyethylene fatty alcohol esters, polyhydroxyethylene fatty acid esters polyhydroxy-

8

ethylene-polyhydroxyethylene condensates and propylene carbonate, and a second solvent which is ethanol which may be at least partly replaced by a compound selected from the group consisting of a medium-chain fatty acid diglyceride and a medium-chain fatty acid triglyceride, and 20-70 parts by weight of propellant, on the basis of halogenated hydrocarbon; and

filling the resulting solution in containers for administration as an aerosol with spray jets between 35 and 500  $\mu$ l.

15. A process according to claim 14, wherein said first solvent is polyethylene glycol.

16. A process according to claim 14, wherein said first solvent is selected from the group consisting of glycerine-polyethylene glycoloxystearate and glycerine-polyethylene glycol oxystearate.

• • • • •

20

25

30

35

40

45

50

55

60

65

109-2



US005352704A

**United States Patent** [19]  
**Okuyama et al.**

[11] **Patent Number:** 5,352,704  
[45] **Date of Patent:** Oct. 4, 1994

[54] **GUANIDINO BENZENE DERIVATIVES**

[75] **Inventors:** Akira Okuyama; Kyozo Naito;  
Hidetoshi Ogino; Toshio Nagase;  
Kiyofumi Ishikawa; Nobuo Tanaka,  
all of Meguro, Japan  
[73] **Assignee:** Banyu Pharmaceutical Co., Ltd.,  
Tokyo, Japan  
[21] **Appl. No.:** 963,528  
[22] **Filed:** Oct. 20, 1992

**Related U.S. Application Data**

[63] **Continuation of Ser. No. 630,985, Dec. 24, 1990, abandoned.**

[30] **Foreign Application Priority Data**

Dec. 22, 1989 [JP] Japan ..... 1-334188

[51] **Int. Cl.** ..... A61K 31/168; C07C 233/64  
[52] **U.S. Cl.** ..... 514/619; 564/168  
[58] **Field of Search** ..... 564/168, 230, 237, 238,  
564/164; 514/619, 620, 634, 631

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

3,824,267 7/1974 Ito et al. .... 562/439  
4,514,416 4/1985 Fujii et al. .... 549/442  
4,820,730 4/1989 Fujii et al. .... 514/510  
4,851,441 7/1989 Higa et al. .... 564/237

**FOREIGN PATENT DOCUMENTS**

0214429 3/1987 European Pat. Off. .  
2436731 5/1979 France .  
2-287021 8/1990 Japan ..... A61K 31/245  
2-243624 9/1990 Japan ..... A61K 31/24  
2-262516 10/1990 Japan ..... A61K 31/245

**Primary Examiner**—Shailendra Kumar  
**Attorney, Agent, or Firm**—Wegner, Cantor, Mueller & Payer

[57] **ABSTRACT**

A guanidinobenzene derivative represented by the formula (I):



wherein R<sup>1</sup> represents a substituent selected from the group consisting of a phenyl group substituted by an amidino group and a naphthyl group substituted by an amidino group, and salt thereof; a process for the production thereof; and an antiviral pharmaceutical composition comprising the compound.

2 Claims, No Drawings

administration, 1 to 2 times a day; for an intranasal administration, 0.1 to 500 mg per administration, 2 to 4 times a day; for eye dropping, 0.1 to 50 mg per administration, 3 to 4 times a day; and as an ointment, 1 to 500 mg per administration, 1 to 3 times a day.

The present pharmaceutical composition can be formulated in any way corresponding to the administration route thereof as described above, and this includes enteral and parenteral formulations.

For an oral administration, the present pharmaceutical composition is preferably formulated in a unit dose form, such as tablets, troches, powders, dragees, particles or capsules. For the formulation of these compositions, a binder such as gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropyl methyl cellulose, methyl cellulose, crystalline cellulose or sodium carboxymethyl cellulose; a filler such as lactose, sucrose, mannitol, potato starch, calcium phosphate, sorbitol or crystalline cellulose; a lubricant such as magnesium stearate, talc, polyethylene glycol or silica; and/or a disintegration agent such as potato starch, lower-substituted hydroxypropyl cellulose, calcium carboxymethyl cellulose or sodium carboxymethyl starch, alone or in combination, are used. Soft capsule may contain a conventional vehicle such as plant oil, polyethylene glycol or glycerol, or an oily suspending agent given hereinafter, a solution, or a wetting agent such as surfactant.

A liquid formulation is, for example, an aqueous or oily suspension, solution, syrup or elixir. Alternatively, a lyophilized product may be reconstructed to form a liquid formulation immediately prior to use. For the liquid formulation, a suspension agent such as methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, tragacanth gum, gelatin or sodium alginate; an emulsifier such as lecithin, sorbitan, fatty acid ester, gum arabic or tragacanth gum; a wetting agent such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, hydrogenated ricinus oil, sesame oil, soybean oil, propylene glycol, polyethylene glycol or ethyl alcohol; a preservative such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate or sorbic acid, and an additive such as simple syrup, sucrose, sorbitol or mannitol, may be used alone or in combination.

As a base for a rectal administration formulation, an oily base such as cocoa butter, white petrol or triglyceride, or a water soluble base such as glycerol, glycerogelatin or macrogol is used.

An additive for an injection formulation includes a dissolving aid such as polyoxyethylene, hardened ricinus oil or sodium benzoate, an osmotic pressure-adjusting agent such as glucose, sodium chloride or glycerol; a stabilizer such as sodium sulfite, anhydrous sodium sulfite, sodium metabisulfite or glycerol may be used alone or in combination.

For an inhalation to a respiratory organ such as the bronchia or nose, an aerosol, inhalation solution, liquid, powders, capsules or ointment can be used. The aerosol may be an oily aerosol comprising a non-ionic surfactant such as alcohol or Span 80, an ampholytic surface active agent such as lecithin, or a dispersant such as cetylalcohol, and a propellant such as butane or Freon (TM); or an aqueous aerosol comprising an osmotic pressure-adjusting agent such as physiological saline, phosphate buffer or acetate buffer, and purified water or injectable distilled water. For the liquid formulation,

for example, polyethylene glycol, sorbitol, polysorbate or physiological saline may be used as a carrier. For powders, for example, crystalline cellulose,  $\alpha$ -cellulose, cross-linked sodium carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl starch or amylose may be used as a carrier. In addition, these powders may be filled in a capsule. For an ointment, for example, polyethylene glycol, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or the like may be used as a carrier. Moreover, the active ingredient may be placed on the mucosa by inhalation or a nasal application, to deliver the ingredient in a sustained manner. For this purpose, the formulation may contain, for example, a cellulose ether such as methyl cellulose, ethyl cellulose, propyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose or hydroxypropyl cellulose, or a synthetic polymer such as polyacrylate or carboxyvinyl polymer, as the base material.

These pharmaceutical compositions can be prepared according to a conventional procedure.

The present pharmaceutical composition may contain one of the present compounds in an amount of about 0.1 to 100%, preferably 0.5 to 90%, by weight of the composition.

Next, the antiviral activity of the present compound is demonstrated by the following pharmacological tests. In the tests the following compounds:

Compound A: 4-guanidinobenzonic acid 4-amidinobenzamide.2 methanesulfonate; and  
Compound B: 4-guanidinobenzonic acid 6-amidino-2-naphthylamide.2 methanesulfonate, were used.

#### Pharmacological test 1. Inhibitory action on plaque formation by human influenza virus

The inhibitory activity of the present compounds A and B on plaque formation by human influenza virus A/WSN was measured according to a method described in Virology Vol. 29, 84-91, 1966.

Namely,  $1 \times 10^6$  MDCK cells (dog kidney cells) were inoculated in 6 cm plastic dish containing D-MEM medium, and cultured in a  $\text{CO}_2$  incubator for 24 hours, and after discarding the medium, 0.1 ml of a diluted virus solution containing about 50 plaque forming units of human influenza virus A/WSN was added to the cultured cells. After shaking, the dish was allowed to stand at room temperature for 30 minutes, a solubilized agar containing a desired amount of a test compound was overlaid. After 3 days culture, the agar layer was removed, and cells were stained with a staining solution to count the number of plaques. Next, a plaque formation inhibition ratio was calculated according to the following equation. The result is shown in Table 1.

Inhibition ratio (%) =  $(1 - T/C) \times 100$   
wherein

T: mean number of plaques in the presence of a test compound;

C: mean number of plaques of control.

Note, in the above test, the D-MEM medium, the solution for diluting the virus, the upper layer agar, and the staining solution were prepared as follows:

#### (D-MEM medium)

First, 9.5 g of powder of Dulbecco's Modified EAGLE MEDIUM "Nissui" was dissolved in 1 l of distilled water (the resulting solution is designated 1 $\times$ DMEM hereinafter), and the solution was autoclaved. L-glutamine (0.584 g), filtered aqueous solution of kanamycin (0.1 g), and 20 ml of a 7.5% sodium bicar-

United States Patent [19]  
Aberg et al.

[11] Patent Number: 5,595,997  
[45] Date of Patent: Jan. 21, 1997

[54] METHODS AND COMPOSITIONS FOR  
TREATING ALLERGIC RHINITIS AND  
OTHER DISORDERS USING  
DESCARBOETHOXYLORATADINE

[75] Inventors: A. K. Gunnar Aberg, Westborough;  
John R. McCollough, Worcester; Rodd  
R. Smith, Shrewsbury, all of Mass.

[73] Assignee: Serracor Inc., Marlborough, Mass.

[21] Appl. No.: 366,651

[22] Filed: Dec. 30, 1994

[51] Int. Cl.<sup>6</sup> A61K 31/44

[52] U.S. Cl. 514/290; 514/291; 514/292

[58] Field of Search 514/290, 291,  
514/292

[56] References Cited

U.S. PATENT DOCUMENTS

4,659,716 4/1987 Villal et al. 514/290  
5,019,391 5/1991 Goshier et al. 514/461  
5,089,496 2/1992 Fivinski et al. 514/253

FOREIGN PATENT DOCUMENTS

0288640 11/1988 European Pat. Off.  
WO83/05707 4/1983 WIPO  
WO92/00283 1/1992 WIPO  
WO92/11034 7/1992 WIPO

OTHER PUBLICATIONS

Berthon et al., "In Vitro Inhibition, by Loratadine and Descarboethoxyloratadine, of Histamine Release from Human Basophils, and of Histamine Release and Intracellular Calcium Fluxes in Rat Basophilic Leukemia Cells (RBL-2H3)" *Biochemical Pharmacology* 47(5), pp. 789-794 (1994).  
Brandes et al., "Enhanced Cancer Growth in Mice Administered Daily Human-Equivalent Doses of Some H<sub>1</sub>-Antihistamines: Predictive In Vitro Correlates" *J. Nat. Can. Inst. Reports*, 86(10), pp. 770-775 (1994).  
Kleine-Tebbe et al., "Inhibition of IgE- and non-IgE-mediated histamine release from human basophil leukocytes in vitro by a histamine H<sub>1</sub>-antagonist, descarboethoxyloratadine" *J. Allergy Clin. Immunol.* 93(2), pp. 494-500 (1994).  
Mindoune et al., "Inhibitory Effect of the H<sub>1</sub> Antagonist Loratadine on Histamine Release from Human Basophils" *Int. Arch. Allergy Immunol.* (105), pp. 12-17 (1994).  
Zhong et al., "HPLC-Bestimmung Von Loratadin und seinem aktiven Metaboliten Descarboethoxyloratadin in Humanpharmen" *Pharmazie* (49) II.10, pp. 736-739 (1994) (English abstract attached).  
Quercia et al., "Focus on loratadine: A new second-generation non-sedating H<sub>1</sub>-receptor antagonist" *Hosp. Formul.* (28), pp. 137-153 (1993).

Product Insert CR-318/17597400 Jul. 1993 Schering Corporation (1992, 1993).

Brandes et al., "Stimulation of Malignant Growth in Rodents by Antidepressant Drugs at Clinically Relevant Doses" *Cancer Research*, (52), pp. 3796-3800 (1992).

Knowles, "Asterizole and Terfenadine-Induced Cardiovascular Effects" *Canadian J. Hosp. Pharm.* 45(1) pp. 33, 37 (1992).

Parkinson et al., "Evaluation of Loratadine as an Inducer of Liver Microsomal Cytochrome P450 in Rats and Mice" *Biochemical Pharmacology*, 43(10), pp. 2169-2180 (1992).

"Antihistamines" Chapter 16 *Side Effects of Drugs Annual* 14, pp. 135-138 Elsevier Science Publishers (1990).

Claissol et al., "Loratadine A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy" *Drugs*, 37, pp. 42-57 (1989).

"Antihistamines" Chapter 16 *Side Effects of Drugs Annual* 12, pp. 142-143 Elsevier Science Publishers (1988).

Simons et al., "Asterizole-Induced Torsades de Pointes" *Lancet* p. 624 (Sep. 10, 1988).

Temple et al., "Loratadine, an Antihistamine, Blocks antigen- and ionophore-induced Leukotriene Release From Human Lung In Vitro" *Prostaglandins*, 35(4), pp. 549-554 (1988).

Hilbert et al., "Pharmacokinetics and Dose Proportionality of Loratadine" *J. Clin. Pharmacol.* (27), pp. 694-698 (1987).

Craft, "Torsades de Pointes After Asterizole Overdose" *British Med. J.* (292), p. 660 (1986).

Barnett et al., "Evaluation of the CNS properties of SCH 29851, a potential non-sedating antihistamine" *Agents and Actions*, 14(3/6), pp. 390-397 (1984).

Wood, "Antiemetic Sickness and Anesthetic Drugs" *Drugs*, (17), 17 pp. 471-479 (1979).

Cohen et al., "Mechanism and Placebo in Treating Vertigo of Vestibular Origin" *Arch. Neurol.* (27), pp. 129-135 (1972).

Andersen et al., "Adverse Drug Interactions Clinically Important for the Dermatologist," *Arch. Dermatol.* 131:468-473, (1995).

Lavrijssen et al., "The Interaction of Ketocozazole, Itraconazole and Erythromycin With the In Vitro Metabolism of Antihistamines in Human Liver Microsomes," Abstract 1233, *Eur. J. Allergy Clin. Immunol.*, 48, Suppl. 16, 34 (1993).

Van Peer et al., "Ketocozazole Inhibits Loratadine Metabolism in Man," Abstract 1234, *Eur. J. Allergy Clin. Immunol.*, 48, Suppl. 16, 34(1993).

Primary Examiner—Theodore J. Cronin  
Attorney, Agent, or Firm—Pennis & Edmonds

[57] ABSTRACT

Methods are disclosed utilizing DCL, a metabolic derivative of loratadine, for the treatment of allergic rhinitis, and other disorders, while avoiding the concomitant liability of adverse side-effects associated with other non-sedating antihistamines.

7 Claims, No Drawings

Descarboethoxyloratadine

Thus, the methods of the present invention are less toxic than methods which use other non-sedating antihistamines.

#### 4.6 Example 6

##### Inhibition of cytochrome P450.

This study is conducted to determine the extent that lorazepam and DCL inhibit human cytochrome P4503A4 (CYP3A4). CYP3A4 is involved in many drug-drug interactions and quantitation of inhibition of CYP3A4 by lorazepam or DCL indicates the potential of such drug-drug interactions. Inhibition is measured using the model substrate testosterone and cDNA-derived CYP3A4 in microsomes prepared from a human lymphoblastoid cell line designated h3A4v3.

##### Study Design:

The inhibition study consists of the determination of the 50% inhibitory concentration ( $IC_{50}$ ) for the test substance. A single testosterone concentration (120  $\mu$ M, approximately twice the apparent  $K_m$ ) and ten test substance concentrations, separated by approximately  $1/2$  log, are tested in duplicate. Testosterone metabolism is assayed by the production of the 6( $\beta$ )-hydroxytestosterone metabolite. This metabolite is readily quantitated via HPLC separation with absorbance detection.

Storage/Preparation of the test substances and addition to the incubations:

The test substances will be stored at room temperature. The test substances will be dissolved in ethanol for addition to the incubations. The solvent concentration will be constant for all concentrations of the test substance.

##### $IC_{50}$ Determination:

Final test substance concentrations will be 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003 and 0  $\mu$ M. Each test concentration will be tested in duplicate incubations in accordance with the method below:

##### Method:

A 0.5 ml reaction mixture containing 0.7 mg/ml protein, 1.3 mM NADP<sup>+</sup>, 3.3 mM glucose-6-phosphate, 0.4 U/ml glucose-6-phosphate dehydrogenase, 3.3 mM magnesium chloride and 120  $\mu$ M testosterone in 100 mM potassium phosphate (pH 7.4) will be incubated at 37° C. for 30 min. A known quantity of 11( $\beta$ )-hydroxytestosterone will be added as an internal standard to correct for recovery during extraction. The reaction mixture will be extracted with 1 ml methylene chloride. The extract will be dried over anhydrous magnesium sulfate and evaporated under vacuum. The sample will be dissolved in methanol and injected into a 4.6x250 mm 5u C18 HPLC column and separated at 50° C. with a mobile phase methanol/water at a flow rate of 1 ml per min. The retention times are approximately 6 min for the 6( $\beta$ )-hydroxy, 8 min for 11( $\beta$ )-hydroxy and 12 min for testosterone. The product and internal standard are detected by their absorbance at 254 nm and quantitated by correcting for the extraction efficiency using the absorbance of the 11( $\beta$ )-hydroxy peak and comparing to the absorbance of a standard curve for 6( $\beta$ )-hydroxytestosterone.

##### Data reporting:

For each test substance, the concentration of 6( $\beta$ )-hydroxytestosterone metabolite in each replicate incubation is determined and the percentage inhibition relative to solvent control is calculated. The  $IC_{50}$  is calculated by linear interpolation.

Useful pharmaceutical dosage forms for administration of the compounds used in the methods of the present invention can be illustrated as follows:

#### 4.7. Example 7

##### Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 0.1 to 10 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

#### 4.8. Example 8

##### Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, lecithin, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 0.1 to 10 milligrams of the active ingredient. The capsules are washed and dried.

#### 4.9 Example 9

##### Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 0.1 to 10 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

The foregoing disclosure includes all the information deemed essential to enable those skilled in the art to practice the claimed invention. Because the cited patents or publications may provide further useful information these cited materials are hereby incorporated by reference in their entirety.

##### What is claimed is:

1. A method of treating allergic rhinitis in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of descarbonylorazepam or a pharmaceutically acceptable salt thereof.
2. The method of claim 1 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.
3. The method of claim 1 wherein said human has a higher than normal propensity for or incidence of cancer.
4. The method of claim 1, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.
5. The method of claim 1 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.
6. The method of claim 5 wherein the amount of DCL administered is from about 0.1 mg to about 5 mg per day.
7. The method of claim 1 wherein the amount of said DCL or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.

\* \* \* \* \*

2020  
Bogotá, D.C.,

**Doctor:**  
**Luis Felipe Castillo Gibsone**  
**Apoderado**

**Oficio N°:** 3795

**ASUNTO:**

|                   |         |
|-------------------|---------|
| Radicación PCT N° | 04-7561 |
| Trámite           | 011     |
| Evento            | 379     |
| Actuación         | 440     |
| Folios            | 009     |

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Reinaldo Pinilla Moreno, en su calidad de apoderado de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

  
**ALIX CARMENZA CESPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones.

**31 MAR. 2006**

El anterior requerimiento fue notificado por fijación en lista de fecha, \_\_\_\_\_.

202021

2020  
Bogotá, D.C.,

**Doctor:**  
**Luis Felipe Castillo Gibsone**  
**Apoderado**

**Oficio N°:** 3796

**ASUNTO:**

|                   |         |
|-------------------|---------|
| Radicación PCT N° | 04-7561 |
| Trámite           | 011     |
| Evento            | 379     |
| Actuación         | 440     |
| Folios            | 020     |

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado del Laboratorio Franco Colombiano Lafranco S.A., y Tecnoquímicas S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

  
**ALIX CARMENZA CESPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones.

**31 MAR. 2006**

El anterior requerimiento fue notificado por fijación en lista de fecha, \_\_\_\_\_.

202021