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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
06-796	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP2005/007340	7 July 2005 (07.07.2005)	14 July 2004 (14.07.2004)

TITLE OF INVENTION
Pharmaceutical Composition Of Piperazine Derivatives

APPLICANT(S) FOR DO/EO/US
Domenico Fanara et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected (Article 3).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau),
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4))
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern documents) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A preliminary amendment.
14. ☒ An Application Data Sheet under 37 CFR 1.76.
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20. Other items or information:
Form PTO/SB/O8A and International Search Report

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☒ Basic national fee (37 CFR 1.492(a)) **$300**	$ 300.00	
22. ☒ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/Us or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$200**	$ 200.00	
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TOTAL OF 21, 22 and 23 =	$ 900.00	

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19 -100 =	/50 =	0	x **$250**	$

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CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$
Total claims	12 -20 =		x **$50**	$
Independent claims	3 -3 =		X **$200**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$360**	$
			TOTAL OF ABOVE CALCULATIONS =	$
☐ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.				
			SUBTOTAL =	$ 900.00
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$
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Michael S. Greenfield
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(54) Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

(57) Abstract: The present invention relates to a liquid composition containing an active substance belonging to the family of substituted benzhydryl piperazines with reduced amounts of preservatives

WO 2006/005507 A2

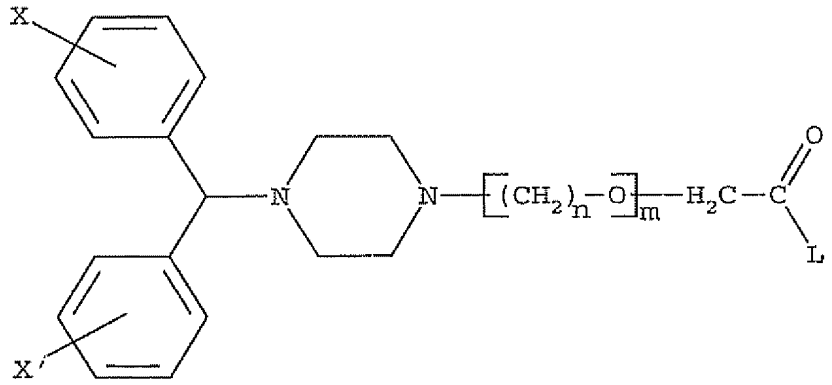
17.80.WO

Pharmaceutical composition of piperazine derivatives

The present invention relates to a liquid pharmaceutical composition containing an active substance such as cetirizine, levocetirizine and efletirizine.

A number of substances belonging to the family of substituted benzhydryl piperazines are known to be substances with useful pharmacological properties.

European Patent EP 58146, filed in the name of UCB, S.A., describes substituted benzhydryl piperazines having the general formula



in which L stands for an -OH or -NH_2 group, X and X', taken separately, stand for a hydrogen atom, a halogen atom, a linear or branched alkoxy radical at C_1 or C_4, or a trifluoromethyl radical, m equals 1 or 2, n equals 1 or 2, as well as their pharmaceutically acceptable salts.

Of these compounds, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid, also known under the name of cetirizine, and its dichlorohydrate are well known for their antihistaminic properties.

The active substances belonging to the family of substituted benzhydryl piperazines specifically include 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid (cetirizine), 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid (efletirizine), their optically active isomers when applicable, as well as their pharmaceutically acceptable salts.

In the pharmaceutical filed, solutions and drops are generally produced as germ-free compositions during their production processes. However, once the seal of the containers is broken, and the pharmaceutical compositions are completely used over a period of time, these pharmaceutical compositions are continuously exposed to

the risk of being contaminated by the microorganisms existing in the environment or the human body, each time the containers are used and their covers are opened or closed.

It has now surprisingly been found that the active substances belonging to the family of substituted benzhydryl piperazines possess a preservative effect in aqueous solutions.

The purpose of the invention concerns a liquid pharmaceutical composition containing an active substance belonging to the family of substituted benzhydryl piperazines chosen among cetirizine, levocetirizine and efletirizine, and a reduced amount of preservatives.

The present invention is based on the unexpected recognition that a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and a reduced amount of preservatives is stable during a long period of time. Stability means the capacity to resists to microbial contamination.

The present invention encompasses a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and an amount of parahydroxybenzoate esters used as preservatives less than 3 mg/ml of the composition, a normal concentration to preserve aqueous solutions.

The present invention encompasses a pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives corresponds to the bactericidal effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.

Generally, the pharmaceutical composition of the invention is liquid and preferably aqueous.

In the pharmaceutical composition of the invention, the active substance is generally selected from the group of cetirizine, levocetirizine, efletirizine, and their pharmaceutically acceptable salts. Preferably, the active substance is selected from the group of cetirizine, levocetirizine, and their pharmaceutically acceptable salts.

The term "cetirizine" refers to the racemate of [2-[4-[(4 chlorophenyl)phenylmethyl] -1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride salt which is well known as cetirizine dihydrochloride; its levorotatory and dextrorotatory enantiomers are known as levocetirizine and dextrocetirizine. Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent 0 058 146, Great Britain Patent 2.225.320, Great Britain Patent 2.225.321, United States Patent

5,478,941, European Patent application 0 601 028, European Patent Application 0 801 064 and International Patent Application WO 97/37982.

The term "levocetirizine" as used herein means the levorotatory enantiomer of cetirizine. More precisely, it means that the active substance comprises at least 90% by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis. Each individual optical isomer may be obtained from its racemic mixture by using conventional means such as disclosed in British patent application No. 2,225,321. Additionally, each individual optical isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution, such as disclosed in U.S. Patents No. 4,800,162 and 5,057,427.

The term "efletirizine" as used herein refers to 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid. Efletirizine is encompassed within general formula I of European patent No. 58146, which relates to substituted benzhydrylpiperazine derivatives. Efletirizine has been found to possess excellent antihistaminic properties. It belongs to the pharmacological class of histamine H_1-receptor antagonists and shows in vitro high affinity and selectivity for H_1-receptors. It is useful as an antiallergic, and antihistaminic agent. Two pseudopolymorphic crystalline forms of efletirizine dihydrochloride, namely anhydrous efletirizine dihydrochloride and efletirizine dihydrochloride monohydrate, are described in the European patent No. 1 034 171, and another pseudopolymorphic form of efletirizine dihydrochloride is described in the international patent application WO 03/009849. Processes for preparing efletirizine or a pharmaceutically acceptable salt thereof have been described in European Patent 1 034 171, and in the international patent applications WO 97/37982 and WO 03/009849.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also its metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the aminoacid salts. The best results have been obtained with dihydrochloride salts.

By preservatives we understand a chemically substance that inhibits the development of microorganisms or, in an ideal instance, kills them; so antimicrobial agent able to limit or avoid the growth of microorganisms such as bacteria, yeast and moulds in a solution. Preservatives will comply with Eur P. and USP requirements: for a product incubated with a large number of bacteria and fungi, the preservative must

kill and reduce a required amount of bacteria and fungi within a prescribed time period.

Examples of preservatives are p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate and their sodium salts), acrinol, methyl rosaniline chloride, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, cetylpyrodium bromide, chlorohexidine, chlorohexidine acetate, benzylalcohol, alcohol, chlorobutanol, isopropanol, ethanol, thimerosal, phenol, sorbic acid, potassium and calcium sorbate, benzoic acid, potassium and calcium benzoate, sodium benzoate, calcium acetate, calcium disodium ethylenediaminetetraacetate, calcium propionate, calcium sorbate, diethyl pyrocarbonate, sulphur dioxide, sodium sulphite, sodium bisulfite, boric acid, sodium tetraborate, propionic acid, sodium and calcium propionate, sodium thiosulfate, or a mixture therefore. Generally, the preservative is selected from the group of thimerosal, chlorohexidine acetate, benzylalcohol, benzalkonium chloride, p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate or a mixture thereof. Preferably the preservative is selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate. Best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.5 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.01 and 1.125 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.1 and 1 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of thimerosal selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.007 and 0.025 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of chlorhexidine acetate selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of

0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.007 and 0.025 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of benzylalcohol selected in the range of 0.0001 and 10 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.05 and 7.5 mg/ml. More preferably it contains an amount of preservatives selected in the range of 1 and 5 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of benzalkonium chloride selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.01 and 0.025 mg/ml.

The amount of the selected preservative is defined by comparison with the amount of parahydroxybenzoate ester leading to the same preservative effect. The optimum amount of preservative used in the invention depends on its nature. The preferred amount of preservative is such that it gives the same preservative effect as an amount of parahydroxybenzoate ester in the range of 0.2 and 1.125 mg/ml of the pharmaceutical composition.

By patient, we understand children, adolescents and adults, preferably of 2 years old. The targeted patients are usually old from 2 years and more.

A preferred daily dosage provides from about 0,0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,001 to about 2 mg per kg of body weight per patient. The best results have been obtained with a daily dosage from about 0,005 to 1 mg per kg of body weight per patient. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administrated over about a 24 hours time period to reach a total given dosage. Best results have been obtained with an administration of a composition of the invention twice a day for infants; and 5 mg once a day for children and adults. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled person in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologicaly active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention include any conventional therapeutical inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, gum arabic, polyalkylene glycol, cellulose compounds and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical compositions according to the present invention may also be administered orally. They may also be administered by nasal instillation, aerosols. The pharmaceutical compositions which can be used for oral administration is liquid, for example, in the form of solutions, syrups, drops and the like.

The pharmaceutical forms, such as drops, nasal drops, eye drops and ear drops are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a stabilizing agent and the like. If appropriate, it is also possible to add sweeteners, coloring agents and the like.

Preferably, the pharmaceutical composition of the invention is administered in traditional form for oral administration, as oral liquid preparation such as syrup.

Best results have been obtained with an oral dosage form, in particular liquid formulations such as syrup for children.

An advantage of the invention is that reducing the concentration of the preservative leads to a reduction of the risk of an allergic reaction in sensitive patients.

Another advantage of the invention is the ability to make easier the manufacturing process avoiding the solubilization of important amounts of preservatives not freely soluble in water.

The invention is further defined by reference to the following examples.

Example 1. Preservative effect of cetirizine.

An oral solution and drops containing cetirizine are prepared. The compositions are given in table 1.

Table 1. – Cetirizine compositions

	Oral solution	Drops
Cetirizine hydrochloride (mg)	1	10
Sorbitol sol. At 70% (mg)	450	-
Glycerine (mg)	200	250
Propyleneglycol (mg)	50	350
Sodium saccharinate (mg)	1	10
Banana flavour (mg)	0.1754	-
Sodium acetate (mg)	4.2	10
Acetic acid	ad pH 5	ad pH 5
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops are inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test are determined. The results are given in tables 2 and 3.

Table 2. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	4.9×10^5	4.7×10^5	3.1×10^5	2.6×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	4.8×10^5
14	< 1	< 1	< 1	2	8.2×10^3
21	< 1	< 1	< 1	< 1	5.5×10^3
28	< 1	< 1	< 1	< 1	5.0×10^3

Table 3. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.5×10^5	3.8×10^5	2.2×10^5	2.6×10^5	1.6×10^6
7	< 100	< 100	< 100	< 100	$< 10^4$
14	< 1	< 1	< 1	< 1	<100
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples.

For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

Example 2. Preservative effect of levocetirizine.

An oral solution and drops containing levocetirizine are prepared. The compositions are given in table 4.

Table 4. – Levocetirizine compositions

	Oral solution	Drops
Levocetirizine hydrochloride (mg)	0.5	5
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops are inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test is determined. The results are given in tables 5 and 6.

Table 5. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.8×10^5	3.5×10^5	3.9×10^5	1.6×10^6
7	150	< 100	< 100	2.8×10^4	1.0×10^6
14	< 1	< 1	< 1	1.4×10^4	4.8×10^5
21	< 1	< 1	< 1	2.6×10^2	2.2×10^5
28	< 1	< 1	< 1	6.2×10^3	5.3×10^5

Table 6. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.5×10^5	3.1×10^5	1.8×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	9.0×10^4
14	< 1	< 1	< 1	< 1	<1000
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus is observed in the inoculated samples. A disappearance of Candida albicans and Aspergillus niger is also observed in the drops.

Example 3. Efficacy of antimicrobial preservation of cetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing cetirizine according to example 1 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) are prepared. The total amounts of p-hydroxybenzoate esters are 0.15 mg/ml, 0.45 mg/ml, 0.75 mg/ml and 1.05 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The results of the tests are given in tables 7 to 14.

Table 7. – Microbial content in inoculated sample of the oral solution containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.1×10^5	4.5×10^5	3.0×10^5	4.0×10^5	4.1×10^6
14	< 1	< 1	< 1	< 1	9.1×10^3
28	< 1	< 1	< 1	< 1	750

Table 8. – Microbial content in inoculated sample of the oral solution containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.2×10^5	4.9×10^5	3.3×10^5	2.9×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	2

Table 9. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	3.9×10^5	4.4×10^5	4.0×10^5	1.9×10^5	1.9×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 10. – Microbial content in inoculated sample of the oral solution containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	3.3×10^5	4.1×10^5	3.1×10^5	1.4×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 11. – Microbial content in inoculated sample of the drops containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.3×10^5	4.0×10^5	2.0×10^5	2.5×10^5	1.5×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 12. – Microbial content in inoculated sample of the drops containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.6×10^5	3.6×10^5	1.7×10^5	2.1×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 13. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p- hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.1×10^5	3.6×10^5	2.6×10^5	2.5×10^5	1.6×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 14. – Microbial content in inoculated sample of the drops containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.9×10^5	3.7×10^5	2.8×10^5	2.2×10^5	1.3×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples. For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria are achieved.

Example 4. Efficacy of antimicrobial preservation of levocetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing levocetirizine according to example 2 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) are prepared. The total amounts of p-hydroxybenzoate esters are 0.375 mg/ml, 0.75 mg/ml and 1.125 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The results of the tests are given in tables 15 to 20.

Table 15. – Microbial content in inoculated sample of the oral solution containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.7×10^5	1.3×10^5	2.8×10^5	3.8×10^5	1.6×10^6
14	< 1	< 1	< 1	1.7×10^4	1.6×10^6
28	< 1	< 1	< 1	< 1	<100

Table 16. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.5×10^5	1.6×10^5	2.4×10^5	3.4×10^6	1.6×10^6
14	< 1	< 1	< 1	5.5×10^2	1.4×10^4
28	< 1	< 1	< 1	< 1	< 1

Table 17. – Microbial content in inoculated sample of the oral solution containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.9×10^5	1.2×10^5	3.0×10^5	3.5×10^5	1.4×10^6
14	< 1	< 1	< 1	<10	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 18. – Microbial content in inoculated sample of the drops containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.2×10^5	2.6×10^5	1.7×10^5	1.8×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 19. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.0×10^5	3.0×10^5	1.8×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 20. – Microbial content in inoculated sample of the drops containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	2.9×10^5	6.9×10^4	2.7×10^5	5.0×10^4	1.5×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples.

For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria are achieved.

Example 5. Nasal solution containing cetirizine and benzalkonium chloride

A solution containing cetirizine is prepared. The composition is given in table 21.

Table 21. – Cetirizine composition

	Nasal solution
Cetirizine hydrochloride (mg)	10
Monobasic sodium phosphate (mg)	10.6
Dibasic sodium phosphate (mg)	29
Benzalkonium chloride (mg)	0.025
Purified water (ml)	ad 1

The efficacy of antimicrobial preservation of this solution is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The recommended efficacy criteria are achieved.

Example 6. Nasal solution containing efletirizine and p-hydroxybenzoate esters.

A solution containing efletirizine is prepared. The composition is given in table 22.

Table 22. – Efletirizine composition

	Nasal solution
Efletirizine hydrochloride (mg)	6
Hydroxypropylmethylcellulose (mg)	5
Monobasic sodium phosphate (mg)	8.1
Dibasic sodium phosphate (mg)	6.3
Edeteate disodium (mg)	0.5
Sodium chloride (mg)	1.93
Sodium hydroxide	ad pH 6.5
p-hydroxybenzoate esters (mg)	0.375
Purified water (ml)	ad 1

The efficacy of antimicrobial preservation of this solution is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The recommended efficacy criteria are achieved.

Example 7. Oral solutions and drops containing levocetirizine and benzylalcohol.

An oral solution and drops containing levocetirizine are prepared. The compositions are given in table 23.

Table 23. – Levocetirizine compositions

	Oral solution	Drops
Levocetirizine hydrochloride (mg)	0.5	5
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Benzylalcohol (mg)	5.0	5.0
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

Example 8. Oral solutions and drops containing efletirizine

An oral solution and drops containing efletirizine are prepared. The compositions are given in table 24.

Table 24. – Efletirizine compositions

	Oral solution	Drops
Efletirizine hydrochloride (mg)	1	10
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	4.2	10
Acetic acid (mg)	ad pH 5	ad pH 5
p-hydroxybenzoate esters (mg)	0.375	0.375
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

Example 9. Eye drops containing efletirizine and thimerosal, chlorhexidine acetate and p-hydroxybenzoate esters.

Three formulations of eye drops containing efletirizine are prepared. The compositions are given in table 25.

Table 25. – Efletirizine compositions

	Eye drops		
Efletirizine hydrochloride (mg)	10	10	10
Boric acid (mg)	20	20	20
Sodium hydroxide	ad pH 7	ad pH 7	ad pH 7
Thimerosal (mg)	0.05	-	-
Chlorhexidine acetate (mg)	-	0.05	-
p-hydroxybenzoate esters (mg)	-	-	0.375
Purified water (ml)	ad 1	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

CLAIMS

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives is such that it leads to the same preservative effects as a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.
2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.
3. A liquid pharmaceutical composition according to claim 1 or 2, characterized in that the preservative is selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.
4. A liquid pharmaceutical composition according to claim 3, characterized in that the preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.
5. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.4 mg/ml of the composition.
6. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of thimerosal selected in the range of 0.0001 and 0.05 mg/ml of the composition.
7. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of chlorhexidine acetate selected in the range of 0.0001 and 0.05 mg/ml of the composition.
8. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of benzylalcohol selected in the range of 0.0001 and 10 mg/ml of the composition.
9. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of benzalkonium chloride selected in the range of 0.0001 and 0.05 mg/ml of the composition.

10. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.

11. A liquid pharmaceutical composition according to any of the claims 1 to 12, characterized in that the active substance is levocetirizine.

12. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 06-796)

Application of:	**Domenico Fanara**	)	
		)	
Serial No.:	**To Be Assigned**	)	**Group Art Unit: TBA**
		)	
Int'l Serial No.:	**PCT/EP2005/007340**	)	**Examiner: TBA**
		)	
Filing Date:	**Herewith**	)	
		)	**Confirmation No.: TBA**
Title: Pharmaceutical Composition Of Piperazine Derivatives		)	
		)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Dear Sir:

Please consider the following amendments and remarks.

Amendments to the claims begin on page 2.

Remarks begin on page 4.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives is such that it leads to the same preservative effects as a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.

2. (Currently Amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein it is an aqueous composition.

3. (Currently amended) A liquid pharmaceutical composition according to claim 1~~ or 2~~, ~~characterized in that~~wherein the preservative is selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.

4. (Currently amended) A liquid pharmaceutical composition according to claim 3, ~~characterized in that~~wherein the preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

5. (Currently amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.4 mg/ml of the composition.

6. (Currently amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein the pharmaceutical composition contains an amount of thimerosal selected in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Currently amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein the pharmaceutical composition contains an amount of chlorhexidine acetate selected in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Currently amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein the pharmaceutical composition contains an amount of benzylalcohol selected in the range of 0.0001 and 10 mg/ml of the composition.

9. (Currently amended) A liquid pharmaceutical composition according to claim 1, ~~characterized in that~~wherein the pharmaceutical composition contains an amount of benzalkonium chloride selected in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Currently amended) A liquid pharmaceutical composition according to ~~any of the preceding claims~~claim 1, ~~characterized in that~~wherein the active substance is cetirizine.

11. (Currently amended) A liquid pharmaceutical composition according to ~~any of the claims 1 to 12~~claim 1, ~~characterized in that~~wherein the active substance is levocetirizine.

12. (Currently amended) A liquid pharmaceutical composition according to ~~any of the preceding claims~~claim 1, ~~characterized in that~~wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

REMARKS

The claims of this U.S. national phase of a PCT application were amended to reduce the number of claims and remove multiple dependencies in order to reduce the filing fee. No new subject matter has been added, nor has the scope of the claims been amended.

Enclosed herewith is the ISR and Form SB/08a listing the art cited in the ISR. We understand copies of the art cited in the ISR will be forwarded to the PTO by the International Authorities.

If there are any questions or comments regarding this Preliminary Amendment or application, the Examiner is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: September 28, 2006

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606
Telephone: 312-913-0001
Facsimile: 312-913-0002

PTO/SB/14 (08-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	06-796
	Application Number	
Title of Invention	Pharmaceutical Composition Of Piperazine Derivatives	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Domenico		Fanara	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Wanze	Country Of Residence[i]	BE
Citizenship under 37 CFR 1.41(b)[i]	IT		

Mailing Address of Applicant:

Address 1	Rue Pont de Soleil		
Address 2	2A		
City	Wanze	State/Province	
Postal Code	B-4520	Country[i]	BE

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jean		Scouvart	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Brussels	Country Of Residence[i]	BE
Citizenship under 37 CFR 1.41(b)[i]	BE		

Mailing Address of Applicant:

Address 1	Tir aux Pigeons, 72		
Address 2			
City	Brussels	State/Province	
Postal Code	B-1150	Country[i]	BE

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Claire		Poulain	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Brussels	Country Of Residence[i]	BE

PTO/SB/14 (08-05)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	06-796
	Application Number	
Title of Invention	Pharmaceutical Composition Of Piperazine Derivatives	

Citizenship under 37 CFR 1.41(b) i	FR			
Mailing Address of Applicant:				
Address 1	23 rue de Jonker			
Address 2				
City	Brussels	**State/Province**		
Postal Code	B1060	**Country**i	BE	

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Michel		Deleers	

Residence Information (Select One) ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Linkebeek	**Country Of Residence**i	BE
Citizenship under 37 CFR 1.41(b) i	BE		
Mailing Address of Applicant:			
Address 1	Square des braves		
Address 2			
City	Linkebeek	**State/Province**	
Postal Code	B1630	**Country**i	BE

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	20306		
Email Address	docketing@mbhb.com	Add Email	Remove Email
Email Address	greenfield@mbhb.com	Add Email	Remove Email

Application Information:

Title of the Invention	Pharmaceutical Composition Of Piperazine Derivatives		
Attorney Docket Number	06-796	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter			
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

PTO/SB/14 (08-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	06-796
	Application Number	
Title of Invention	Pharmaceutical Composition Of Piperazine Derivatives	

Publication Information:	
☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ US Representative (37 CFR 11.9)
Customer Number	20306		

Domestic Priority Information:

This section allows for the applicant to claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c). Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/EP2005/007340	2005-07-07

Additional Domestic Priority Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
04016519.3	EP	2004-07-14	◉ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☑

PTO/SB/14 (08-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	06-796
	Application Number	
Title of Invention	Pharmaceutical Composition Of Piperazine Derivatives	

Organization Name	UCB, S.A.		
Mailing Address Information:			
Address 1	60, Allee de la Recherche		
Address 2			
City	Brussels	**State/Province**	
Country [i] BE		Postal Code	B-1070
Phone Number		Fax Number	
Email Address			
Additional Assignee Data may be generated within this form by selecting the **Add** button.		Add	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Michael S. Greenfield/			Date (YYYY-MM-DD)	2006-09-28
First Name	Michael	Last Name	Greenfield	Registration Number	37142

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/08a (08-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	06-796

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5504113	A	1996-04-02	Lucero et al.	
	2	6319927	B1	2001-11-20	Martin	
	3	6432961	B1	2002-08-13	De Longueville et al.	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2004004705	WO	A	2004-01-15	Shannon Biotechnology		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	06-796

	2	0605203	EP	A	1994-07-06	Senju Pharma Co.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☑ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Michael S. Greenfield/	Date (YYYY-MM-DD)	2006-09-28
Name/Print	Michael S. Greenfield	Registration Number	37142

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
17.80.WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/007340	07/07/2005	14/07/2004

Applicant

UCB FARCHIM SA

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

This international search report consists of a total of 4 sheets

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

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
17.80.WO		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/007340	07/07/2005	14/07/2004
Applicant		
UCB FARCHIM SA		

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

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

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

1. **Basis of the report**

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

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

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

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

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

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/007340

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/08 A61K31/495

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 2004/004705 A (SHANNON BIOTECHNOLOGY LTD ; WALTERS JOHN ANTHONY (GB)) 15 January 2004 (2004-01-15) page 7, line 5 - line 23 page 16, line 20 - line 21 page 20 - page 21; example 1 claims 8,9	1,2,10, 12
X	US 5 504 113 A (LUCERO ET AL) 2 April 1996 (1996-04-02) figures 1,2 table II column 1, lines 5-23 column 2, lines 3-13 column 3, lines 25-31	1,2,9, 10,12

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex

* Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2006	13/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Villa Riva, A

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/007340

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 6 319 927 B1 (MARTIN PETER) 20 November 2001 (2001-11-20) column 2, lines 41-53 column 4, lines 11-26,39-42 examples 3-6	1,8,10, 12
A	US 6 432 961 B1 (DE LONGUEVILLE MARC ET AL) 13 August 2002 (2002-08-13) column 4, line 34 - line 37	1-12
A	EP 0 605 203 A (SENJU PHARMA CO) 6 July 1994 (1994-07-06) page 3, line 25 - line 53 page 11; example 5	1-12

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/007340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004004705 A	15-01-2004	AU 2003251152 A1	23-01-2004
US 5504113 A	02-04-1996	US 5658948 A	19-08-1997
US 6319927 B1	20-11-2001	US 6258814 B1	10-07-2001
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		SK 147493 A3	06-07-1994
		TW 401300 B	11-08-2000
		US 5419898 A	30-05-1995

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor:	Domenico Fanara
Filer:	Michael S. Greenfield/Erika Eklund
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	300	300
Natl Stage Search Fee - Report provided	1642	1	400	400
National Stage Exam - all other cases	1633	1	200	200
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**900**

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Application Number:	10599451
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First Named Inventor:	Domenico Fanara
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Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages
1	Transmittal letter	06-796_Transmittal.pdf	56242	no	3
Warnings:					
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2		06-796_Specification.pdf	785204	yes	19

	Multipart Description		
	Doc Desc	**Start**	**End**
	Abstract	1	1
	Specification	2	17
	Claims	18	19

Warnings:					
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3		06-796_Preliminary_Amendment.pdf	31319	yes	4

	Multipart Description		
	Doc Desc	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	4

Warnings:					
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4	Application Data Sheet	06-796_Application_Data_Sheet.pdf	1762454	no	5
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Filed	06-796_IDS.pdf	1024988	no	4
Warnings:					
Information:					

6	Documents submitted with 371 Applications	06-796_371_Documents.pdf	195304	no	5
Warnings:					
Information:					
7	Fee Worksheet (PTO-875)	fee-info.pdf	8393	no	2
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(54) Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

(57) Abstract: The present invention relates to a liquid composition containing an active substance belonging to the family of substituted benzhydryl piperazines with reduced amounts of preservatives.

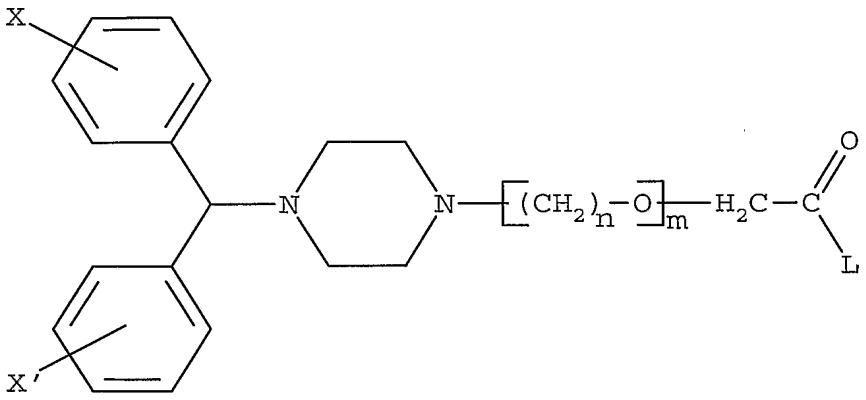
WO 2006/005507 A2

Pharmaceutical composition of piperazine derivatives

The present invention relates to a liquid pharmaceutical composition containing an active substance such as cetirizine, levocetirizine and efletirizine.

A number of substances belonging to the family of substituted benzhydryl piperazines are known to be substances with useful pharmacological properties.

European Patent EP 58146, filed in the name of UCB, S.A., describes substituted benzhydryl piperazines having the general formula



in which L stands for an -OH or -NH_2 group, X and X', taken separately, stand for a hydrogen atom, a halogen atom, a linear or branched alkoxy radical at C_1 or C_4, or a trifluoromethyl radical, m equals 1 or 2, n equals 1 or 2, as well as their pharmaceutically acceptable salts.

Of these compounds, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid, also known under the name of cetirizine, and its dichlorohydrate are well known for their antihistaminic properties.

The active substances belonging to the family of substituted benzhydryl piperazines specifically include 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid (cetirizine), 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid (efletirizine), their optically active isomers when applicable, as well as their pharmaceutically acceptable salts.

In the pharmaceutical filed, solutions and drops are generally produced as germ-free compositions during their production processes. However, once the seal of the containers is broken, and the pharmaceutical compositions are completely used over a period of time, these pharmaceutical compositions are continuously exposed to

the risk of being contaminated by the microorganisms existing in the environment or the human body, each time the containers are used and their covers are opened or closed.

It has now surprisingly been found that the active substances belonging to the family of substituted benzhydryl piperazines possess a preservative effect in aqueous solutions.

The purpose of the invention concerns a liquid pharmaceutical composition containing an active substance belonging to the family of substituted benzhydryl piperazines chosen among cetirizine, levocetirizine and efletirizine, and a reduced amount of preservatives.

The present invention is based on the unexpected recognition that a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and a reduced amount of preservatives is stable during a long period of time. Stability means the capacity to resists to microbial contamination.

The present invention encompasses a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and an amount of parahydroxybenzoate esters used as preservatives less than 3 mg/ml of the composition, a normal concentration to preserve aqueous solutions.

The present invention encompasses a pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives corresponds to the bactericidal effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.

Generally, the pharmaceutical composition of the invention is liquid and preferably aqueous.

In the pharmaceutical composition of the invention, the active substance is generally selected from the group of cetirizine, levocetirizine, efletirizine, and their pharmaceutically acceptable salts. Preferably, the active substance is selected from the group of cetirizine, levocetirizine, and their pharmaceutically acceptable salts.

The term "cetirizine" refers to the racemate of [2-[4-[(4 chlorophenyl)phenylmethyl] -1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride salt which is well known as cetirizine dihydrochloride; its levorotatory and dextrorotatory enantiomers are known as levocetirizine and dextrocetirizine. Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent 0 058 146, Great Britain Patent 2.225.320, Great Britain Patent 2.225.321, United States Patent

5,478,941, European Patent application 0 601 028, European Patent Application 0 801 064 and International Patent Application WO 97/37982.

The term "levocetirizine" as used herein means the levorotatory enantiomer of cetirizine. More precisely, it means that the active substance comprises at least 90% by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis. Each individual optical isomer may be obtained from its racemic mixture by using conventional means such as disclosed in British patent application No. 2,225,321. Additionally, each individual optical isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution, such as disclosed in U.S. Patents No. 4,800,162 and 5,057,427.

The term “efletirizine” as used herein refers to 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid. Efletirizine is encompassed within general formula I of European patent No. 58146, which relates to substituted benzhydrylpiperazine derivatives. Efletirizine has been found to possess excellent antihistaminic properties. It belongs to the pharmacological class of histamine H_1-receptor antagonists and shows in vitro high affinity and selectivity for H_1-receptors. It is useful as an antiallergic, and antihistaminic agent. Two pseudopolymorphic crystalline forms of efletirizine dihydrochloride, namely anhydrous efletirizine dihydrochloride and efletirizine dihydrochloride monohydrate, are described in the European patent No. 1 034 171, and another pseudopolymorphic form of efletirizine dihydrochloride is described in the international patent application WO 03/009849. Processes for preparing efletirizine or a pharmaceutically acceptable salt thereof have been described in European Patent 1 034 171, and in the international patent applications WO 97/37982 and WO 03/009849.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also its metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the aminoacid salts. The best results have been obtained with dihydrochloride salts.

By preservatives we understand a chemically substance that inhibits the development of microorganisms or, in an ideal instance, kills them; so antimicrobial agent able to limit or avoid the growth of microorganisms such as bacteria, yeast and moulds in a solution. Preservatives will comply with Eur P. and USP requirements: for a product incubated with a large number of bacteria and fungi, the preservative must

kill and reduce a required amount of bacteria and fungi within a prescribed time period.

Examples of preservatives are p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate and their sodium salts), acrinol, methyl rosaniline chloride, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, cetylpyrodium bromide, chlorohexidine, chlorohexidine acetate, benzylalcohol, alcohol, chlorobutanol, isopropanol, ethanol, thimerosal, phenol, sorbic acid, potassium and calcium sorbate, benzoic acid, potassium and calcium benzoate, sodium benzoate, calcium acetate, calcium disodium ethylenediaminetetraacetate, calcium propionate, calcium sorbate, diethyl pyrocarbonate, sulphur dioxide, sodium sulphite, sodium bisulfite, boric acid, sodium tetraborate, propionic acid, sodium and calcium propionate, sodium thiosulfate, or a mixture therefore. Generally, the preservative is selected from the group of thimerosal, chlorohexidine acetate, benzylalcohol, benzalkonium chloride, p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate or a mixture thereof. Preferably the preservative is selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate. Best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.5 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.01 and 1.125 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.1 and 1 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of thimerosal selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.007 and 0.025 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of chlorhexidine acetate selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of

0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.007 and 0.025 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of benzylalcohol selected in the range of 0.0001 and 10 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.05 and 7.5 mg/ml. More preferably it contains an amount of preservatives selected in the range of 1 and 5 mg/ml.

In a particular embodiment of the invention, the pharmaceutical composition contains an amount of benzalkonium chloride selected in the range of 0.0001 and 0.05 mg/ml of the composition. Preferably, it contains an amount selected in the range of 0.005 and 0.035 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.01 and 0.025 mg/ml.

The amount of the selected preservative is defined by comparison with the amount of parahydroxybenzoate ester leading to the same preservative effect. The optimum amount of preservative used in the invention depends on its nature. The preferred amount of preservative is such that it gives the same preservative effect as an amount of parahydroxybenzoate ester in the range of 0.2 and 1.125 mg/ml of the pharmaceutical composition.

By patient, we understand children, adolescents and adults, preferably of 2 years old. The targeted patients are usually old from 2 years and more.

A preferred daily dosage provides from about 0,0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,001 to about 2 mg per kg of body weight per patient. The best results have been obtained with a daily dosage from about 0,005 to 1 mg per kg of body weight per patient. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administrated over about a 24 hours time period to reach a total given dosage. Best results have been obtained with an administration of a composition of the invention twice a day for infants; and 5 mg once a day for children and adults. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled person in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologicaly active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention include any conventional therapeutical inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, gum arabic, polyalkylene glycol, cellulose compounds and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical compositions according to the present invention may also be administered orally. They may also be administered by nasal instillation, aerosols. The pharmaceutical compositions which can be used for oral administration is liquid, for example, in the form of solutions, syrups, drops and the like.

The pharmaceutical forms, such as drops, nasal drops, eye drops and ear drops are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a stabilizing agent and the like. If appropriate, it is also possible to add sweeteners, coloring agents and the like.

Preferably, the pharmaceutical composition of the invention is administered in traditional form for oral administration, as oral liquid preparation such as syrup.

Best results have been obtained with an oral dosage form, in particular liquid formulations such as syrup for children.

An advantage of the invention is that reducing the concentration of the preservative leads to a reduction of the risk of an allergic reaction in sensitive patients.

Another advantage of the invention is the ability to make easier the manufacturing process avoiding the solubilization of important amounts of preservatives not freely soluble in water.

The invention is further defined by reference to the following examples.

Example 1. Preservative effect of cetirizine.

An oral solution and drops containing cetirizine are prepared. The compositions are given in table 1.

Table 1. – Cetirizine compositions

	Oral solution	Drops
Cetirizine hydrochloride (mg)	1	10
Sorbitol sol. At 70% (mg)	450	-
Glycerine (mg)	200	250
Propyleneglycol (mg)	50	350
Sodium saccharinate (mg)	1	10
Banana flavour (mg)	0.1754	-
Sodium acetate (mg)	4.2	10
Acetic acid	ad pH 5	ad pH 5
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops are inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test are determined. The results are given in tables 2 and 3.

Table 2. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	4.9×10^5	4.7×10^5	3.1×10^5	2.6×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	4.8×10^5
14	< 1	< 1	< 1	2	8.2×10^3
21	< 1	< 1	< 1	< 1	5.5×10^3
28	< 1	< 1	< 1	< 1	5.0×10^3

Table 3. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.5×10^5	3.8×10^5	2.2×10^5	2.6×10^5	1.6×10^6
7	< 100	< 100	< 100	< 100	$< 10^4$
14	< 1	< 1	< 1	< 1	<100
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples.

For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

Example 2. Preservative effect of levocetirizine.

An oral solution and drops containing levocetirizine are prepared. The compositions are given in table 4.

Table 4. – Levocetirizine compositions

	Oral solution	Drops
Levocetirizine hydrochloride (mg)	0.5	5
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops are inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test is determined. The results are given in tables 5 and 6.

Table 5. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.8×10^5	3.5×10^5	3.9×10^5	1.6×10^6
7	150	< 100	< 100	2.8×10^4	1.0×10^6
14	< 1	< 1	< 1	1.4×10^4	4.8×10^5
21	< 1	< 1	< 1	2.6×10^2	2.2×10^5
28	< 1	< 1	< 1	6.2×10^3	5.3×10^5

Table 6. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.5×10^5	3.1×10^5	1.8×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	9.0×10^4
14	< 1	< 1	< 1	< 1	<1000
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus is observed in the inoculated samples. A disappearance of Candida albicans and Aspergillus niger is also observed in the drops.

Example 3. Efficacy of antimicrobial preservation of cetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing cetirizine according to example 1 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) are prepared. The total amounts of p-hydroxybenzoate esters are 0.15 mg/ml, 0.45 mg/ml, 0.75 mg/ml and 1.05 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The results of the tests are given in tables 7 to 14.

Table 7. – Microbial content in inoculated sample of the oral solution containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.1×10^5	4.5×10^5	3.0×10^5	4.0×10^5	4.1×10^6
14	< 1	< 1	< 1	< 1	9.1×10^3
28	< 1	< 1	< 1	< 1	750

Table 8. – Microbial content in inoculated sample of the oral solution containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.2×10^5	4.9×10^5	3.3×10^5	2.9×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	2

Table 9. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	3.9×10^5	4.4×10^5	4.0×10^5	1.9×10^5	1.9×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 10. – Microbial content in inoculated sample of the oral solution containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	3.3×10^5	4.1×10^5	3.1×10^5	1.4×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 11. – Microbial content in inoculated sample of the drops containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.3×10^5	4.0×10^5	2.0×10^5	2.5×10^5	1.5×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 12. – Microbial content in inoculated sample of the drops containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.6×10^5	3.6×10^5	1.7×10^5	2.1×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 13. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p- hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.1×10^5	3.6×10^5	2.6×10^5	2.5×10^5	1.6×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 14. – Microbial content in inoculated sample of the drops containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.9×10^5	3.7×10^5	2.8×10^5	2.2×10^5	1.3×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples. For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria are achieved.

Example 4. Efficacy of antimicrobial preservation of levocetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing levocetirizine according to example 2 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) are prepared. The total amounts of p-hydroxybenzoate esters are 0.375 mg/ml, 0.75 mg/ml and 1.125 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The results of the tests are given in tables 15 to 20.

Table 15. – Microbial content in inoculated sample of the oral solution containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.7×10^5	1.3×10^5	2.8×10^5	3.8×10^5	1.6×10^6
14	< 1	< 1	< 1	1.7×10^4	1.6×10^5
28	< 1	< 1	< 1	< 1	<100

Table 16. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.5×10^5	1.6×10^5	2.4×10^5	3.4×10^5	1.6×10^6
14	< 1	< 1	< 1	5.5×10^2	1.4×10^4
28	< 1	< 1	< 1	< 1	< 1

Table 17. – Microbial content in inoculated sample of the oral solution containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.9×10^5	1.2×10^5	3.0×10^5	3.5×10^5	1.4×10^6
14	< 1	< 1	< 1	<10	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 18. – Microbial content in inoculated sample of the drops containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.2×10^5	2.6×10^5	1.7×10^5	1.8×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 19. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.0×10^5	3.0×10^5	1.8×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 20. – Microbial content in inoculated sample of the drops containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	2.9×10^5	6.9×10^4	2.7×10^5	5.0×10^4	1.5×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples.

For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria are achieved.

Example 5. Nasal solution containing cetirizine and benzalkonium chloride

A solution containing cetirizine is prepared. The composition is given in table 21.

Table 21. – Cetirizine composition

	Nasal solution
Cetirizine hydrochloride (mg)	10
Monobasic sodium phosphate (mg)	10.6
Dibasic sodium phosphate (mg)	29
Benzalkonium chloride (mg)	0.025
Purified water (ml)	ad 1

The efficacy of antimicrobial preservation of this solution is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The recommended efficacy criteria are achieved.

Example 6. Nasal solution containing efletirizine and p-hydroxybenzoate esters.

A solution containing efletirizine is prepared. The composition is given in table 22.

Table 22. – Efletirizine composition

	Nasal solution
Efletirizine hydrochloride (mg)	6
Hydroxypropylmethylcellulose (mg)	5
Monobasic sodium phosphate (mg)	8.1
Dibasic sodium phosphate (mg)	6.3
Edeteate disodium (mg)	0.5
Sodium chloride (mg)	1.93
Sodium hydroxide	ad pH 6.5
p-hydroxybenzoate esters (mg)	0.375
Purified water (ml)	ad 1

The efficacy of antimicrobial preservation of this solution is determined according to the European Pharmacopoeia (Chap. 5.1.3.). The recommended efficacy criteria are achieved.

Example 7. Oral solutions and drops containing levocetirizine and benzylalcohol.

An oral solution and drops containing levocetirizine are prepared. The compositions are given in table 23.

Table 23. – Levocetirizine compositions

	Oral solution	Drops
Levocetirizine hydrochloride (mg)	0.5	5
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Benzylalcohol (mg)	5.0	5.0
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

Example 8. Oral solutions and drops containing efletirizine

An oral solution and drops containing efletirizine are prepared. The compositions are given in table 24.

Table 24. – Efletirizine compositions

	Oral solution	Drops
Efletirizine hydrochloride (mg)	1	10
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	4.2	10
Acetic acid (mg)	ad pH 5	ad pH 5
p-hydroxybenzoate esters (mg)	0.375	0.375
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

Example 9. Eye drops containing efletirizine and thimerosal, chlorhexidine acetate and p-hydroxybenzoate esters.

Three formulations of eye drops containing efletirizine are prepared. The compositions are given in table 25.

Table 25. – Efletirizine compositions

	Eye drops		
Efletirizine hydrochloride (mg)	10	10	10
Boric acid (mg)	20	20	20
Sodium hydroxide	ad pH 7	ad pH 7	ad pH 7
Thimerosal (mg)	0.05	-	-
Chlorhexidine acetate (mg)	-	0.05	-
p-hydroxybenzoate esters (mg)	-	-	0.375
Purified water (ml)	ad 1	ad 1	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). In all cases the recommended efficacy criteria are achieved.

CLAIMS

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives is such that it leads to the same preservative effects as a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.
2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.
3. A liquid pharmaceutical composition according to claim 1 or 2, characterized in that the preservative is selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.
4. A liquid pharmaceutical composition according to claim 3, characterized in that the preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.
5. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected in the range of 0.0001 and 1.4 mg/ml of the composition.
6. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of thimerosal selected in the range of 0.0001 and 0.05 mg/ml of the composition.
7. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of chlorhexidine acetate selected in the range of 0.0001 and 0.05 mg/ml of the composition.
8. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of benzylalcohol selected in the range of 0.0001 and 10 mg/ml of the composition.
9. A liquid pharmaceutical composition according to claim 1, characterized in that the pharmaceutical composition contains an amount of benzalkonium chloride selected in the range of 0.0001 and 0.05 mg/ml of the composition.

10. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.

11. A liquid pharmaceutical composition according to any of the claims 1 to 12, characterized in that the active substance is levocetirizine.

12. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

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Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Pharmaceutical composition of piperazine derivatives

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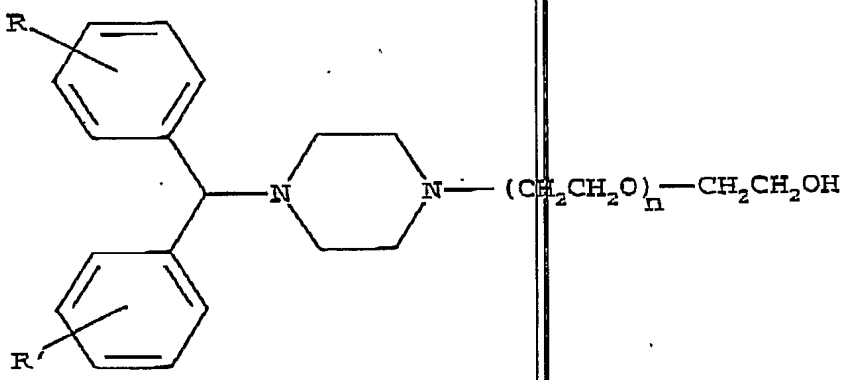
Pharmaceutical composition of piperazine derivatives

The present invention relates to a liquid pharmaceutical composition containing an active substance belonging to the family of substituted benzhydryl piperazines.

A number of substances belonging to the family of substituted benzhydryl piperazines are known to be substances with useful pharmacological properties.

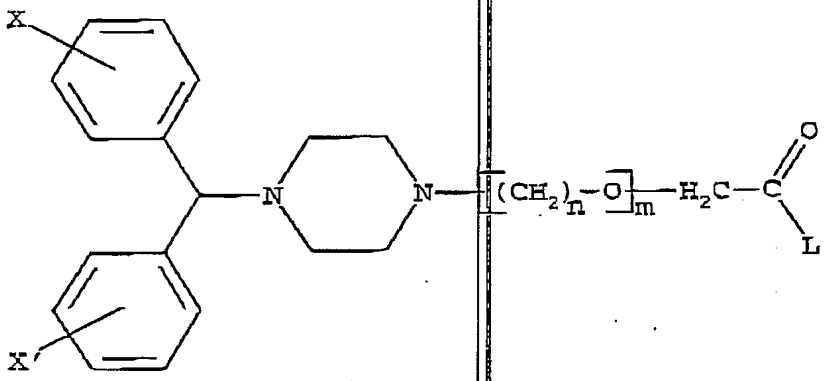
Patent GB 817231, for example, filed in the name of UCB, S.A., describes substituted benzhydryl piperazines having the general formula



in which R and R^1 independently of one another represent a hydrogen or halogen atom, an alkyl or alkoxy group, it being possible for R and R^1 to be in the ortho, meta or para position, and n stands for the number 1 or 2, as well as their pharmaceutically acceptable salts.

In particular, these compounds include 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]ethanol, in particular, also known under the name of hydroxyzine, and its dichlorohydrate, which are well known for their antihistaminic and tranquillising properties.

Patent EP 58146, filed in the name of UCB, S.A., describes substituted benzhydryl piperazines having the general formula



in which L stands for an -OH or -NH_2 group, X and X', taken separately, stand for a hydrogen atom, a halogen atom, a linear or branched alkoxy radical at C_1 or C_4, or a trifluoromethyl radical, m equals 1 or 2, n equals 1 or 2, as well as their pharmaceutically acceptable salts.

Of these compounds, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid, also known under the name of cetirizine, and its dichlorohydrate are well known for their antihistaminic properties.

The active substances belonging to the family of substituted benzhydryl piperazines specifically include 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid (cetirizine), 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]ethanol (hydroxyzine), 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid (efletirizine), 1-[(4-chlorophenyl]phenylmethyl]-4-[(3-methylphenyl]methyl]piperazine (meclizine) or 1-[(4-tert-butylphenyl)methyl]-4-[(4-chlorophenyl)phenylmethyl]piperazine (buclizine), their optically active isomers when applicable, as well as their pharmaceutically acceptable salts.

In the pharmaceutical filed, solutions and drops are generally produced as germ-free compositions during their production processes. However, once the seal of the containers is broken, and the pharmaceutical compositions are completely used over a period of time, these pharmaceutical compositions are continuously exposed to the risk of being contaminated by the microorganisms existing in the environment or the human body, each time the containers are used and their covers are opened or closed.

It has now surprisingly been found that the active substances belonging to the family of substituted benzhydryl piperazines possess a preservative effect in aqueous solutions.

The purpose of the invention concerns a liquid pharmaceutical composition containing an active substance belonging to the family of substituted benzhydryl piperazines and a reduced amount of preservatives.

The present invention is based on the unexpected recognition that a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and a reduced amount of preservatives is stable during a long period of time. Stability means the capacity to resists to microbial contamination.

The present invention encompasses a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and an amount of parahydroxybenzoate esters used as preservatives less than 3 mg/ml of the composition, a normal concentration to preserve aqueous solutions.

The present invention encompasses a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives corresponds to the bactericidal effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.

Generally, the pharmaceutical composition of the invention is liquid and preferably aqueous.

By active substances belonging to the family of substituted benzhydryl piperazines, we understand also their optically active isomers and their pharmaceutically acceptable salts.

In the pharmaceutical composition of the invention, the active substance is generally selected from the group of cetirizine, levocetirizine, hydroxyzine, efletirizine, meclizine, buclizine , and their pharmaceutically acceptable salts. Preferably, the active substance is selected from the group of cetirizine, levocetirizine, and their pharmaceutically acceptable salts.

The term "cetirizine" refers to the racemate of [2-[4-[(4 chlorophenyl)phenylmethyl] -1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride salt which is well known as cetirizine dihydrochloride; its levorotatory and dextrorotatory enantiomers are known as levocetirizine and dextrocetirizine. Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent 0 058 146, Great Britain Patent 2.225.320, Great Britain Patent 2.225.321, United States Patent 5,478,941, European Patent application 0 601 028, European Patent Application 0 801 064 and International Patent Application WO 97/37982.

The term "levocetirizine" as used herein means the levorotatory enantiomer of cetirizine. More precisely, it means that the active substance comprises at least 90% by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis. Each individual optical isomer may be obtained from its racemic mixture by using conventional means such as disclosed in British patent application No. 2,225,321. Additionally, each individual optical isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution, such as disclosed in U.S. Patents No. 4,800,162 and 5,057,427.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also its metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the aminoacid salts. The best results have been obtained with dihydrochloride salts.

International patent application 94/06429 describes a method utilising levocetirizine for the treatment of allergic asthma.

Generally, the pharmaceutical composition of the invention contains an amount of preservatives selected in the range of 0.01 and 1.4 mg/ml of the composition. Preferably, it contains an amount of preservatives selected in the range of 0.2 and 1.125 mg/ml. More preferably it contains an amount of preservatives selected in the range of 0.3 and 1 mg/ml. The best results have been obtained with an amount of 0.375 to 0.75 mg/ml of the composition. The amount of the selected preservative is defined by comparison with the amount of parahydroxybenzoate ester leading to the same preservative effect. The optimum amount of preservative used in the invention depends on its nature. The preferred amount of preservative is such that it gives the same preservative effect as an amount of parahydroxybenzoate ester in the range of 0.2 and 1.125 mg/ml of the pharmaceutical composition.

By preservatives we understand a chemically substance that inhibits the development of microorganisms or, in an ideal instance, kills them; so antimicrobial agent able to limit or avoid the growth of microorganisms such as bacteria, yeast and moulds in a solution. Preservatives will comply with Eur P. and USP requirements: for a product incubated with a large number of bacteria and fungi, the preservative must kill and reduce a required amount of bacteria and fungi within a prescribed time period.

Examples of preservatives are p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate and their sodium salts), acrinol, methyl rosaniline chloride, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, cetylpyrodium bromide, chlorohexidine, benzylalcohol, alcohol, chlorobutanol, isopropanol, ethanol, thimerosal, cresol, phenol, resorcin, sorbic acid, potassium and calcium sorbate, benzoic acid, potassium and calcium benzoate, sodium benzoate, calcium acetate, calcium disodium ethylenediaminetetraacetate, calcium propionate, calcium sorbate, diethyl pyrocarbonate, sulphur dioxide, sodium sulphite, sodium bisulfite, boric acid, sodium tetraborate, propionic acid, sodium and calcium propionate, nisin, sodium thiosulfate, or a mixture therefore. Generally, the preservative is selected from the group of p-hydroxybenzoate esters (methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , butyl parahydroxybenzoate , C1-C20 alkyl parahydroxybenzoate or a mixture thereof. Preferably the preservative is selected from the group of sodium benzoate, methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate. Best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.

By patient, we understand children, adolescents and adults, preferably of 2 years old. The targeted patients are usually old from 2 years and more.

A preferred daily dosage provides from about 0,0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient. A particularly preferred daily dosage is from about 0.001 to about 2 mg per kg of body weight per patient. The best results have been obtained with a daily dosage from about 0,005 to 1 mg per kg of body weight per patient. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administrated over about a 24 hours time period to reach a total given dosage. Bests results have been obtained with an administration of a composition of the invention twice a day for infants; and 5 mg once a day for children and adults. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled person in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologicaly active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention include any conventional therapeutical inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, gum arabic, polyalkylene glycol and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical compositions according to the present invention may also be administered orally. They may also be administered by nasal instillation, aerosols. The pharmaceutical compositions which can be used for oral administration is liquid, for example, in the form of solutions, syrups, drops and the like.

The pharmaceutical forms, such as drops, nasal drops, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a stabilizing agent and the like. If appropriate, it is also possible to add preservations, sweeteners, coloring agents and the like.

Preferably, the pharmaceutical composition of the invention is administered in traditional form for oral administration, as oral liquid preparation such as syrup.

Best results have been obtained with an oral dosage form, in particular liquid formulations such as syrup for children.

An advantage of the invention is that reducing the concentration of the preservative leads to a reduction of the risk of an allergic reaction in sensitive patients.

Another advantage of the invention is the ability to make easier the manufacturing process avoiding the solubilization of important amounts of preservatives not freely soluble in water.

The invention is further defined by reference to the following examples.

Example 1. Preservative effect of cetirizine.

An oral solution and drops containing cetirizine were prepared. The compositions are given in table 1.

Table 1. – Cetirizine compositions

	Oral solution	Drops
Cetirizine hydrochloride (mg)	1	10
Sorbitol sol. At 70% (mg)	450	-
Glycerine (mg)	200	250
Propyleneglycol (mg)	50	350
Sodium saccharinate (mg)	1	10
Banana flavour (mg)	0.1754	-
Sodium acetate (mg)	4.2	10
Acetic acid	ad pH 5	ad pH 5
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests were realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops were inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test were determined. The results are given in tables 2 and 3.

Table 2. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	4.9×10^5	4.7×10^5	3.1×10^5	2.6×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	4.8×10^5
14	< 1	< 1	< 1	2	8.2×10^3
21	< 1	< 1	< 1	< 1	5.5×10^3
28	< 1	< 1	< 1	< 1	5.0×10^3

Table 3. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.5×10^5	3.8×10^5	2.2×10^5	2.6×10^5	1.6×10^6
7	< 100	< 100	< 100	< 100	$< 10^4$
14	< 1	< 1	< 1	< 1	<100
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples. For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

Example 2. Preservative effect of levocetirizine.

An oral solution and drops containing levocetirizine were prepared. The compositions are given in table 4.

Table 4. – Levocetirizine compositions

	Oral solution	Drops
Levocetirizine hydrochloride (mg)	0.5	5
Maltitol-Lycasin 80-55 (mg)	400	-
Glycerine 85 %(mg)	235.2	294.1
Propyleneglycol (mg)	-	350
Sodium saccharinate (mg)	0.5	10
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Purified water (ml)	ad 1	ad 1

The antimicrobial preservative effectiveness tests were realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution and the drops were inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATC C6538, Candida albicans ATCC10231 and Aspergillus niger ATCC16404. The number of viable microorganisms per ml of preparations under test were determined. The results are given in tables 5 and 6.

Table 5. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.8×10^5	3.5×10^5	3.9×10^5	1.6×10^6
7	150	< 100	< 100	2.8×10^4	1.0×10^5
14	< 1	< 1	< 1	1.4×10^4	4.8×10^5
21	< 1	< 1	< 1	2.6×10^2	2.2×10^5
28	< 1	< 1	< 1	6.2×10^3	5.3×10^5

Table 6. – Microbial content in inoculated sample of the drops

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.5×10^5	3.1×10^5	1.8×10^5	1.7×10^6
7	< 100	< 100	< 100	< 100	9.0×10^4
14	< 1	< 1	< 1	< 1	<1000
21	< 1	< 1	< 1	< 1	< 1
28	< 1	< 1	< 1	< 1	< 1

In both cases, a rapid disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus is observed in the inoculated samples.
A disappearance of Candida albicans and Aspergillus niger is also observed in the drops.

Example 3. Efficacy of antimicrobial preservation of cetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing cetirizine according to example 1 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight). The total amounts of p-hydroxybenzoate esters were 0.15 mg/ml, 0.45 mg/ml, 0.75 mg/ml and 1.05 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops was determined according to the European Pharmacopoeia (Chap. 5,1.3.). The results of the tests is given in tables 7 to 14.

Table 7. – Microbial content in inoculated sample of the oral solution containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.1×10^5	4.5×10^5	3.0×10^5	4.0×10^5	4.1×10^6
14	< 1	< 1	< 1	< 1	9.1×10^3
28	< 1	< 1	< 1	< 1	750

Table 8. – Microbial content in inoculated sample of the oral solution containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	5.2×10^5	4.9×10^5	3.3×10^5	2.9×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	2

Table 9. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	3.7×10^5	2.3×10^6
0	3.9×10^5	4.4×10^5	4.0×10^5	1.9×10^5	1.9×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 10. – Microbial content in inoculated sample of the oral solution containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	5.5×10^5	4.6×10^5	4.0×10^5	$3,7 \times 10^5$	2.3×10^6
0	3.3×10^5	4.1×10^5	3.1×10^5	1.4×10^5	1.2×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 11. – Microbial content in inoculated sample of the drops containing 0.15 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.3×10^5	4.0×10^5	2.0×10^5	2.5×10^5	1.5×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 12. – Microbial content in inoculated sample of the drops containing 0.45 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.6×10^5	3.6×10^5	1.7×10^5	2.1×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 13. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p- hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	4.1×10^5	3.6×10^5	2.6×10^5	2.5×10^5	1.6×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

Table 14. – Microbial content in inoculated sample of the drops containing 1.05 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	4.0×10^5	3.4×10^5	3.6×10^5	3.5×10^5	1.8×10^6
0	3.9×10^5	3.7×10^5	2.8×10^5	2.2×10^5	1.3×10^6
14	< 1	< 1	< 1	< 1	<100
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples. For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria were achieved.

Example 4. Efficacy of antimicrobial preservation of levocetirizine aqueous solutions by p-hydroxybenzoate esters.

Oral solutions and drops containing levocetirizine according to example 2 but also containing mixtures of p-hydroxybenzoate esters (methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight). The total amounts of p-

hydroxybenzoate esters were 0.375 mg/ml, 0.75 mg/ml and 1.125 mg/ml. The efficacy of antimicrobial preservation of these solutions and drops was determined according to the European Pharmacopoeia (Chap. 5.1.3.). The results of the tests is given in tables 15 to 20.

Table 15. – Microbial content in inoculated sample of the oral solution containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.7×10^5	1.3×10^5	2.8×10^5	3.8×10^5	1.6×10^6
14	< 1	< 1	< 1	1.7×10^4	1.6×10^5
28	< 1	< 1	< 1	< 1	<100

Table 16. – Microbial content in inoculated sample of the oral solution containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.5×10^5	1.6×10^5	2.4×10^5	3.4×10^5	1.6×10^6
14	< 1	< 1	< 1	5.5×10^2	1.4×10^4
28	< 1	< 1	< 1	< 1	< 1

Table 17. – Microbial content in inoculated sample of the oral solution containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.9×10^5	1.2×10^5	3.0×10^5	3.5×10^5	1.4×10^6
14	< 1	< 1	< 1	<10	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 18. – Microbial content in inoculated sample of the drops containing 0.375 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.2×10^5	2.6×10^5	1.7×10^5	1.8×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 19. – Microbial content in inoculated sample of the drops containing 0.75 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.0×10^5	3.0×10^5	1.8×10^5	1.4×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

Table 20. – Microbial content in inoculated sample of the drops containing 1.125 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	2.9×10^5	6.9×10^4	2.7×10^5	5.0×10^4	1.5×10^6
14	< 1	< 1	< 1	< 1	< 1000
28	< 1	< 1	< 1	< 1	< 1

In all cases, the disappearance of Pseudomonas aeruginosa, Escherichia Coli, Staphylococcus aureus and Candida albicans is observed in the inoculated samples. For Aspergillus niger, the number of viable spores is significantly reduced in the oral solution while a rapid disappearance is observed in the drops.

In all cases the recommended efficacy criteria were achieved.

CLAIMS

1. A liquid pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, and in the case of other preservatives corresponds to the bactericidal effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1.5 mg/ml.
2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.
3. A liquid pharmaceutical composition according to claim 1 or 2, characterized in that the preservative is selected from the group of sodium benzoate, methyl parahydroxybenzoate, ethyl parahydroxybenzoate , propyl parahydroxybenzoate , a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate , and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.
4. A liquid pharmaceutical composition according to claim 3, characterized in that the preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.
5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the pharmaceutical composition contains an amount of preservatives selected in the range of 0.01 and 1.4 mg/ml of the composition.
6. A liquid pharmaceutical composition according to claim 5, characterized in that the pharmaceutical composition contains an amount of preservatives selected in the range of 0.2 and 1.125 mg/ml.
7. A liquid pharmaceutical composition according to claim 6, characterized in that the pharmaceutical composition contains an amount of preservatives selected in the range of 0.3 and 1 mg/ml.
8. A liquid pharmaceutical composition according to claim 7, characterized in that the pharmaceutical composition contains an amount of preservatives selected in the range of 0.375 to 0.75 mg/ml of the composition.
9. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.
10. A liquid pharmaceutical composition according to any of the claims 1 to 8, characterized in that the active substance is levocetirizine.

ABSTRACT

The present invention relates to a liquid composition containing an active substance belonging to the family of substituted benzhydryl piperazines with reduced amounts of preservatives.

DO/EO WORKSHEET

U.S. Appl. No. 10/599451 International Appl. No. EP2005/007340

Application filed by: ☐ 20 months ☐ 30 months

WIPO PUBLICATION INFORMATION:

Publication No.: WO2006/005507 A2 Publication Language: ☑ English ☐ Japanese ☐ German ☐ French ☐ Other: _____

Publication Date: Jan 19, 2006 Not Published: ☐ U.S. only designated ☐ EP request

Screening Done by: JLL

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- ☑ International Application *(RECORD COPY)*
- ☐ Article 19 Amendments
- ☐ PCT/IB/331
- ☐ PCT/IPEA/409 IPER (PCT/IPEA/416 on front)
- ☐ Annexes to 409
- ☑ Priority Document (s) No. 1
- ☐ International Appl. on Double Sided Paper *(COPIES MADE)*
- ☐ Request form PCT/RO/101
- ☑ PCT/ISA/210 - Search Report
- ☐ Search Report References
- ☐ Other: _____

RECEIPTS FROM THE APPLICANT *(other than checked above)*:

- ☑ Basic National Fee *(or authorization to charge)*
- ☑ Description
- ☑ Claims
- ☐ Words in the Drawing Figure(s) - (# of dwgs. 12)
- ☐ Article 19 Amendments
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered:
    - ☐ not a page for page substitution
    - ☐ other: _____
- ☐ Annexes to 409
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered:
    - ☐ not a page for page substitution
    - ☐ other: _____
- ☑ Preliminary Amendment(s) Filed on: 1. Sept 28, 2006 2. _____ 3. _____
- ☑ Information Disclosure Statement(s) Filed on: 1. Sept 28, 2006 2. _____ 3. _____
- ☐ Assignment Document
- ☐ Power of Attorney/ Change of Address
- ☐ Substitute Specification Filed on: 1. _____ 2. _____
- ☐ Small Entity
- ☐ Oath/ Declaration (executed)
  - ☐ surcharge was paid at the time of filing
- ☐ DNA Diskette ☐ Sequence Listing
- ☐ Other: 1. _____ 2. _____

NOTES: ☑ I.A. used as Specification ☐ Other:

35 U.S.C. 371 - Receipt of Request (PTO-1390)	Sept 28, 2006
Date Acceptable Oath/Declaration Received	
Date of Completion of requirements under 35 U.S.C. 371	
102(e) Date	
Date of Completion of DO/ EO 903 - Notification of Acceptance	
Date of Completion of DO/ EO 905 - Notification of Missing Requirements	May 17, 2007
Date of Completion of DO/ EO 906 - Notification of Missing 102(e) Requirements	
Date of Completion of DO/ EO 907 - Notification of Acceptance for 102(e) Date	
Date of Completion of DO/ EO 909 - Notification of Abandonment	
Date of Completion of DO/ EO 911 - Application Accepted Under 35 U.S.C. 111	
Date of Completion of DO/ EO 916 - Notification of Defective Response	
Date of Completion of DO/ EO 910 - Notification to Comply w/ Seq. Requirements	

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 10/599451

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY TYPE ☐		OTHER THAN SMALL ENTITY
U.S. NATIONAL STAGE FEES			RATE / FEE	OR	RATE / FEE
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300	BASIC FEE	OR	BASIC FEE 300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 100 / $ 200	EXAM. FEE		EXAM. FEE 200
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	ALL other situations = $ 250 / $ 500	SEARCH FEE		SEARCH FEE 400
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =		X $ 250 =
TOTAL CHARGEABLE CLAIMS	12 minus 20 =	* —	X $ 25 =	OR	X $ 50 =
INDEPENDENT CLAIMS	1 minus 3 =	* —	X $ 100 =	OR	X $ 200 =
MULTIPLE DEPENDENT CLAIM PRESENT	— ☐		+ $ 180 =	OR	+ $ 360 =
			TOTAL	OR	TOTAL 900

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/599451

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1			1			
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TOTAL IND.			1			
TOTAL DEP.			11			
TOTAL CLAIMS			12			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/599451

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
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TOTAL IND.	1		1			
TOTAL DEP	12		11			
TOTAL CLAIMS	13		12			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.						
TOTAL DEP						
TOTAL CLAIMS						

PTO - 1360 (REV. 11/04)

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

PTO/SB/06 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 10/599,451

CLAIMS AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
BASIC FEE (37 CFR 1.16(a))				$	OR		$300
TOTAL CLAIMS (37 CFR 1.16(c))	13 minus 20 =	*	X $ =		OR	X $ =	100.00
INDEPENDENT CLAIMS (37 CFR 1.16(b))	1 minus 3 =	*	X $ =		OR	X $ =	400.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(d))			+ $ =		OR	+ $ =	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL		OR	TOTAL	900.00

CLAIMS AS AMENDED – PART II

AMENDMENT A (Amdt. 9/28/06)

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	* 12	Minus	** 13	=
Independent (37 CFR 1.16(b))	* 1	Minus	*** 1	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $ =		OR	X $ =	
X $ =		OR	X $ =	
+ $ =		OR	+ $ =	
TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	900.00

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	*	Minus	**	=
Independent (37 CFR 1.16(b))	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X $ =		OR	X $ =	
X $ =		OR	X $ =	
+ $ =		OR	+ $ =	
TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total (37 CFR 1.16(c))	*	Minus	**	=
Independent (37 CFR 1.16(b))	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(d))				

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X $ =		OR	X $ =	
X $ =		OR	X $ =	
+ $ =		OR	+ $ =	
TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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PTO/SB/08a (08-03)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	06-796

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5504113	A	1996-04-02	Lucero et al.	
	2	6319927	B1	2001-11-20	Martin Peter	
	3	6432961	B1	2002-08-13	De Longueville Marc et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	WO 2004/004705	WO	A	2004-01-15	Shannon Biotechnology Ltd.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBA
	Examiner Name	TBA
	Attorney Docket Number	06-796

	2	EP 0 605 203	EP	A	1994-07-06	Senju Pharma Co.		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Database WPI, Section Ch, Week 198551, Derwent Publications Ltd., London, GB; Class A96, AN 1985-319295, XP002309643, & JP 60 204712 A (SS Pharmaceutical KK), 16 October 1985 (1985-10-16) *abstract*	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBA
	Examiner Name	TBA
	Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Michael S. Greenfield/	Date (YYYY-MM-DD)	2006-11-20
Name/Print	Michael S. Greenfield	Registration Number	37,142

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/004705 A2

(51) International Patent Classification[7]: A61K 31/192, 31/167, 31/616, 31/4545, 31/341, 31/495, 45/06, 38/01, 35/20, 35/78, 31/718, 31/7016, 31/702, A61P 29/00

(21) International Application Number: PCT/GB2003/002866

(22) International Filing Date: 3 July 2003 (03.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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0217130.4	24 July 2002 (24.07.2002)	GB
0227595.6	26 November 2002 (26.11.2002)	GB
0229315.7	17 December 2002 (17.12.2002)	GB
0300052.8	3 January 2003 (03.01.2003)	GB

(71) Applicant *(for all designated States except US)*: SHANNON BIOTECHNOLOGY LTD [GB/GB]; Houghton Manor, 24 Thicket Road, Houghton, Cambridgeshire PE28 2BQ (GB)

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: WALTERS, John, Anthony [GB/GB]; 18 Gordon Richards Close, Newmarket, Suffolk CB8 0BH (GB)

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(54) Title: PHARMACEUTICAL FORMULATIONS

(57) Abstract: Provided is a composition comprising one or more pharmaceutically active substances, a salt, and/or a protein, and/or carbohydrate, wherein the composition is capable of being dissolved or suspended in an aqueous solution to form a drink product in which the pharmaceutically active substance is suitable for storage.

PHARMACEUTICAL FORMULATIONS

FIELD OF THE INVENTION

The present invention concerns a pharmaceutical composition comprising medicinal active components, which composition can be dissolved or suspended in water to form a drink product that is suitable for storage. The composition comprises salts, proteins and/or carbohydrates to stabilise the pharmaceutical in water sufficiently for the drink product to be stored for sale in a wholesale or retail outlet or shop. The ready-to-drink formulation is advantageous, because it can be marketed as a ready made up, single dose product that can simply be drunk by the consumer with no need for the consumer to take the time and trouble to dissolve or suspend the pharmaceutical themselves. The product is fast acting and quick and easy to use, compared with existing products.

BACKGROUND OF THE INVENTION

Up-to-now medicinal active components generally have to be mixed with various additives and stabilisers to create a mixture which could be processed into powders, tablets, caplets (capsule-shaped tablets), liquid filled capsules, concentrated suspensions, syrups and tinctures.

The choice and utilisation of the appropriate binders and adhesives, disintegrating agents, fillers, lubricants, wetting agents/surfactants (galenism) is in some quarters of the industry considered an art. The research and development times for recipes in galenism are high and this influences the cost of the final product.

Further problems exist when the dose of the active ingredient is very small and has to be homogeneously distributed into the matrix of a large amount of "additives". A very homogenous distribution of the active component in a tablet recipe must be obtained and guaranteed before compressing the mixture. The coefficient of variation in the concentration of the medicinal active component from tablet-to-tablet must be very, very small.

In addition, all the added components may have a significant impact on the performance of a tablet or capsule, especially as regards bioavailability. Bioavailability is typically defined by:

'the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action'. Many so-called 'innocuous' additives and stabilisers used in the tabletting process can themselves affect the availability of the active substances for absorption.

Also, in the case of powdered active and excipient mixtures when compressed to form tablets, the tablets' hardness will influence their solubility very strongly. If a tablet is swallowed whole, the bioavailability may be influenced strongly too. The components of the mixture generally arrive in the stomach with an ill-defined particle size distribution, which adversely affects absorption.

The bioavailability of the active ingredient may also be affected in another way by the pressure applied during the tablet manufacture. Pressure generates heat that might deleteriously affect the active substances. It also disturbs the disintegration time of the tablet, consequently producing a poorer absorption rate.

Fast dissolving tablets have been designed to attempt to solve the above problems. However, such tablets require a large number of processing steps in their manufacture, and require know-how and specific additives to create a convenient 'to-the-consumer' tablet. The additives have an influence on the bioavailability and the absorption potential in the body, as discussed above. Further, the dispersion of the actives by, for example, effervescence, may result in a significant amount of the active coating the glass or container in which the dissolving tablet was dissolved. Accordingly, such tablets are still associated with a number of problems.

The possible influence of the numerous additives on the active component(s) is not as well evaluated as the medicinal active component itself. Hence, reducing these additives or avoiding them totally is important for increasing the effectiveness of the product.

This point is illustrated in package inserts which usually include a 'check before you take' message. One such message, for example, reads 'Do not take this medicine if you are allergic to any of the above mentioned ingredients'. This allergic threat may be known to the

consumer regarding the medicinal active component itself, but perhaps not for other components, as the allergic risk of many additives is not common knowledge among consumers. The safety record of such additives is patchy.

The number of additives that are declared in the package insert may be relatively large. For example, in NUROFEN® (the medicinal active component is ibuprofen) the tablet contains, in addition to the active component, fifteen other components. Paracetamol from ANADIN® contains, besides the active component, seven other substances and aspirin from ANADIN® contains five other substances.

The consumer has to swallow the tablet or capsules as a whole, or has to crush or crumble the tablets, and to disperse the (in most cases not totally soluble) tablet components in water and to drink the dispersion. During travelling or in places with poor water quality the necessary water or drink may not be available for the application of a medicine. Sometimes it is necessary to drink further amounts of water to deliver the medicine to the stomach.

If suspension or syrups are offered, a dosage using a spoon, teaspoon or a specially designed plastic spoon or device is necessary. Often after consumption of a medicine a drink is taken to remove the taste of the medicine.

There is also a problem in that the consumer sometimes does not read the package insert. In the case of an effervescent tablet the tablet must be dissolved in water before administration and not swallowed undissolved.

Sometimes it is very inconvenient for the consumer and occasionally not quite clear how to administer correctly the effervescent tablets; the package insert is ambiguous:

By way of example here are several exerts from treatment regimens:

".....Tablet is to be crushed and thoroughly dispersed in at least 120ml of drinking water; this solution is to be drunk, followed by approximately another 120ml of water".....

Comment: The procedure is definitively not standardised: what is *crushed*? To what extent? To a consumer what are 120ml? What is *thoroughly dispersed*?

".....The contents of one sachet are to be dissolved in water and swallowed"..... Comment: How do you empty the contents of a sachet quantitatively reproducibly?

".....The tablets should be either swallowed whole or dissolved in a glass of water"..... Comment: With a very high likelihood there will be a difference in the immediate bioavailability.

".....Take the medicine with a full glass of water or fruit juice. Add the liquid to the water."..... Comment: a full glass cannot be mixed correctly with the liquid.

A further two examples: (1) People are often aware that aspirin might have the potential for stomach ulceration. To reduce this likelihood people often take aspirin with milk to coat the stomach. However, the lactic acid present in the milk accentuates the natural acidity of aspirin, exacerbating this contra-indication. (2) Coffee and orange juice taken with alendronate reduces bioavailability by approximately 60%.

These examples show the more defined a medicinal component (i.e. without additives) is and the more defined the administration is, the better.

Accordingly, it is an aim of the present invention to solve the problems associated with known products. It is a further aim of the invention to provide a medicinal product in a form that is simple and straightforward for the consumer to take. Thus, the present invention aims to provide a ready-to-drink product, in which the pharmaceutical is pre-dissolved, or a product in which the pharmaceutical is ready to be dissolved in an aqueous solution, or in water, provided for this purpose as part of the product.

SUMMARY OF THE INVENTION

Thus, the present invention provides a composition comprising:

(a) one or more pharmaceutically active substances; and

(b) a salt, and/or a protein, and/or a carbohydrate;

wherein the composition is capable of being dissolved or suspended in an aqueous solution to form a drink product, in which the pharmaceutically active substance is suitable for storage.

The ready-to-drink product is advantageous, because it stabilises the pharmaceutical agent using ingredients normally present in a soft drink, rather than standard excipients, which have a number of problems as outlined above. On the whole soft drinks ingredients have an exceptional history of safety, but where a problem is known it is clearly defined e.g. "contains a source of phenylalanine" (e.g. in the case of artificial sweeteners, such as aspartame, which have contra-indications for sufferers of phenyl ketouria). Thus the ready-to-drink products of the present invention allow the consumer to choose a product with less chance of side effects and that is much more palatable than conventional products. The customer who has an allergy or suffers from another such side effect is now able to choose an alternative medicine and avoid the possibility that this could also contain a component to which he or she is allergic.

In the context of the present invention, suitable for storage means for storage in a wholesale outlet, before distribution, and/or in a retail outlet before sale to the customer. Generally, the pharmaceutically active component should be stable for many months in solution or suspension, in order for it to be suitable for such storage. The composition of the present invention is typically stable in aqueous solution under ambient conditions (less than 25°C at atmospheric pressure) for a period of 6 months or more, preferably 12 months or more, and more preferably 15 months or more. Most preferably it should be stable for 18 months or more. By stable, it is meant that 80 wt.% or more, preferably 90 wt.% or more, of the active ingredient remains unchanged as compared with the original quantity of that ingredient. Products that are dissolved on consumption by the consumer have a much lower stability. Typically, 10 wt.% of the active ingredient of such compositions decays or degrades within a period of 6 weeks or less.

The aqueous solution mentioned may be any suitable aqueous solution, including distilled and/or de-ionised water, tap water, still water, sparkling water, and any of the above with

added ingredients for stabilising the final solution/suspension or making the solution/suspension palatable.

The pharmaceuticals employed in the present invention are not especially limited. However, it is preferred that the one or more pharmaceutically active substances comprise one or more analgesics. Preferably the one or more analgesics are selected from ibuprofen and paracetamol (acetaminophen).

In a further embodiment, the present invention provides a composition comprising:

(a) one or more pharmaceutically active substances; and

(b) a salt, and/or a protein;

wherein the salt and/or the protein, and at least one of the pharmaceutically active substances, are soluble or sparingly soluble in water, and wherein the salt and/or protein are present in the composition in an amount of from 5 wt.% or less, such that the composition is capable of being dissolved in an aqueous solution to form a drink product.

Without being bound by theory, it is believed that he presence of a relatively small quantity of salt and/or protein is sufficient to render the composition stable for storage when dissolved in an aqueous solution. Known compositions which are designed for dissolution and consumption are not stable for storage, and instead comprise large quantities of salts and other excipients to aid in dissolution. For example, such products comprise large quantities of citric acid and sodium hydrogencarbonate in order to generate effervescence which aids dissolution and palatability of the product. However, these salts destabilise the pharmaceutical ingredient in these quantities, rendering the compositions unsuitable for storage in dissolved form.

Preferably the salt and/or protein is present in an amount of from 0.001-5 wt.%, more preferably from 0.001-2 wt.% and most preferably from 0.001-1 wt.%.

The pharmaceutical may be any pharmaceutical that is soluble or sparingly soluble in water, and is not otherwise limited. Preferably, the pharmaceutical comprises an analgesic, and more preferably it comprises paracetamol (acetaminophen).

The composition may comprise further additives as desired. It is especially preferred that the composition further comprises a carbohydrate. The carbohydrate may be present in the composition in an amount of from 0-20 wt.%, preferably from 0.1-20 wt.%, most preferably from 0.1-10 wt.%.

In a still further embodiment, the present invention provides a composition comprising:

(a) one or more pharmaceutically active substances; and

(b) 20 wt.% or less carbohydrate and/or 5 wt.% or less protein;

wherein at least one of the pharmaceutically active substances is capable of forming a suspension in water, such that the composition is capable of being suspended in an aqueous solution to form a drink product.

Without being bound by theory, it is believed that he presence of a relatively small quantity of carbohydrate is sufficient to render the composition stable for storage when suspended in an aqueous solution, by controlling the viscosity of the solution. As discussed above, known compositions which are designed for dissolution and consumption are not stable for storage, and instead comprise large quantities of carbohydrates and/or other excipients such as salts to aid in dissolution and suspension. Such products, in common with those for dissolvable species, often comprise large quantities of citric acid and sodium hydrogencarbonate in order to generate effervescence which aids dissolution and palatability of the product. However, these salts destabilise the pharmaceutical ingredient in these quantities, as discussed above.

The one or more pharmaceutically active substances in this embodiment of the invention are not especially limited, provided that they are capable of forming a suspension in aqueous solution. Preferably, the one or more pharmaceutical agents are selected from ibuprofen, loratadine, ranitidine, and cetirizine.

The composition may comprise further additives as desired. It is especially preferred that the composition further comprises a salt. The salt, (and the protein if present) may present in the composition in an amount of from 0-20 wt.%, preferably from 0.001-15 wt.%, more preferably 0.001-10 wt.%, and most preferably 0.001-6 wt.%.

The composition according to any of the above embodiments may comprise a salt, as already discussed. Any salt may be employed, provided that it does not adversely affect the utility of the composition. Preferably, the salt is selected from sodium chloride, sodium citrate, magnesium citrate, potassium chloride, potassium citrate, and sodium bicarbonate.

The composition according to any of the above embodiments may comprise a protein, as already discussed. Any protein may be employed, provided that it does not adversely affect the utility of the composition. Thus, the protein may be soluble, sparingly soluble, or may be capable of forming suspension, or a colloidal suspension in aqueous solution. Typically the protein is selected from a protein comprising lactoglobin, caseinate, and/or a protein derived from whey and/or soya. When whey protein is employed, the whey protein preferably comprises a whey protein extract comprising 60 wt.% or more of protein.

The composition according to any of the above embodiments may comprise a carbohydrate, as already discussed. Any carbohydrate may be employed, provided that it does not adversely affect the utility of the composition. Preferably, the carbohydrate is selected from maltodextrin, modified starch, fructo-oligosaccharides, lactose and galactose. When maltodextrin is employed, it is preferred that the maltodextrin is selected from maltodextrin with dextrose equivalent 4-8, maltodextrin with dextrose equivalent 8-12, and maltodextrin with dextrose equivalent 18-20.

As already alluded to, the present composition is particularly advantageous, since it can be readily made up into a ready-to-drink pharmaceutical product, with clear advantages to the consumer. Thus, generally the composition is formulated such that the one or more pharmaceutically active substances may be absorbed into the body via the digestive system.

Other pharmaceuticals and medicaments may be present in addition to the pharmaceutical mentioned above. Such further pharmaceuticals are not especially limited, provided that they do not interfere to the detriment of the effectiveness of the composition. The further medicine may thus be selected depending on the nature of the illness that the composition is designed to treat. Thus, in some embodiments, the composition may comprises one or more

further pharmaceutically active substances selected from antioxidants, nicotine, phospholipids, immune stimulants, agents effective against vascular disease, antihistamines, anti-obesity agents, agents effective against psoriasis, agents effective against an alcohol-induced hangover, agents effective against an anaesthesia-induced hangover, agents effective in the treatment of a cerebro vascular stroke, and agents effective in the treatment of bone disease.

In order to aid in dissolving or suspending the compositions of the present invention, the pharmaceutically active substances typically have an average particle diameter of less than 100 microns. However, larger particle sizes are possible, provided that the dissolution/suspension process is adapted accordingly. Preferably, the pharmaceutically active substances have an average particle diameter of less than 30 microns.

The composition according to the present invention may comprise further components for increasing the palatability of the ready-to-drink product. Thus, the composition may additionally comprise a simple sugar, if desired. Typically, the simple sugar is selected from lactose, galactose, glucose, fructose and any monomer sugar. The composition may further comprise flavourings, preservatives, sweetening agents, antioxidants, phospholipids, energy and/or immune stimulants, calcium and/or phytoestrogens. Such agents are well known in the soft drinks industry, and any such agents may be employed in the present compositions, provided that their effectiveness is not impaired.

The present invention further provides a method of making a composition as defined in any preceding claim, which method comprises blending the pharmaceutically active substance with the salt, and/or the protein, and/or the carbohydrate, and/or any further ingredients, and sieving the blended ingredients through a screen to form the composition. Optionally, the composition may be further processed into tablets, or other forms suitable for dissolution/suspension, if desired.

Further provided by the present invention is a drink product comprising a composition as defined in any preceding claim, which is dissolved or dispersed in aqueous solution. The drink product is a medicinal product and is stable for storage as discussed above. Generally

is in a 'one shot' dosage format. This means that when the whole drinks product is consumed, the consumer receives a standard dose of the medicament or pharmaceutical present in the drinks product. The drinks product is typically flavoured, coloured, and/or sweetened in order to give it the taste and appearance of a soft drink. The concentration of the pharmaceutical in the drink product is not especially limited, and depends on the pharmaceutical employed. Typical concentrations of pharmaceutical agent in solution range from approximately 1 μg/ml to approximately 70 mg/ml. The preferred type of product is a one 'shot' product, in which the drink can be finished in one swallow. The typical volume of drink in a single one 'shot' dose would be approximately 30 ml. Other products can be envisaged in which the volume is greater or smaller than this. The concentration of the pharmaceutical may be altered accordingly in order to ensure that a standard dose is still delivered.

The drink product of the present invention typically exhibits a pH of from 2.8-8.2. More preferably it has a pH of from 3.3-4.5 and most preferably a pH of from 3.8-4.4. This aids in stabilising the pharmaceutical ingredient, and is also desirable from a palatability viewpoint. Such pH values are well suited to the addition of fruit flavours and/or juices, which have a pH in a similar range.

The present invention also provides a method of making a drink product as defined above, comprising dissolving or suspending a composition as defined above to form an aqueous solution or suspension. The quantity of water or aqueous solution employed is not especially limited, since it is the quantity of the pharmaceutical in the composition that determines the correct standard dose. Preferably sufficient liquid should be added to substantially fully dissolve or suspend the pharmaceutically active ingredient. It is also preferred that the water, or aqueous solution, employed is heavily vortexed. This aids dissolution/suspension and allows lower quantities of additives to be employed.

The invention further provides a system for storing a medicinal product, which system comprises a container and a closure, wherein the closure comprises a compartment in which a composition may be stored separately from the contents of the container, and wherein the closure further allows the composition to be released into the container as required. The

container may be in the form of a bottle, sachet or other container suitable for holding a liquid and is preferably formed from glass or plastics material. The closure may be any form of closure, but is generally in the form of a cap or lid. The closure is preferably childproof.

In the above system, the compartment (or chamber) typically contains a composition of the present invention. However, the system is not limited to containing such compositions. Preferably, the system compartment contains one or more pharmaceutically active substances, which are unsuitable for storage in aqueous solution or in aqueous suspension.

The advantage of the system is that the composition may be stored in dry form, such that even pharmaceuticals that are inherently unstable in aqueous solution may be stored (such as aspirin). Preferably, the system comprises the correct quantity of solution in the container for dissolving/suspending the pharmaceutical, avoiding normal consumer uncertainties in such dry products that need to be dissolved on consumption.

Thus, it is preferred that the system comprises a pharmaceutical that is unstable in aqueous solution or suspension. Typically, the pharmaceutical is an analgesic. Preferably, the pharmaceutically active substance comprises aspirin.

The container may be empty if desired, in which case the consumer may fill the container with water. If necessary a level marker may be provided on the container for indicating the optimum quantity of water to add. Preferably, however, the container comprises water. Any type of water may be employed, such as distilled water, deionised water, tap water, still water and sparkling water. Preferably, the water is flavoured and/or sweetened.

It is especially preferred that the system of the present invention is adapted such that the contents of the closure compartment may be released into the container using a push mechanism. A preferred mechanism is shown in Figure 1. Preferably, the compartment or chamber is in communication with the container when the push mechanism is in the open configuration, and communication is prevented when it is in the closed position. Preferably, the compartment is isolated from the container by a frusto-conical section of the push mechanism, or a plunger, having an edge (e.g. at the widest portion of the conical section)

which abuts the casing of the closure. In the open position, the push mechanism edge sinks below the bottom edge of the closure casing to expose a gap through which the composition can fall into the communicating container.

Further provided by the present invention is a method for forming a medicinal drink in the container of a system as defined above, which method comprises:

(a) releasing the contents of the closure compartment into the container; and

(b) agitating the container to dissolve or disperse the contents of the closure compartment in the contents of the container.

The invention also provides use of a composition as defined above in the manufacture of a medicament that is effective as an analgesic. Preferably, the medicament is in the form of a drink product.

The invention will now be described in further detail by way of example only, with reference to the following Figure, in which:

Figure 1, shows the operation and components of a preferred system according to the present invention.

DESCRIPTION OF THE INVENTION

The invention refers to the solution of numerous problems inherent in the present formulations of drugs by offering a 'Ready-to-Drink' product comprising formulations of pharmaceutically active components without the addition of form-giving substances that might also have an effect on the efficacy and digestibility of the compressed tablets. Further, the 'Ready-to-Drink' products are very convenient to handle.

In particular the present invention aims to provide formulations for pharmaceutically active component using knowledge of the stabilisation of medicines in water combined with soft drinks manufacturing expertise: the use of a range of quick and short release sugars that do not provoke an insulin response in combination with a salt balance that is essentially isotonic for rapid delivery of all the components to the blood.

Accordingly, the present invention provides a composition comprising one or more pharmaceutically active substances, wherein the composition is capable of being dissolved or suspended in an aqueous solution to form a drink product.

The compositions comprising the pharmaceutically active substances are capable of being dissolved or dispersed (suspended) in water, without the normally used additives for the formulation of tablets, capsules, effervescent tablets, syrups, liquid filled capsules etc., thus forming the 'Ready-to-Drink' product.

Some pharmaceutically active substances, including aspirin, are not chemically stable in water and cannot be maintained in their active form in aqueous solution for any length of time. Therefore, it is required that these substances are kept separate from water until their use is required. It is an object of the present invention to provide a specific container integrated into the 'Ready-to-Drink' product that is capable of keeping the compositions comprising the pharmaceutically active substances separate from the aqueous solution until their consumption is required.

Accordingly the 'Ready-to-Drink' product of the present invention further comprises a drink container including a closure, wherein the closure comprises a compartment in which a liquid or dry composition can be stored separately from the contents of the container, and wherein the closure further allows the liquid or dry composition to be released into the container when desired allowing it to be dissolved or dispersed in the container contents.

A further advantage of the present invention could be that a lower amount of the active component is needed in this new application in the Ready-to-Drinks format, as it is very likely that the bioavailability will be better. The drug enters the gastro-intestinal tract in a well-defined form and absorption can occur immediately.

Such 'Ready-to-Drink' products are very convenient to the consumer and handling is very easy. No special 'glass of water' with an unspecified water-quantity or another drink must be

available. Also the consumer cannot administer the drug with an inadequate drink. Thus inconvenient dosages, using a spoon or a special device is not necessary.

Through use of the invention of the Ready-to-Drinks it is guaranteed that the correct dosage in the correct solvent (water) is swallowed and very importantly the possibility of over-dose is dramatically reduced, because it is only possible to ingest a limited amount of water per hour.

In the case of Ready-to-Drinks the rate of absorption of the medicines from the mouth into the bloodstream will be faster than, for example, a tablet as the drug is immediately ready for absorption and does not need to be released from a tablet's matrix through the process of dissolution.

Above all, these Ready-to-Drink drug formulations offer the option to conceal a bad, e.g. a bitter taste or smell by the addition of sweeteners, natural and or nature-identical flavours and flagrances. These sweeteners, natural flavours and flagrances could be chosen from a variety of components of which no side effects have been identified to date.

In addition, it is possible to use the active medicinal principle in combination with a base solvent, such as a so-called functional drink, for which no side effects have been known to date. For example, the use of a food supplement appetite suppressant hydroxycitric acid in combination with an anti-obesity drug.

In some cases a medicinally active compound is not structurally stable from a chemical point of view, and even cannot not be stored stably in the special chamber integrated into the cap. In this case it is necessary to prepare a special powder/granulate of the medicinal active component to be able to automatically weigh and dose the component with the necessary high precision into the special container integrated into the cap and/or fill the chamber in an inert atmosphere.

The Ready-to Drink system can in particular be applied to analgesics, specifically the best-known analgesics, acetaminophen (paracetamol), ibuprofen and aspirin. Accordingly the

invention is exemplified below in terms of these pharmaceutically active substances. However, it is noted that the Ready-to-Drinks system can be applied to any number of pharmaceutically active substances that are capable of being absorbed into the body via the digestive system. The present invention therefore covers formulations comprising one or more pharmaceutically active substances selected from antioxidants for assisting the fight against physiological stress, nicotine to aid the quitting of cigarettes, combinations of phospholipids for assisting liver function, immune stimulants, agents effective against vascular disease (in particular cardiovascular disease and atherosclerosis), antihistamines, anti-obesity agents, agents effective against psoriasis, agents effective against an alcohol-induced hangover, agents effective against an anaesthesia-induced hangover, agents effective in the treatment of a cerebrovascular stroke, agents effective in the treatment of bone disease such as calcium and phytoestrogens and agents that aid weight loss such as hydroxycitric acid.

In one embodiment of this invention a single analgesic (acetaminophen, aspirin or ibuprofen) is combined with simple, dimeric and/or polymeric sugars, anions and cations, flavourings, stabilisation ingredients, preservatives and sweetening agents to produce a flavoured drink with good shelf life for the convenient and immediate consumption of an analgesic to deliver fast relief from pain with an acceptable taste and mouth feel.

Preferably the analgesic is provided in a quantity for a specific medical efficacy. More preferably the product comprises 10 mg to 2000 mg of analgesic in a serving size of 10 ml to 500 ml. More preferably the serving size is 100ml to 250ml.

Typically the invention contains 100mg to 700mg of analgesic in a solution of ca 4% carbohydrates, with nature identical flavourings, in a still (non-carbonated) spring water.

The drink product preferably comprises 0.1 to 20 wt.%% carbohydrates, more preferably 1 to 7 wt.% carbohydrates. The carbohydrates can be complex carbohydrates or simple sugars. The complex carbohydrates can be oligosaccharides or polysaccharides. Preferably the complex carbohydrate is maltodextrin, derived from potato or more preferably derived from

wheat. The simple sugars can be lactose, glucose, fructose, galactose, dextrose or any monomer sugar with homologous metabolic function.

The complex carbohydrates and simple sugars can also be substituted using either a single different complex carbohydrate alone or in combination with other simple sugars. Alternatively the complex carbohydrate can be the same type but be a combination of different chain lengths e.g. one part DE (Dextrose Equivalent) 8, one part DE10-12 and one part DE18-20.

The sugars in the drink may be balanced in order that the osmolarity of the solution is isotonic.

Sugars can be added either individually or in combination. Further, artificial sweeteners such as acesulfame K or sucrolose, or a combination of artificial and natural sweeteners can be used.

Further the drink product may comprise citric acid and/or ascorbic acid as well as potassium chloride, sodium chloride and/or sodium bicarbonate.

Additionally the drink product may comprise other flavourings that would result in the product being organoleptically acceptable, depending on target consumer preference. Flavourings such as lemon emulsion or grapefruit flavour may be added. Cooling agents such as clove oil or maltol can be added at organoleptically acceptable levels to detract from the burning taste of the active pharmaceutical ingredient.

The drink product may further comprise preservatives such as potassium sorbate and/or sodium benzoate.

If preservatives are not required a form of pasteurisation can be used instead, provided none of the ingredients were heat labile. Another alternative would be dosing with 100-300ppm dimethyl dicarbonate and the mandatory quarantining of the product for 24 hours.

The ready-to-drinks product preferably comprises distilled water, spring water or mineral water, or any grade of water suitable for the manufacture of medicines. In a further embodiment an increase in the speed of absorption of the pharmaceutical active component in the Ready-to-Drinks may be facilitated by carbonating the drink, thus increasing the surface area of the liquid interacting with the absorbing surfaces of buccal epithelia cells or mucosal lining of the stomach.

Typically, a dry blend is made of all the components, excluding the preservatives and sweeteners. This blend is dispersed into water in a syrup tank to make a concentrate. A pre-dissolved solution(s) of sweetener and or preservative is then added. The concentrate is then mixed in-line with spring water and bottled aseptically on a standard neck-handling bottle filling line. Throughout, the process is GMP compliant and all ingredients used are to USP standards. In addition, during the in-line mixing stage either dimethyl carbonate (known as the Velcrin process) or ozone or hydrogen peroxide may be used to further sterilise the product or the final capped product subjected to sufficient irradiation to ensure its sterilisation.

In a further embodiment of the invention the ready-to-drinks product comprises an active pharmaceutical ingredient that is insoluble or substantially insoluble in water. In order to disperse a medicine that is insoluble in aqueous solution typically two routes are available – emulsification or use of traditional viscosity increasing agents such as guar gum and or xanthum gums. However, according to this invention the viscosity of the of the solution is raised using a combination of complex, but biologically digestible complex carbohydrates and/or proteins, that allow an effective and sustainable dispersion of the insoluble or partially insoluble pharmaceutically active ingredient to be achieved.

In one aspect of the invention the pharmaceutically active ingredient is ibuprofen. Preferably the ibuprofen is provided in a quantity for a specific medical efficacy. More preferably the drink product comprises 10 mg to 2000 mg of ibuprofen in a serving size of 10 ml to 500 ml. More preferably the serving size is 100ml to 250ml. Most preferably the drink product comprises 100 mg to 500 mg of ibuprofen.

Preferably the ibuprofen has an average particle diameter of 5 to 100 microns, more preferably 5 to 50 microns, more preferably 5 to 40 microns and most preferably 5 to 30 microns.

The bulk density of the active pharmaceutical ingredient is established by standard means (e.g. decanting the active pharmaceutical ingredient into a pre-weighed measuring container, noting the volume it occupies and calculating its mass (kg) per litre). This method is limited to active pharmaceutical ingredients with bulk densities of no more than 3 kg/litre.

Preferably the ibuprofen has a bulk density of between 0.08 and 2 kg/litre, more preferably 0.08 and 1.5 kg/litre, more preferably 0.08 and 1.0 kg/litre, more preferably 0.08 and 0.7 kg/litre, most preferably 0.08 and 0.65 kg/litre.

The bulk density of the active pharmaceutical ingredient should be equivalent to that of the complex carbohydrate and the protein ± 20%.

In this embodiment of the invention the complex carbohydrate is maltodextrin, preferably present at 0.1 to 20% w/v, more preferably 2 to 20% w/v, most preferably 4 to 20% w/v.

In a further preferred embodiment of the invention the maltodextrin is dextrose equivalent 4-8, more preferably dextrose 8-12, more preferably dextrose equivalent 10-12.

However, the complex carbohydrate can be replaced by one or a combination of indigestible complex sugars, for example fructooligosaccharides.

The protein is derived from milk or soy e.g. lactoferrin from milk or an ensemble of whey protein isolate or protein hydrolysates from soy or whey. In a preferred embodiment of the invention the protein is derived from whey.

Fractions of over 35% whey protein, more preferably over 55% whey protein, more preferably over 80% whey protein, most preferably an instantised (agglomerated to aid aqueous solubility) of more than 90% whey protein content is used.

However, the whey protein can be totally or partially replaced as an ingredient by any soluble human digestible form of protein, or peptides or combination of peptides, provided that they were soluble or formed a colloidal suspension in the finished product. These proteins can be hydrolysed or fragmented in order to aid their solubility in aqueous solution.

In a preferred embodiment of the invention the final protein concentration in the drink is 0.1 to 40 % w/v, more preferably 2-40% w/v, even more preferably 10 to 40% and most preferably 20-40% w/v.

In a preferred embodiment of the invention the Ready-to-Drink container consists of a plastic or glass bottle with preferably between 100ml and 300ml capacity and the closure comprises a lid or a cap. More preferably the bottle is an opaque PET bottle, with tamper-evident 28mm closure and label.

The Ready-to-Drinks bottles are conceived in such a way that they are easy to open by adult consumers. The cap is specially designed so that children cannot open it without having read or understood the necessary procedure of how to press and turn the cap to open the bottle ("child proof cap"). The cap might be designed such that it can only be opened once and cannot be used to reseal the medicine's container – thus preventing storage of a part dose and reducing the possibility of incorrect consumption.

In a further embodiment of the invention the ready-to-drinks product comprises an active pharmaceutical ingredient that is substantially water labile and does not remain stable in aqueous solution. Accordingly this active pharmaceutical ingredient is mixed or blended with the other ingredients as described above into a dry composition. However this dry composition is not mixed with the aqueous solution until its use is required.

In order to accommodate the dry composition a further aspect of the invention is that the closure cap of the ready to drink container may include a compartment in which the composition comprising the pharmaceutically active compound or a combination of pharmaceutically active compounds, are stored until consumption of the Ready-to-Drinks is

required. By pressing and/or turning the cap the active ingredient falls into the water This device always has to be used if the medicinal active compound is not stable from a chemical structure point of view e.g. water labile.

If this closure cap with the integrated chamber for the medicinal active component is applied it is opened by pressing and turning the special child proof cap.

The Ready-to-Drinks should either be taken before meals (that is on an empty stomach) to increase the amount of drug absorbed into the system or taken after meals (in cases where the medicinal active component may cause irritation to the gastro-intestinal tract). The proper administration time is the same as recommended for the drug in e.g. tablet format.

EXAMPLES

The present invention will now be described in more detail, by way of example only, with reference to the following specific embodiments.

Example 1 - Solution of Paracetamol in water

Final Amounts in Ready to Drink Paracetamol

Pack size 150 ml

Ingredients	grammes
Paracetamol	1.000
Citric acid	1.500
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate	0.045
Sodium benzoate	0.023
Acesulfame K	0.054
Colourings	if needed
Carbonated water with CO2 to 2.6 vols	Up to 150
Or simply water to	Up to 150

The process for the manufacture of a still finished product requires the accurate weighing out of the materials listed above. The medicine, citric acid and acesulfame K are then pre-blended

in a double-cone blender, typically 3000 litre capacity for 10 minutes, and the resulting blend is then sieved through a fine gauge screen, typically 100 microns.

A typical batch size for the product is 10,000 litres ca 66,600 bottles. A standard 10,000 litre mixing tank with a horizontally rotating agitator (40 rpm) is filled with ca 1,000 litres of reverse osmosed water and the blended ingredients added. Stirring takes place for 20 minutes until a homogeneous suspension is present. At this time a further 7,500 litres of reverse osmosed water is added and stirring is reduced to half the previous speed for 10 minutes. During this period the preservatives are dissolved in 5 litres of water at 55 degrees Celsius. The preservatives are then added, followed by the flavourings. The volume is finally made up to 10,000 litres and stirring is switched on at 20 rpm for the remainder of the process.

In the case of a carbonated finished product. The blended product is first suspended in 1,000 litres. Mixing is as above. Next the warm preservative solution is added and then the flavourings. The volume is then made up to 1,600 litres and mixed in line with carbonated reverse osmosed water and bottle off. Dispersion is achieved in line by small constrictions every 2 metres in the stainless steel pipe-work.

The filling process occurs on standard soft-drinks industry neck-handling equipment with positive clean air flow across all points where the beverage is exposed to air. Typical achievable fill rates are 28,000 bottles per hour.

As a result of the metallic taste profile of paracetamol, grapefruit is used as one of the better masking flavourings. It is possible to substitute for other flavours that would also be organoleptically acceptable, depending on a consumer's preference. Similarly, where required the artificial sweetener could be substituted for other individual artificial sweeteners or combinations of artificial sweeteners. Sugars such as dextrose, glucose or fructose could also be added to sweeten – either individually or again in combination. If preservatives were not required a form of pasteurisation would be used instead, provided none of the ingredients were heat labile.

Example 2

This example concerns paracetamol in an isotonic solution for the treatment of alcohol induced hangover.

This product is provide in 250 ml package and delivers 1000 mg of paracetamol in an oral rehydration base which is isotonic (336 mmol/l osmolarity). The process of manufacture is as identical to that in example 1 above, however the routine necessary for artificial sweeteners is omitted as they are not present in the formulation.

Final Amounts in Ready to Drink Paracetamol in
Isotonic Solution
Pack size 250 ml

Ingredients	grammes
Paracetamol	1.000
Citric acid	0.396
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate	0.045
Sodium benzoate	0.023
Sodium chloride	0.733
Potassium chloride	0.633
Sodium bicarbonate	0.700
Glucose	6.683
Sucrose	8.037
Fructose	0.090

The process is as in example 1 above except the medicine, citric acid, sodium chloride, potassium chloride, sodium bicarbonate, glucose, sucrose and fructose are pre-blended in a double-cone blender, typically 3000 litre capacity for 20 minutes, and the resulting blend is then sieved through a fine gauge screen, typically 100 microns.

A typical batch size for the product is 10,000 litres ca 40,000 bottles. A standard 10,000 litre mixing tank with a horizontally rotating agitator (50 rpm) is filled with ca 2,000 litres of reverse osmosed water and the blended ingredients added. Stirring takes place for 25 minutes until a homogeneous suspension is present. At this time a further 7,000 litres of reverse

osmosed water is added and stirring is reduced to half the previous speed for 10 minutes. During this period the preservatives are dissolved in 5 litres of water at 55 degrees Celsius. The preservatives are then added, followed by the flavourings. The volume is finally made up to 10,000 litres and stirring is switched on at 20 rpm for the remainder of the process.

In the case of a carbonated finished product. The blended product is first suspended in 1,000 litres. Mixing is as above. Next the warm preservative solution is added and then the flavourings. The volume is then made up to 1,600 litres and mixed in line with carbonated reverse osmosed water and bottled off. Dispersion is achieved in line by small constrictions every 2 metres in the stainless steel pipe-work.

It is possible to substitute for other flavours that would also be organoleptically acceptable, depending on a consumer's preference. Similarly, where required the artificial sweetener could be substituted for other individual artificial sweeteners or combinations of artificial sweeteners. Sugars such as dextrose, glucose or fructose could also be added to sweeten – either individually or again in combination. If preservatives were not required a form of pasteurisation would be used instead, provided none of the ingredients were heat labile. Or dosing with 100ppm of dimethyl dicarbonate and the mandatory quarantining of the product for 24 hours may be appropriate.

Example 3

One modification of the above formulation would be the substitution of glucose and sucrose with a combination of complex and simple sugars that are less insulinogenic:

Final Amounts in Ready to Drink Paracetamol in
Isotonic Salts and Complex and Simple Sugars
Pack size 250 ml

Ingredients	grammes
Paracetamol	1.000
Citric acid	0.396
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate	0.045
Sodium benzoate	0.023
Sodium chloride	0.733
Potassium chloride	0.633
Sodium bicarbonate	0.700
Maltodextrin	6.683
Acesulfame K	0.090
Lactose	8.037

Here the pre-blend would contain the medicine, citric acid, sodium chloride, potassium chloride, sodium bicarbonate, maltodextrin and lactose. Lactose could be further substituted for galactose. The manufacturing process would be as described for the isotonic version stated immediately above.

Again flavours could be omitted or substituted to meet the organoleptic requirements of the target consumer. Similarly, the artificial sweetener (acesulfame K) used to sweet in replacement for the glucose that was omitted, could itself be replaced by another artificial sweetener e.g. sucrolose or a combination of artificial or natural sweeteners. The complex carbohydrate (maltodextrin) and simple sugar (lactose) could also be substituted using either a single different complex carbohydrate alone or in combination with other simple sugars. Or the complex carbohydrate could be the same type but be a combination of different chain lengths e.g. one part DE (Dextrose Equivalent) 8, one part DE10-12 and one part DE18-20.

Example 4

It is envisaged that where the medicine is substituted with for example a poor tasting compound like ibuprofen it would also be desirable to use a method as described elsewhere in this patent to suspend the insoluble medicine and also a cooling agent to detract from the

burning taste of the product, such a cooling agent could be extract of clove oil or maltol. These would be added at levels that would provide an organoleptically acceptable beverage.

Suspension of Ibuprofen in water:

Final Amounts in Ready to Drink Ibuprofen

Pack size 150 ml

Ingredients	grammes
Ibuprofen	0.400
Citric acid	1.500
Maltodextrin	6.000
Isolated protein	4.000
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate (preservative)	0.045
Sodium benzoate (preservative)	0.023
Acesulfame K (artificial sweetener)	0.054
Colourings	if needed
Water	Up to 150

In order to achieve an effective and sustainable dispersion of ibuprofen in water it is first necessary to blend the ibuprofen with a combination of maltodextrin (DE 10-12) and isolated protein, e.g. lactoferrin from milk or an ensemble of whey protein isolate. The medicine, the modified starch and the protein are placed in a large stainless steel container ca 2000 litres in no particular order and a nozzle capable of dispensing clean air at ca 40 PSI is mounted 40 cm above the top of the powder on a rotating propeller. The unit is sealed and the rotator spun at 40 RPM for 3 minutes and then the air is switched on at 40 PSI for a further 5 minutes. At the end of this time both the air and the rotator are switched off and the unit remains sealed for a further 10 minutes. This pre blend is then transferred to a standard 3000 litre double cone blender at blending performed at 40 RPM for 5 minutes. The citric acid and sweeteners are then added to the blender and blending starts as before for an additional 10 minutes. The blended powder is then put through the same process as above with the addition of preservatives etc applied as before.

It is possible to substitute for other flavours that would also be organoleptically acceptable, depending on a consumer's preference. Similarly, where required the artificial sweetener

could be substituted for other individual artificial sweeteners or combinations of artificial sweeteners. Sugars such as dextrose, glucose or fructose could also be added to sweeten – either individually or again in combination. If preservatives were not required a form of pasteurisation would be used instead, provided none of the ingredients were heat labile.

Example 5

Another alternative would be dosing with 100ppm dimethyl dicarbonate. For the purpose of dispersion and suspension the complex carbohydrate could be replaced by one or a combination of complex sugars, for example fructo-oligosaccharides. Similarly the protein component maybe replaced by an ensemble of peptides or combination of proteins other than those derived from milk, provided that they were soluble in the finished product.

Suspension of Ibuprofen in water:

Final Amounts in Ready to Drink Ibuprofen

Pack size 125 ml

Ingredients	Grammes
Ibuprofen	0.400
Citric acid	1.500
Maltodextrin	6.000
Isolated whey protein (instantised)	4.000
Lemon emulsion flavour	0.150
Grapefruit flavour	0.083
Potassium sorbate (preservative)	0.045
Sodium benzoate (preservative)	0.023
Acesulfame K (artificial sweetener)	0.054
Colourings	if needed
Water	Up to 125

In order to achieve an effective and sustainable dispersion of ibuprofen in water it is first necessary to blend the ibuprofen with a combination of maltodextrin (ideally DE 10-12) and isolated protein, e.g. lactoferrin from milk or an ensemble of whey protein isolate or protein hydrolysates from soy or whey.

This is a key inventive step: in order to disperse a medicine that is insoluble in aqueous solution typically two routes are available - emulsification or use of traditional viscosity increasing agents such as guar gum and or xanthum gums. Here neither are used a combination of complex, but biologically digestible complex carbohydrates and proteins are used.

The particle size of the Active Pharmaceutical Ingredient (API) is selected to be between 5 microns and 30 microns.

The bulk density of the Active Pharmaceutical Ingredient (API) is first established by standard means (e.g. decanting the API into a pre-weighed measuring containing, noting the volume it occupies and calculating its mass (kg) per litre). In this example ibuprofen of 0.6 kg/litre is suitable. This method is limited to APIs with bulk density of more than 3 kg/litre.

The bulk density of the carbohydrate polymer and the protein should be matched to the bulk density of the API.

The medicine, the modified starch and the protein are placed in a large stainless steel container ca 2000 litres in no particular order and a nozzle capable of dispensing clean air at ca 40 PSI is mounted 40 cm above the top of the powder on a rotating propeller. The unit is sealed and the rotator spun at 40 RPM for 3 minutes and then the air is switched on at 40 PSI for a further 5 minutes. At the end of this time both the air and the rotator are switched off and the unit remains sealed for a further 10 minutes. This pre blend is then transferred to a standard 3000 litre double cone blender at blending performed at 40 RPM for 5 minutes. The citric acid and sweeteners are then added to the blender and blending starts as before for an additional 10 minutes. The blended powder is then put through the same process as above with the addition of preservatives etc applied as before.

It is possible to substitute for other flavours that would also be organoleptically acceptable, depending on a consumer's preference. Similarly, where required the artificial sweetener could be substituted for other individual artificial sweeteners or combinations of artificial sweeteners. Sugars such as dextrose, glucose or fructose could also be added to sweeten –

either individually or again in combination. If preservatives were not required a form of pasteurisation would be used instead, provided none of the ingredients were heat labile. Another alternative would be dosing with 100-300ppm dimethyl dicarbonate and the mandatory quarantining of the product for 24 hours may be appropriate.

For the purpose of dispersion and suspension the complex carbohydrate could be replaced by one or a combination of indigestible complex sugars, for example fructo-oligosaccharides. Similarly the protein component maybe replaced by an ensemble of peptides or combination of proteins other than those derived from milk, provided that they were soluble or formed a colloidal suspension in the finished product.

Example 6

This example concerns an ibuprofen suspension in an isotonic solution for the treatment of alcohol-induced hangover.

This product is provide in 250ml package and delivers 400mg of ibuprofen in an oral rehydration base which is isotonic (336mmol/l osmolarity). The process of manufacture is as identical to that in example 4 above, however the routine necessary for artificial sweeteners is omitted as they are not present in the formulation.

Final Amounts in Ready to Drink Ibuprofen in Isotonic Solution

Pack size 250 ml

Ingredients	Grammes
Ibuprofen	0.400
Citric acid	0.396
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate	0.045
Sodium benzoate	0.023
Sodium chloride	0.733
Potassium chloride	0.633
Sodium bicarbonate	0.700
Glucose	6.683
Sucrose	8.037
Fructose	0.090

The process is as in the above example except the medicine, citric acid, sodium chloride, potassium chloride, sodium bicarbonate, glucose, sucrose and fructose are subjected to the air blending as above and the resulting blend is then sieved through a fine gauge screen, typically 200 microns.

A typical batch size for the product is 10,000 litres ca 40,000 bottles. A standard 10,000 litre mixing tank with a horizontally rotating agitator (50 rpm) is filled with ca 2,000 litres of reverse osmosed water and the blended ingredients added. Stirring takes place for 25 minutes until a homogeneous suspension is present. At this time a further 7,000 litres of reverse osmosed water is added and stirring is reduced to half the previous speed for 10 minutes. During this period the preservatives are dissolved in 5 litres of water at 55 degrees Celsius. The preservatives are then added, followed by the flavourings. The volume is finally made up to 10,000 litres and stirring is switched on at 20 rpm for the remainder of the process.

It is possible to substitute for other flavours that would also be organoleptically acceptable, depending on a consumer's preference. Similarly, where required the artificial sweetener could be substituted for other individual artificial sweeteners or combinations of artificial sweeteners. Sugars such as dextrose, glucose or fructose could also be added to sweeten; either individually or again in combination, however this would clearly modify the

osmolarity of the solution and it may not longer be isotonic. If preservatives were not required a form of pasteurisation would be used instead, provided none of the ingredients were heat labile. Or dosing with 100-300ppm of dimethyl dicarbonate and the mandatory quarantining of the product for 24 hours may be appropriate.

Example 7

One modification of the above formulation would be the substitution of glucose and sucrose with a combination of complex and simple sugars that are less insulinogenic.

Final Amounts in Ready to Drink Ibuprofen in
Isotonic Salts and Complex and Simple Sugars
Pack size 250 ml

Ingredients	Grammes
Ibuprofen	0.400
Citric acid	0.396
Lemon emulsion	0.150
Grapefruit flavour	0.083
Potassium sorbate	0.045
Sodium benzoate	0.023
Sodium chloride	0.733
Potassium chloride	0.633
Sodium bicarbonate	0.700
Maltodextrin	6.683
Acesulfame K	0.090
Lactose	8.037

Here the pre-blend would contain the medicine, citric acid, sodium chloride, potassium chloride, sodium bicarbonate, maltodextrin and lactose. Lactose could be further substituted for galactose. The manufacturing process would be as described for the isotonic version stated immediately above.

Again flavours could be omitted or substituted to meet the organoleptic requirements of the target consumer, e.g. the addition of a cooling agent to detract from the burning taste of the API, such a cooling agent could be extract of clove oil or maltol. These would be added at levels that would provide an organoleptically acceptable beverage.

Similarly, the artificial sweetener (acesulfame K) used to sweet in replacement for the glucose that was omitted, could itself be replaced by another artificial sweetener e.g. sucrolose or a combination of artificial or natural sweeteners. The complex carbohydrate (maltodextrin) and simple sugar (lactose) could also be substituted using either a single different complex carbohydrate alone or in combination with other simple sugars. Or the complex carbohydrate could be the same type but be a combination of different chain lengths e.g. one part DE (Dextrose Equivalent) 8, one part DE10-12 and one part DE18-20.

Example 8 - Aspirin dosed into the cap-integrated container

Aspirin is unstable in water and could not be made as a Ready to Drink with a shelf life of any commercially useful period. Instead a cap that is both childproof and also houses a compartment has been designed, into which aspirin has been previously dispensed. During the production process the standard 28 mm wide closure is screwed onto 150 ml bottle which contains either simple water or flavoured water or sweetened and flavoured water. The process of unscrewing the novel cap from the container results in the compartment holding the medicine to open and dispense the medicine into the liquid in the container to produce the Ready to Drink medicine for immediate consumption. Figure 1 sets out the in principle design of such a cap with integrated medicine compartment.

It is possible to construct numerous different designs that result in the action of unscrewing the closed cap fitted to the container such that the integrated medicine compartment opens concomitantly.

The Production of a standardized medicinal extract from tobacco leaves to produce a drink containing nicotine at 2mg, 4mg and 8mg per bottle.

The process is as follows: pre-dried tobacco leaves are first ground to produce a series of flakes. A standard industrial kibbler is suitable. Subsequently, batch lots of 500 kg are placed in a large muslin sack, the sack sealed by drawing of a draw string and the sealed sack immersed in a 10,000 litre tank containing 5,000 litres of reverse osmosed water with sodium

metabisulphite present at 500 pm and the solution's temperature maintained at 80 degrees Celsius. An rotary agitator is present in the tank and set at 40 rpm. This is switched on for 6 minutes. At the end of this period the sack is removed from the tank, pressed to extract the balance of water from it, the tank covered and the thermostat switched off. A sample is taken and a HPLC assay run to determine the nicotine content of the solution. The tank is allowed to cool to 55 degrees at which point the solution is ready for bottling. The total volume of the solution is then adjusted using reverse osmosed water containing sodium metabisulphite at 100 ppm to the desired 2mg or 4mg or 6mg or 8mg nicotine content per 250ml. Bottling again takes place on a standard bottling line with positive pressure clean air flow over all points where the liquid is exposed to the atmosphere.

Alternative methods known in the art may be used to circumvent the microbiological risk of using natural products in this process. Examples include other preservatives or combinations of preservatives such as sodium benzoate and or potassium sorbate, flash pasteurisation or other forms of pasteurisation, or hot filling the product. Or again 100ppm of dimethyl dicarbonate may be added and the product quarantined for 24 hours.

Organoleptically the product tastes very much like black tea and for some markets it may be necessary to add either natural or artificial sweeteners or a combination of both. These are added post steeping of the leaves and in an amount and manner described elsewhere above.

The process may be further modified such that the bag is replaced with some other enclosure that allowed water to circulate through a collection of whole or fragmented leaves. Alternative temperatures and steep times may be employed to accommodate the natural variation in the starting material e.g. its water and or wax content and or fibre content all have an impact on the extraction temperature and the period of extraction.

The resulting nicotine containing water offers a good alternative to current nicotine gums and patches available to aid the quitting of cigarettes. It provides a rapid means of delivering the nicotine and also still allows the user to hold something – a cup or bottle in their hand – which is also considered an important part of the addiction.

It is also possible that other addictive drugs may be solubilised and provided in water and that a range of naturally occurring medicines derived from plant matter may be extracted in a similar manner to the above.

CLAIMS

1. A composition comprising:

(a) one or more pharmaceutically active substances; and

(b) a salt, and/or a protein, and/or a carbohydrate;

wherein the composition is capable of being dissolved or suspended in an aqueous solution to form a drink product, in which the pharmaceutically active substance is suitable for storage.

2. A composition according to claim 1, wherein the one or more pharmaceutically active substances comprise one or more analgesics.

3. A composition according to claim 2, wherein the one or more analgesics are selected from ibuprofen and acetaminophen.

4. A composition comprising:

(a) one or more pharmaceutically active substances; and

(b) a salt, and/or a protein;

wherein the salt and/or the protein, and at least one of the pharmaceutically active substances, are soluble or sparingly soluble in water, and wherein the salt and/or protein are present in the composition in an amount of 5 wt.% or less, such that the composition is capable of being dissolved in an aqueous solution to form a drink product.

5. A composition according to claim 4, wherein the one or more pharmaceutically active substances comprise paracetamol.

6. A composition according to claim 4 or claim 5, which composition further comprises a carbohydrate.

7. A composition according to any of claims 4-6, wherein the carbohydrate is present in the composition in an amount of from 0.1-20 wt.%.

8. A composition comprising:

(a) one or more pharmaceutically active substances; and

(b) 20 wt.% or less carbohydrate and/or 5 wt.% or less protein;

wherein at least one of the pharmaceutically active substances is capable of forming a suspension in water, such that the composition is capable of being suspended in an aqueous solution to form a drink product.

9. A composition according to claim 8, wherein the one or more pharmaceutically active substances are selected from ibuprofen, loratadine, ranitidine, and cetirizine.

10. A composition according to claim 8 or claim 9, which composition further comprises a salt.

11. A composition according to any of claims 8-10, wherein the salt, and/or the protein if present, is present in the composition in an amount of from 0.001-15 wt.%.

12. A composition according to any preceding claim, wherein the salt is selected from sodium chloride, sodium citrate, magnesium citrate, potassium chloride, potassium citrate, and sodium bicarbonate.

13. A composition according to any preceding claim wherein the protein is soluble, sparingly soluble, or is capable of forming suspension, or a colloidal suspension in aqueous solution.

14. A composition according to any preceding claim, wherein the protein is selected from a protein comprising lactoglobin, caseinate, and/or a protein derived from whey and/or soya.

15. A composition according to claim 14, wherein the whey protein comprises a whey protein extract comprising 60 wt.% or more of protein.

16. A composition according to any preceding claim, wherein the carbohydrate is selected from maltodextrin, modified starch, fructo-oligosaccharides, lactose and galactose.

17. A composition according to claim 16, wherein the maltodextrin is selected from maltodextrin with dextrose equivalent 4-8, maltodextrin with dextrose equivalent 8-12, and maltodextrin with dextrose equivalent 18-20.

18. A composition according to any preceding claim, wherein the composition is formulated such that the one or more pharmaceutically active substances may be absorbed into the body via the digestive system.

19. A composition according to any preceding claim, which composition comprises one or more further pharmaceutically active substances selected from antioxidants, nicotine, phospholipids, immune stimulants, agents effective against vascular disease, antihistamines, anti-obesity agents, agents effective against psoriasis, agents effective against an alcohol-induced hangover, agents effective against an anaesthesia-induced hangover, agents effective in the treatment of a cerebro vascular stroke, and agents effective in the treatment of bone disease.

20. A composition according to any preceding claim, wherein the pharmaceutically active substances have an average particle diameter of less than 100 microns.

21. A composition according to claim 20, wherein the pharmaceutically active substances have an average particle diameter of less than 30 microns.

22. A composition according to any preceding claim, wherein the composition additionally comprises a simple sugar.

23. A composition according to claim 22, wherein the simple sugar is selected from lactose, galactose, glucose, fructose and any monomer sugar.

24. A composition according to any preceding claim, wherein the composition further comprises flavourings, preservatives, sweetening agents, antioxidants, phospholipids, energy and/or immune stimulants, calcium and/or phytoestrogens.

25. A method of making a composition as defined in any preceding claim, which method comprises blending the pharmaceutically active substance with the salt, and/or the protein, and/or the carbohydrate, and/or any further ingredients, and sieving the blended ingredients through a screen to form the composition.

26. A drink product comprising a composition as defined in any preceding claim, which is dissolved or dispersed in aqueous solution.

27. A drink product according to claim 26, which drink product exhibits a pH of from 2.8-8.2.

28. A method of making a drink product as defined in claim 27, comprising dissolving or suspending a composition as defined in any of claims 1-24 to form an aqueous solution or suspension.

29. A system for storing a medicinal product, which system comprises a container and a closure, wherein the closure comprises a compartment in which a composition may be stored separately from the contents of the container, and wherein the closure further allows the composition to be released into the container as required.

30. A system according to claim 29, wherein the compartment contains a composition as described in any one of claims 1-24.

31. A system according to claim 29, wherein the compartment comprises one or more pharmaceutically active substances, which are unsuitable for storage in aqueous solution or in aqueous suspension.

32. A system according to claim 30, wherein the one or more pharmaceutically active substances comprise aspirin.

33. A system according to any of claims 29-32, wherein the container comprises water.

34. A system according to claim 33, wherein the water is flavoured and/or sweetened.

35. A system according to any of claims 29-34, wherein the contents of the cap compartment may be released into the container using a push mechanism

35. A method for forming a medicinal drink in the container of a system as defined in any of claims 29-34, which method comprises:

(a) releasing the contents of the closure compartment into the container; and

(b) agitating the container to dissolve or disperse the contents of the closure compartment in the contents of the container.

36. Use of a composition as defined in any of claims 1-24 in the manufacture of a medicament that is effective as an analgesic.

37. Use according to claim 36, wherein the medicament is in the form of a drink product.

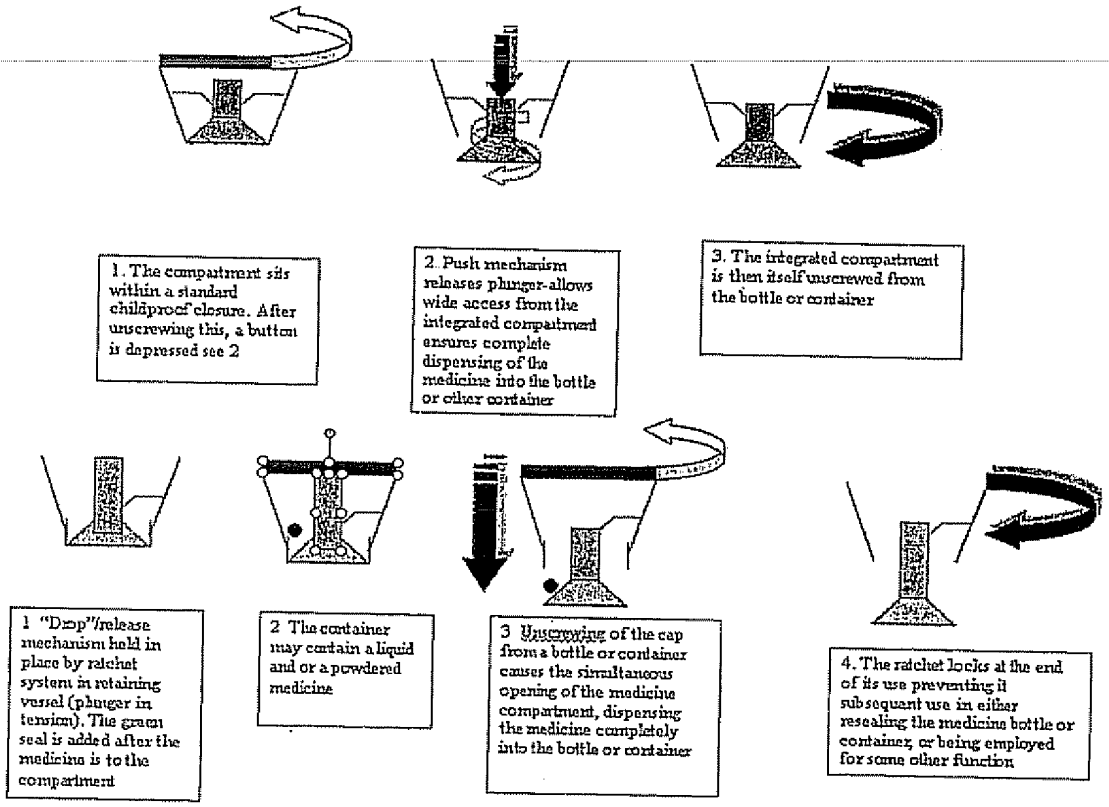
1. The compartment sits within a standard childproof closure. After unscrewing this, a button is depressed see 2
2. Push mechanism releases plunger-allows wide access from the integrated compartment ensures complete dispensing of the medicine into the bottle or other container
3. The integrated compartment is then itself unscrewed from the bottle or container
1 "Drop"/release mechanism held in place by ratchet system in retaining vessel (plunger in tension). The gram seal is added after the medicine is to the compartment
2 The container may contain a liquid and or a powdered medicine
3 Unscrewing of the cap from a bottle or container causes the simultaneous opening of the medicine compartment, dispensing the medicine completely into the bottle or container
4. The ratchet locks at the end of its use preventing it subsequent use in either resealing the medicine bottle or container, or being employed for some other function

FIGURE 1

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(54) Antiallergic composition for ophthalmic or nasal use.

(57) There is disclosed an antiallergic composition for ophthalmic or nasal use, comprising cetirizine or a salt thereof as an active ingredient. The antiallergic composition may further contain a cyclodextrin compound, as well as a surfactant and/or a water soluble polymer.

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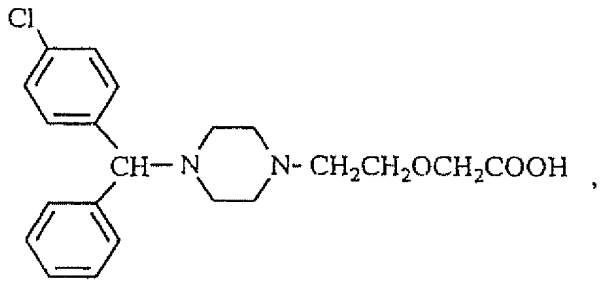
FIELD OF THE INVENTION

The present invention relates to an antiallergic composition for ophthalmic or nasal use, and more particularly, it relates to a cetirizine-containing antiallergic composi tion which is useful for the treatment of allergic diseases in the fields of ophthalmology and otorhinology.

BACKGROUND OF THE INVENTION

Cetirizine is an antiallergic compound of the formula:



the chemical name of which is [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid.

Cetirizine is well known to have an antiallergic effect, for example, by oral administration, and it is particularly useful as an antiallergic agent with significant specificity to histamine (see, e.g., JP-B 63-11353).

In the ophthalmic or nasal allergic diseases, taking the former as an example, systemic symptoms are frequently associated with ophthalmic symptoms, in which case the oral administration of an antiallergic agent is effective for their treatment. There are, however, some cases where no systemic abnormality can be detected even if marked changes are found in the eyes, and in particular, lesions found only in the eyes are not always accompanied by systemic abnormality. In such cases, topical therapy is preferred to systemic therapy because of its safety and effectiveness. This relationship between the systemic and topical symptoms holds true even in the field of otorhinology.

As an ophthalmic solution containing cetirizine, there is disclosed an anti allergic and antihistaminic composition (see, e.g., JP-A 4-9339). This composition comprises an antiallergic agent and an antihistaminic agent capable of exhibiting effective antihistaminic action when used in combination with the antiallergic agent. Cetirizine is exemplified as such an antihistaminic agent that is one of the essential ingredients of the composition.

However, no report has hitherto been made of an effect attained by the ophthalmic application of an antiallergic composition containing cetirizine as only one active ingredient.

Cetiridine has, although it is readily soluble in water, a disadvantage that a solution of cetirizine at low concentrations (below 1 w/v%) may cause the deposition of insoluble matter with the lapse of time, thereby decreasing the stability as an aqueous solution. This seems because cetirizine is one of the diphenylmethane derivatives capable of forming molecular aggregates (see, e.g., Masayuki Nakagaki (ed.), "Bussei-Butsuri (Material Science)," Nankodo, Tokyo, 1986, pp. 238-239). On the other hand, a solution of cetirizine at high concentrations where no insoluble matter will be deposited has strong irritating properties when applied in ophthalmic or nasal use, and it cannot be used as an ophthalmic or nasal solution. For this reason, there have not yet been developed an antiallergic composition for practical use containing cetirizine as the main active ingredi ent, which can be applied as an ophthalmic or nasal solution.

In general, it is difficult in most cases to prepare an ophthalmic or nasal solution with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used.

Cyclodextrin compounds are well known to have a property of taking various drugs into their central portion to form clathrate compounds of these drugs because they are cyclic sugars. Therefore, cyclodextrin compounds have hitherto been used for the purpose of making a solution of various slightly-soluble drugs or improving the stability of drugs. However, when a cyclodextrin compound is blended with a certain drug, it becomes difficult in most cases to exhibit the efficacy of the drug, and this problem is particularly serious for external preparations.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have intensively studied to develop a cetirizine-containing ophthalmic or nasal solution with satisfactory safety and stability, which can overcome the above-described disadvantages of cetirizine and which has no irritating properties to eyes and nasal mucosae. As the result, they have found that the addition of a cyclodextrin compound to an aqueous solution of cetirizine can reduce the deposition of insoluble matter even at low concentrations where molecular aggregates of cetirizine will be found in conventional cases. They have also found that an aqueous solution of cetirizine blended with a cyclodextrin compound can suppress the irritation of cetirizine to eyes or nasal mucosae even at high concentrations where such an irritation will be found in conventional cases, and that such an aqueous solution can maintain a sufficient inhibitory effect on allergic diseases of ocular or nasal portions. Further, they have found that the addition of a surfactant and/or a water-soluble polymer to an aqueous solution of cetirizine blended with a cyclodextrin compound can prevent the association of cetirizine in the aqueous solution for a long period of time. Thus, they have completed the present invention.

That is, the present invention provides an antiallergic composition for oph thalmic or nasal use, characterized in that it comprises cetirizine or a salt thereof as an active ingredient. It may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

The antiallergic composition of the present invention has almost no irritation to eyes and nasal mucosae, and it can be effectively used as a prophylactic and therapeutic agent for allergic diseases in the fields of ophthalmology and otorhinology, such as allergic conjunctivitis (e.g., conjunctival pollinosis), vernal conjunctivitis, uveitis and allergic rhinitis.

DETAILED DESCRIPTION OF THE INVENTION

The antiallergic composition of the present invention contains cetirizine or a salt thereof as an active ingredient. Examples of the salt of cetirizine are inorganic acid salts such as hydrochloride, sulfate, nitrate and phosphate; and organic acid salts such as acetate, citrate, tartrate and maleate.

The antiallergic composition of the present invention may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

Typical examples of the cyclodextrin compound are α-cyclodextrin, β-cycledextrin, γ-cyclodextrin, hydroxypropyl β-cyclodextrin, dimethyl β-cyclodextrin, maltosyl β-cyclodextrin and β-cyclodextrin sulfate. Particularly preferred are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of cetirizine. It is, however, desirable that the amount of cycle dextrin compound is 0.5 to 3.0 times, preferably 1.0 to 2.0 times, as much as the mole of cetirizine.

The surfactants are preferably of the non-ionic type. Typical examples of the non-ionic surfactant are polysorbate 80, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60. These surfactants may be used alone or in combination.

The water-soluble polymer includes cellulose derivatives, vinyl polymers and polyols. Examples of the cellulose derivative are alkylcelluloses such as methylcellulose and carboxymethylcellulose; and hydroxyalkylcelluloses such as hydroxypropylcellulose and hydroxyethylcellulose. Typical examples of the vinyl polymer are polyvinyl pyrrolidone and polyvinyl alcohol. Typical examples of the polyol are a series of macrogol 200 to 6000. These water-soluble polymers may be used alone or in combination.

The amount of surfactant or water-soluble polymer to be used may vary with its kind and the concentration of cetirizine. It is, however, desirable that the amount of surfactant is 0.01 to 1.0 time, preferably 0.05 to 0.5 times, as much as the weight of cetirizine, and the amount of water-soluble polymer is 0.01 to 10.0 times, preferably 0.02 to 5.0 times, as much as the weight of cetirizine.

The antiallergic composition of the present invention can be used within the pH range adopted for ordinary ophthalmic or nasal solutions, and it is usually adjusted to pH 4.0 to 9.0, preferably pH 5.0 to 8.0.

The antiallergic composition of the present invention may further contain any conventional additives in suitable amounts, which are used in ordinary ophthalmic or nasal solutions, e.g., preservatives such as p-hydroxybenzoates, benzalkonium chloride and chlorobutanol; chelating agents such as disodium edetate and sodium citrate; agents for making isotonic solutions, such as sodium chloride, sorbitol and glycerin; buffer agents such as phosphates, boric acid and citrates; and pH controlling agents such as hydrochloric acid, acetic acid and sodium hydroxide. The amount of additive to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic or nasal solutions.

The antiallergic composition of the present invention may further contain any therapeutic ingredients

other than cetirizine in suitable amounts, so long as the excellent advantages attained by the present invention are not deteriorated.

The antiallergic composition of the present invention may have various dosage forms which are pharmaceutically acceptable in the field of ophthalmology or otorhinology, such as solutions, suspensions, emulsions, gels and ointments. It may also be prepared, for example, in aqueous solution form and then lyophilized in powder form, which is reconstructed into an aqueous solution with distilled water at the time of use.

The concentration of cetirizine in the antiallergic composition of the present invention may vary with the administration route and allergic symptoms. It is, however, usually in the range of about 0.01 to 4.0 w/v%, preferably about 0.05 to 2.0 w/v%. For example, when used as an ophthalmic solution for adult patients, the antiallergic composi tion of the present invention is preferably administrated about 3 to 6 times a day in a dose of one to several drops at each time. When used as a nasal solution, the antiallergic corn position of the present invention is preferably atomized and inhaled about 3 to 6 times a day in a dose of 1 to 2 sprays at each time into the nasal cavity with an atomizer.

The present invention will be further illustrated by way of the following test examples and working examples, which are not to be construed to limit thereof.

Test Example 1: Eye irritation test in rabbits

(Method)

Using male Japanese white rabbits without any abnormality in the anterior parts of their eyes (4 groups of 3 rabbits), Composition C, D, E or F prepared in solution form according to the formulation shown in Table 1 was instilled into the right eyes of the rabbits in the corresponding group and only the vehicle into their left eyes 8 times a day at 1-hour intervals in a dose of one drop at each time for 5 days. For evaluation, a macroscopic examination of the anterior parts of the eyes and a corneal fluorescein staining assay were performed before the first instillation on day 1, 30 minutes after the last instillation on each of days 1, 3 and 5 of treatment, and on day 6.

TABLE 1

Ingredient (w/v%)	Compositions									
	A	B	C	D	E	F	G	H	J	K
Active ingredient										
Cetirizine hydrochloride	0.25	0.4	0.5	1.0	1.0	1.0	1.0	1.0	1.0	2.0
Additional ingredients										
α-Cyclodextrin	-	-	-	-	2.1	-	-	-	-	-
β-Cyclodextrin	-	-	-	-	-	2.45	-	-	-	4.9
γ-Cyclodextrin	-	-	-	-	-	-	2.81	-	-	-
Polyvinyl pyrrolidone	-	-	-	-	-	-	-	2.05	-	-
Chlorobutanol	-	-	-	-	-	-	-	-	0.3	-
Vehicle										
Con. glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Boric acid	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

(Results)

In the groups of rabbits topically dosed with Solution C or D, redness was observed on the palpebral conjunctiva and nictitating membrane after the last instillation on day 1. Particularly, in the group of rabbits given Solution D, their symptoms were so severe that individual blood vessels to be clearly observed on the normal palpebral conjunctiva were not definitely discernible. In addition, bulbar conjunctival vasodilation and palpebral conjunctival edema were observed. The redness as mentioned above was still observed even 16 hours after the last administration on day 1 and up to the beginning of instillation on day 2. The observation on day 3 of treatment also found redness of the conjunctiva as in the observation after the last instillation on day 1 but with an increased severity in both groups, indicating that cetirizine has a strong irritating effect on the conjunctiva. In the corneal fluorescein stain assay performed at the completion of instillation treatment, dye spots were observed over the entire corneal area in both groups, indicating that cetirizine also irritates the corneal epithelium. Judging that the rabbit eyes could not tolerate further instillation, the treatment with Solution C or D was discontinued on day 3.

In the group of rabbits given Solution E containing a cyclodextrin compound, slight redness was observed on the palpebral and bulbar conjunctivae after the last instillation on day 1, while very small amounts of discharge were found in some rabbits of the group dosed with Solution F. However, neither the redness nor the eye discharge as found on day 1 was no longer observed on and after day 3. Even in the corneal fluorescein staining assay done at the end of treatment, no change was found from the condition before the treatment and all the findings were invariably within the normal range, clearly indicating that a reduction in ocular irritation can be attained by the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride. The eyes treated with the vehicle showed no sign of irritation caused by the vehicle.

Test Example 2: Toxicity test by instillation into rabbit eyes

(Method)

Using male Japanese white rabbits in good health without any abnormality in the ophthalmological examination (2 groups of 5 rabbits), ophthalmic composition F or K prepared in solution form according to the formulation shown in Table 1 was instilled into both eyes of the rabbits in the corresponding group 8 times a day in a dose of one drop at each time for 28 days. The rabbits were examined for the general condition, food con sumption, body weight and ophthalmological items (macroscopic observation of the anterior part of eyes, observation of the corneal stained spots and fundus oculi, measurement of the intraocular tension) with the lapse of time for 28 days, after which they were subjected to urinalysis, hematological examination, blood chemical examination, autopsy, organ weight measurement, histopathological examination of the eyeball and electron microscopic examination of the cornea.

(Results)

With respect to the instillation of Solution F or K, no abnormality was found in the ophthalmological examination, general condition and other examinations.

Test Example 3: Effect on rat histamine-induced conjunctivitis

(Method)

Male Wistar rats of about 100 g in weight were injected subconjunctivally each with 50 µl of 0.1 w/v% histamine at the upper eyelid. Each of the following test ophthalmic compositions in solution form was instilled into both eyes of the rats in the corresponding group at a dose of 3 µl for each eye 40 and 20 minutes before the histamine injection. The rats were sacrificed one hour after the histamine injection. The palpebral conjunctival edema weight was measured, and the edema inhibition rate was calculated using the edema weight of the physiological saline group as the maximal response. As the test ophthalmic solutions, a solution prepared by dissolving cetirizine hydrochloride in the vehicle (2.0 w/v% conc. glycerin, 0.4 w/v% aqueous boric acid and sodium hydroxide (q.s.); pH 7.0) to have a specified final concentration (hereinafter referred to as CE ophthalmic solution), a solution prepared by dissolving equimolar amounts of cetirizine hydrochloride and either α- or β-cyclodextrin in the vehicle at a specified final concentration (hereinafter referred to as CE + α-CD ophthalmic solution and CE + β-CD ophthalmic solution, respectively) and a solution prepared by dissolving diphenhydramine hydrochloride in the vehicle (hereinafter referred to as DPH ophthalmic solution) were

used.

(Results)

In the rat model of histamine-induced conjunctivitis, cetirizine hydrochloride exhibited an inhibition rate of about 88.8% at the concentration of 0.5 w/v%, indicating that cetirizine hydrochloride has a sufficient antihistaminic effect even when topically used in the field of ophthalmology.

To compare the efficacy against histamine-induced conjunctivitis of cetirizine hydrochloride when formulated with α- or β-cyclodextrin, the cetirizine hydrochloride concentration (mM) of each ophthalmic solution which exhibited a 50% inhibition of the edema (IC_{50}) was determined using the edema rate of the physiological saline-instilled rat group as a control. The IC_{50} values obtained for the test ophthalmic solutions are shown in Table 2.

TABLE 2
Inhibitory Effect of Cetirizine on Histamine-induced Conjunctivitis

Test ophthalmic solution	IC_{50}*
CE	2.05 mM
CE + α-CD	1.97
CE + β-CD	2.76
DPH	120.0

*: The concentration of cetirizine hydrochloride which gives 50% inhibition of histamine-induced rat conjunctivitis

As shown in Table 2, the IC_{50} value of CE ophthalmic solution was 2.05 mM (about 0.1 w/v%), indicating that cetirizine hydrochloride has an antihistaminic effect to a certain extent even below irritating concentrations. The groups of rats treated with CE or CE + α-CD ophthalmic solution gave substantially equal IC_{50} values, indicating that, in this experimental system, α-cyclodextrin does not substantially affect the efficacy of cetirizine hydrochloride. The IC_{50} value in the group of rats treated with CE + β-CD ophthalmic solution was somewhat higher than that found in the group of rats treated with CE ophthalmic solution (containing cetirizine hydrochloride alone). This fact suggests that the addition of β-cyclodextrin to a composition of cetirizine hydrochloride causes a slight decrease in the efficacy of cetirizine hydrochloride in this experimental system but the degree of decrease is so small that the efficacy of cetirizine hydrochloride can be well maintained.

Test Example 4: Eye irritation test in humans

(Method)

There is some difference in irritation response between the human and animal eyes when an ophthalmic solution is instilled thereinto. In addition, some subjective factors such as a feeling after the use should be considered in case of human eyes. It is, therefore, be concluded that ophthalmic solutions without any irritation to human eyes are more preferred, and any strongly irritative composition cannot be put to practical use. In this regard, Compositions A, B, D, E, F, G, H, J and K in solution form as shown in Table 1 were evaluated for the feeling after their use when instilled into the eyes of human subjects (I, II, III and IV). The results are shown in Table 3.

TABLE 3
Irritation to Human Eyes

Ophthalmic composition	Human subjects			
	I	II	III	IV
A	−	+	−	+
B	+	+	++	++
D	+++	+++	+++	+++
E	−	−	−	−
F	−	−	−	−
G	−	−	−	−
H	+++	++	+++	+++
J	+++	+++	+++	+++
K	−	−	−	−

−: No irritation or discomfort
+: Slight irritation
++: Moderate irritation (pain)
+++: Strong irritation

(Results)

Among the cyclodextrin-free ophthalmic compositions, i.e., Compositions A, B and D in solution form, Solution A containing 0.25 w/v% cetirizine hydrochloride gave slight irritation only to two of four subjects, indicating that the irritation of cetirizine hydrochloride to human eyes is significantly reduced at relatively low concentrations. In contrast, Solutions B and D both having a cetirizine hydrochloride concentration of 0.4 w/v% or more gave irritation to all the subjects, and in particular, Solution D was so much irritative that it has no practical use.

On the other hand, Solutions E, F, G and K each containing α-, β- or γ-cyclodextrin caused no ocular irritation, although their cetirizine hydrochloride concentrations were as high as 1 w/v%. It was, therefore, clear that the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride can reduce the irritation response of eyes to cetirizine hydrochloride and the resulting composition in solution form can be used safely as an ophthalmic solution.

Solution H containing polyvinyl pyrrolidone which caused no ocular irritation but has the property of forming complexes with many different substances, and Solution J containing chlorobutanol which has local anesthetic action and is usually used for reducing the local pain caused by an injection, gave strong ocular irritation, indicating that neither polyvinyl pyrrolidone nor chlorobutanol is suitable as an additional ingredient for the object of the present invention, that is, for suppressing ocular irritation caused by cetirizine or salts thereof.

Test Example 5: Human Nasal Mucosal Irritation Test

(Method)

It can also be said that nasal solutions without any irritation to human noses are more preferred as is true of ophthalmic solutions, and any strongly irritative composi tion cannot be put to practical use. In this regard, Solutions C, D and F were evaluated for the feeling after their use when sprayed into the noses of human subjects (I, II and III). The results are shown in Table 4.

TABLE 4
Irritation to Human Noses

Ophthalmic composition	Human subjects		
	I	II	III
C	−	+	−
D	++	+++	+++
F	−	−	+

−: No irritation or discomfort
+: Slight irritation
++: Moderate irritation (pain)
+++: Strong irritation

(Results)

When Solution C was sprayed into the nose, one of three subjects felt it irritative. When Solution D was applied, all the subjects felt strong irritation which persisted for a fairly long time, indicating that a composition containing only cetirizine hydrochloride in the vehicle is also irritative to nasal mucosae.

On the other hand, Solution F containing β-cyclodextrin gave slight irritation only to one of three subjects, although the cetiridine hydrochloride concentration thereof was the same as that of Solution D giving strong irritation. Moreover, the irritation from Solution F disappeared in a brief time. It is, therefore, clear that the addition of a cycle dextrin compound to a composition of cetirizine or a salt thereof can suppress the irritation to nasal mucosae and such a composition in solution form can be used as a nasal solution.

Test Example 6: Stability Test

(Method)

Compositions A and K shown in Table 5, and Compositions L to N and P to R shown in Table 5 were prepared in solution form. Each of the solutions was filtered through a membrane filter of 0.45 μm mesh, followed by filling into a glass ampoule. These ampoules were stored at room temperature for 6 months, during which they were subjected to macroscopic observation for the presence of insoluble matter with the lapse of time.

TABLE 5

Ingredient (w/v%)	Compositions					
	L	M	N	P	Q	R
Active ingredient						
Cetirizine hydrochloride	0.25	2.0	2.0	2.0	2.0	2.0
Additional ingredients						
β-Cyclodextrin	0.61	4.9	4.9	4.9	4.9	4.9
Hydroxypropylmethylcellulose	-	0.2	-	-	-	-
Polyvinyl alcohol	-	-	0.2	-	-	-
Polysorbate 80	-	-	-	0.2	-	-
Polyvinyl pyrrolidone	-	-	-	-	2.0	-
Macrogol 4000	-	-	-	-	-	1.0
Vehicle						
Conc. glycerin	2.0	2.0	2.0	2.0	2.0	2.0
Boric acid	0.4	0.4	0.4	0.4	0.4	0.4
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0	7.0	7.0

(Results)

The deposition of insoluble matter was observed in the ampoule of Solution A after one day from the beginning of the storage at room temperature. The ampoules of Solution K and L exhibited a slight deposition of insoluble matter after six months. In contrast, no deposition of insoluble matter was found in the ampoules of Solution M, N and P to R even after six months.

It was, therefore, found that the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride can reduce the association of cetirizine and the addition of a surfactant or a water-soluble polymer to a composition of cetirizine hydrochloride and a cyclodextrin compound can prevent the association of cetirizine, thereby making it possible to obtain an antiallergic composition in stable solution form. It was also found that a combination of cetiridine hydrochloride only with a surfactant or a water-soluble polymer cannot prevent the deposition of insoluble matter.

Example 1

An ophthalmic composition was prepared in lyophilized powder form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.5 g
Boric acid	5.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride and boric acid are dissolved in about 80 ml of distilled water, and the solution is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml. The solution thus obtained is sterilized by filtration, and dispensed in 2 ml portions, which are then lyophilized, resulting in an ophthalmic composition. At the time of use, the ophthal mic composition is dissolved in 5 ml of distilled water for injection.

Example 2

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	2.1 g
Boric acid	2.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, α-cyclodextrin and boric acid are dissolved in about 80 ml of distilled water, and the solution is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 3

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	2.1 g
Hydroxypropylmethylcellulose	0.1 g
Boric acid	2.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, α-cyclodextrin and boric acid are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 4

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	2.0 g
β-cyclodextrin	4.93 g
Hydroxypropylmethylcellulose	0.2 g
Boric acid	2.5 g
Disodium edetate	0.02 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, β-cyclodextrin, boric acid and disodium edetate are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 5

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.3 g
α-cyclodextrin	0.8 g
Polyvinyl alcohol	0.2 g
Sodium acetate	0.1 g
Propylene glycol	2.0 g
Methylparaben	0.2 g
Propylparaben	0.1 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which polyvinyl alcohol, methylparaben and propylparaben are dissolved. After cooling to room temperature, cetirizine hydrochloride, α-cyclodextrin, sodium acetate and propylene glycol are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 6

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
β-cyclodextrin	2.47 g
Hydroxypropylmethylcellulose	0.1 g
Boric acid	1.25 g
Disodium edetate	0.01 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, β-cyclodextrin, boric acid and disodium edetate are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 7

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.5 g
Hydroxypropyl β-cyclodextrin	1.6 g
Polyvinyl pyrrolidone	1.0 g
Macrogol 4000	1.0 g
Potassium dihydrogenphosphate	0.1 g
Mannitol	5.1 g
Benzalkonium chloride	0.005 g
Potassium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, hydroxypropyl β-cyclodextrin, polyvinyl pyrrolidone, macrogol 4000, potassium dihydrogenphosphate, mannitol and benzalkonium chloride are dissolved in about 80 ml of distilled water. The solution thus obtained is adjusted to pH 7.5 by the addition of aqueous potassium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 8

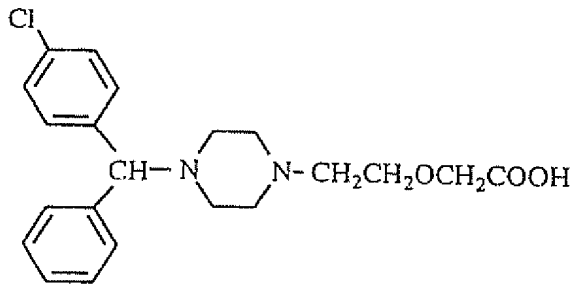
A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	1.0 g
β-cyclodextrin	1.5 g
Sodium citrate	0.05 g
Sodium chloride	0.9 g
Potassium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, α-cyclodextrin, β-cyclodextrin, sodium citrate and sodium chloride are dissolved in about 80 ml of distilled water. The solution thus obtained is adjusted to pH 6.5 by the addition of aqueous potassium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Claims

1. An antiallergic composition for ophthalmic or nasal use, comprising a compound of the formula:



or a salt thereof as an active ingredient.

2. An antiallergic composition according to claim 1, further comprising a cyclodextrin compound.

3. An antiallergic composition according to claim 2, wherein said cyclode xtrin compound is selected from the group consisting of α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin.

4. An antiallergic composition according to claim 2, further comprising a surfactant.

5. An antiallergic composition according to claim 2 or 4, further comprising water-soluble polymer.

6. An antiallergic composition according to claim 4, wherein said surfactant is of the non-ionic type.

7. An antiallergic composition according to claim 6, wherein said non-ionic surfactant is selected from the group consisting of polysorbate 80 and polyoxyethylene hydrogenated castor oil.

8. An antiallergic composition according to claim 5, wherein said water soluble polymer is selected from cellulose derivatives, vinyl polymers and polyols.

9. An antiallergic composition according to claim 8, wherein said cellulose derivatives include alkylcelluloses and hydroxyalkylcelluloses.

10. An antiallergic composition according to claim 9, wherein said alkyl celluloses include methylcellulose and

carboxymethylcellulose.

11. An antiallergic composition according to claim 9, wherein said hydroxy-alkylcelluloses include hydroxy-propylmethylcellulose and hydroxyethylcellulose.

12. An antiallergic composition according to claim 8, wherein said vinyl polymers include polyvinyl alcohol and polyvinyl pyrrolidone.

13. An antiallergic composition according to claim 8, wherein said polyols include macrogol 4000.

14. Use of a compound or salt thereof, as defined in claim 1, for the manufacture of an antiallergic medicament for ophthalmic or nasal use.

Electronic Acknowledgement Receipt

EFS ID:	1322916
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	20-NOV-2006
Filing Date:	
Time Stamp:	11:18:08
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Transmittal.pdf	117615	no	1
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Filed	IDS.pdf	690677	no	4
Warnings:					
Information:					
3	Foreign Reference	WO_2004_004705.pdf	1658650	no	40
Warnings:					
Information:					
4	Foreign Reference	EP_0605203_A2.pdf	541694	no	14
Warnings:					
Information:					
5	NPL Documents	XP_002309643.pdf	86465	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3095101		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):
  Copies of Three (3) Cited Reference

Remarks

No fee is believed due. However, please charge any underpayments to Deposit Account No. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	November 20, 2006	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	November 20, 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/599,451	Domenico Fanara	06-796

INTERNATIONAL APPLICATION NO.	
PCT/EP05/07340	
I.A. FILING DATE	PRIORITY DATE
07/06/2005	07/14/2004

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

CONFIRMATION NO. 9142

371 FORMALITIES LETTER

OC000000023931881

Date Mailed: 05/18/2007

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Copy of the International Application filed on 09/28/2006
- Copy of the International Search Report filed on 09/28/2006
- Preliminary Amendments filed on 09/28/2006
- Information Disclosure Statements filed on 09/28/2006
- U.S. Basic National Fees filed on 09/28/2006
- Priority Documents filed on 09/28/2006

The applicant needs to satisfy supplemental fees problems indicated below.

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.492(h) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** Surcharge.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

JOHN L ANDERSON

Telephone: (703) 308-9140 EXT 211

PART 2 - OFFICE COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/599,451	PCT/EP05/07340	06-796

FORM PCT/DO/EO/905 (371 Formalities Notice)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: TBD
Serial No. 10/599,451	)	
	)	Art Unit: TBD
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	
	)	

RESPONSE TO THE NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) MAILED MAY 18, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice mailed May 18, 2007, enclosed please find the combined Declaration and Power of Attorney document.

Please charge Deposit Account, No. 13-2490 in the amount of $130.00 for the Declaration surcharge.

Respectfully submitted,

Dated: July 18, 2007

By: /Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, 31st Floor
Chicago, IL 60606
(312) 913-2114

Case No.: 06-796

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"Pharmaceutical Composition of Piperazine Derivatives"

the specification of which is the U.S. National Phase of **PCT/EP2005/00340** filed on **July 7, 2005**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s):

	Number	Country	Day/Month/Year Filed
1.	**04016519.3**	**EP**	**14 July 2004**

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

	Application Number	Filing Date
1.		

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

Application Number Filing Date

1.

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and I direct that all correspondence be addressed to that Customer Number.

Customer Number: **020306**
Principal attorney or agent: **Michael S. Greenfield**
Telephone number: **312-913-0001**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **FANARA Domenico**

Inventor's signature: _____ Date: 28/06/2007

Residence: Wanze
Citizenship: Italian
Post Office Address: Rue Pont de Soleil 2A, B-4520 Wanze (Belgium)

Full name of second joint inventor: **SCOUVART Jean**

Inventor's signature: _____ Date: 03 JUL 2007

Residence: Bruxelles
Citizenship: Belgian
Post Office Address: Tir aux Pigeons 72, B-1150 Bruxelles (Belgium)

Full name of third joint inventor: **POULAIN Claire**

Inventor's signature: CPoulain Date: 28 June 07

Residence: Brussels
Citizenship: ~~Belgian~~ French. CPoulain 28 June 07
Post Office Address: ~~rue de Jonker 23, B-1060 Brussels~~ (Belgium) CPoulain 28 June 07
8 rue Gachard - B-1050 Ixelles

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HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

Full name of third joint inventor: **DELEERS Michel**

Inventor's signature: _____ Date: 28.06.2007

Residence: Linkebeek

Citizenship: Belgian

Post Office Address: Square des Braves, 12, B-1630 Linkebeek (Belgium)

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Michael S. Greenfield/Erika Eklund
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	1984471
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	18-JUL-2007
Filing Date:	
Time Stamp:	15:04:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$130
RAM confirmation Number	321
Deposit Account	132490
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	117699 2a2447c3361c879803abf08bfff7036a095c732a	no	1
Warnings:					
Information:					
2	Applicant Response to Pre-Exam Formalities Notice	06-796_Response.pdf	87174 3c0bfce3a5971d1ba994cff2a51d961020da8ac7	no	1
Warnings:					
Information:					
3	Oath or Declaration filed	06-796_Declaration.pdf	98344 39770966a1ec417a7a9c2b62e083a6b62bed33ac	no	3
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8173 2313145bfcdee4453eb964c5b18b4d03d0235b17	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	311390		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☒ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☒ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below): Executed combined Declaration and Power of Attorney (3 sheets).

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	July 18, 2007	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	July 18, 2007

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 08/21/2007

JANDERSO SALE #00000002 Mailroom Dt: 07/18/2007 132490 10599451
01 FC : 1617 130.00 DA

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 08/21/2007

JANDERSO ADJ #00000002 Mailroom Dt: 07/18/2007
Seq No: 321 Sales Acctg Dt: 07/19/2007 132490 10599451
01 FC : 1051 130.00 CR

DO/EO WORKSHE

U.S. Appl. No. 10/599451 International Appl. No. EP2005/007340

Application filed by: ☐ 20 months ☐ 30 months

WIPO PUBLICATION INFORMATION:

Publication No.: WO2006/005507 A2 Publication Language: ☑ English ☐ Japanese ☐ German ☐ French ☐ Other: _____ Screening Done by: JLL

Publication Date: Jan 19, 2006 Not Published: ☐ U.S. only designated ☐ EF request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- ☑ International Application (RECORD COPY)
- ☐ Article 19 Amendments
- ☐ PCT/IB/331
- ☐ PCT/IPEA/409 IPER (PCT/IPEA/416 on front)
- ☐ Annexes to 409
- ☑ Priority Document (s) No. 1
- ☐ International Appl. on Double Sided Paper (COPIES MADE)
- ☐ Request form PCT/RO/101
- ☑ PCT/ISA/210 - Search Report
- ☐ Search Report References
- ☐ Other: _____

RECEIPTS FROM THE APPLICANT (other than checked above):

- ☑ Basic National Fee (or authorization to charge)
- ☑ Description
- ☑ Claims
- ☐ Words in the Drawing Figure(s) - (# of dwgs. 12)
- ☐ Article 19 Amendments
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered:
    - ☐ not a page for page substitution
    - ☐ other: _____
- ☐ Annexes to 409
  - ☐ english transl. of annexes NOT present
  - ☐ entered ☐ not entered:
    - ☐ not a page for page substitution
    - ☐ other: _____
- ☑ Preliminary Amendment(s) Filed on: 1. Sept 28, 2006 2. _____ 3. _____
- ☑ Information Disclosure Statement(s) Filed on: 1. Sept 28, 2006 2. _____ 3. _____
- ☐ Assignment Document
- ☐ Power of Attorney/ Change of Address
- ☐ Substitute Specification Filed on: 1. _____ 2. _____
- ☐ Small Entity
- ☑ Oath/ Declaration (executed)
  - ☐ surcharge was paid at the time of filing
- ☐ DNA Diskette ☐ Sequence Listing
- ☐ Other: 1. _____ 2. _____

NOTES: ☑ I.A. used as Specification ☐ Other:

35 U.S.C. 371 - Receipt of Request (PTO-1390)	Sept 28, 2006
Date Acceptable Oath/Declaration Received	July 18, 2007
Date of Completion of requirements under 35 U.S.C. 371	July 18, 2007
102(e) Date	July 18, 2007
Date of Completion of DO/EO 903 - Notification of Acceptance	Aug 21, 2007
Date of Completion of DO/EO 905 - Notification of Missing Requirements	May 17, 2007
Date of Completion of DO/EO 906 - Notification of Missing 102(e) Requirements	
Date of Completion of DO/EO 907 - Notification of Acceptance for 102(e) Date	
Date of Completion of DO/EO 909 - Notification of Abandonment	
Date of Completion of DO/EO 911 - Application Accepted Under 35 U.S.C. 111	
Date of Completion of DO/EO 916 - Notification of Defective Response	
Date of Completion of DO/EO 910 - Notification to Comply w/ Seq. Requirements	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/599,451	07/18/2007	Domenico Fanara	06-796

CONFIRMATION NO. 9142

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL60606

Date Mailed. 08/23/2007

NOTICE OF NEW OR REVISED PROJECTED PUBLICATION DATE

The above-identified application has a new or revised projected publication date. The current projected publication date for this application is 11/29/2007. If this is a new projected publication date (there was no previous projected publication date), the application has been cleared by Licensing & Review or a secrecy order has been rescinded and the application is now in the publication queue.

If this is a revised projected publication date (one that is different from a previously communicated projected publication date), the publication date has been revised due to processing delays in the USPTO or the abandonment and subsequent revival of an application. The application is anticipated to be published on a date that is more than six weeks different from the originally-projected publication date.

More detailed publication information is available through the private side of Patent Application Information Retrieval (PAIR) System. The direct link to access PAIR is currently http://pair.uspto.gov. Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Questions relating to this Notice should be directed to the Office of Patent Publication at 1-888-786-0101.

PART 1 - ATTORNEY/APPLICANT COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
10/599,451	07/18/2007	1614	1030	06-796	12	1

CONFIRMATION NO. 9142

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL60606

FILING RECEIPT

Date Mailed: 08/24/2007

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Domenico Fanara, Wanze, BELGIUM;
Jean Scouvart, Brussels, BELGIUM;
Claire Poulain, Brussels, BELGIUM;
Michel Deleers, Linkebeek, BELGIUM;

Assignment For Published Patent Application

UCB, S.A., Brussels, BE

Power of Attorney: The patent practitioners associated with Customer Number 020306

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP05/07340 07/06/2005

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 04016519.3 07/14/2004

If Required, Foreign Filing License Granted: 08/21/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US10/599,451**

Projected Publication Date: 11/29/2007

Non-Publication Request: No

Early Publication Request: No

Title

Pharmaceutical Composition Of Piperazine Derivatives

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/599,451	Domenico Fanara	06-796

INTERNATIONAL APPLICATION NO.	
PCT/EP05/07340	
I.A. FILING DATE	PRIORITY DATE
07/06/2005	07/14/2004

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

CONFIRMATION NO. 9142

371 ACCEPTANCE LETTER

OC000000025481593

Date Mailed: 08/24/2007

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

07/18/2007	07/18/2007
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 09/28/2006
- Copy of the International Search Report filed on 09/28/2006
- Preliminary Amendments filed on 09/28/2006
- Information Disclosure Statements filed on 09/28/2006
- Oath or Declaration filed on 07/18/2007
- U.S. Basic National Fees filed on 09/28/2006
- Priority Documents filed on 09/28/2006

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

JOHN L ANDERSON
Telephone: (703) 308-9140 EXT 211

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/599,451	07/18/2007	Domenico Fanara	06-796

CONFIRMATION NO. 9142

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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CHICAGO, IL60606

Title: Pharmaceutical Composition Of Piperazine Derivatives

Publication No. US-2007-0275974-A1
Publication Date: 11/29/2007

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Pre-Grant Publication Division, 703-605-4283

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 02/08/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
02/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Applicant is required to elect for each of (i)-(vi):

(i) a single disclosed active substance, elected from:

(i-a) cetirizine (claims 1, 10);

(i-b) levocetirizine (claims 1, 11); or

(i-c) efletirizine (claim 1);

(ii) a single disclosed preservative compound or a single disclosed mixture of preservatives (elect each preservative compound present from species recited in claims 3-5);

(iii) whether thimerosal is:

(iii-a) present (claim 6); or

(iii-b) absent (claim 1);

(iv) whether chlorhexidine acetate is:

(iv-a) present (claim 7); or

(iv-b) absent (claim 1);

(v) whether benzylalcohol is:

(v-a) present (claim 8); or

(v-b) absent (claim 1);

and

(vi) whether benzalkonium chloride is:

(vi-a) present (claim 9); or

(vi-b) absent (claim 1).

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

2. The claims are deemed to correspond to the species listed above in the following manner:

(i-a) claims 1-10, 12

(i-b) claims 1-9, 11-12

(i-c) claims 1-9, 12

(ii) all claims

(iii-a) all claims

(iii-b) claims 1-5, 7-12

(iv-a) all claims

(iv-b) claims 1-6, 8-12

(v-a) all claims

(v-b) claims 1-7, 9-12

(vi-a) all claims

(vi-b) claims 1-8, 10-12

The following claim(s) are generic: claims 1-9, 12 are generic for (i); claims 1-3, 6-12 are generic for (ii); claims 1-5, 7-12 are generic for (iii); claims 1-5, 7-12 are generic for (iv); claims 1-6, 8-12 are generic for (v); claims 1-7, 9-12 are generic for (vi).

3. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The technical feature linking the species is a liquid pharmaceutical composition with an active substance selected from cetirizine, levocetirizine and efletirizine and a preservative with an effect equivalent to an amount of parahydroxybenzoate ester between 0 and 1.5 mg/mL. Walters (WO 2004/004705 A2; 2004 Jan; IDS 11/20/2006 reference) teaches aqueous (liquid) compositions comprising pharmaceutically active substances (abstract); pharmaceutical agents include cetirizine (p. 7, 4th paragraph; claims 8-9); preservatives such as potassium sorbate and/or sodium benzoate (p. 16, paragraph 7), preservative concentrations include 0.045 g/150 mL (0.3 mg/mL)

potassium sorbate and 0.023 g /150 mL (0.15 mg /mL) sodium benzoate (both concentrations are well below the equivalent effect concentration of 1.5 mg/mL parahydroxybenzoate esters; p. 20, Example 1). Therefore, since the technical feature has been taught in the prior art, the technical feature linking the species does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Accordingly, the species are not so Linked by the same or a corresponding special technical feature as to form a single general inventive concept.

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions

unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TPT/
Timothy P. Thomas
Patent Examiner

2/6/08
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE OFFICE COMMUNICATION MAILED FEBRUARY 8, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office communication mailed February 8, 2008. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on March 6, 2008.

Date: March 6, 2008 /Michael S. Greenfield/
Michael S. Greenfield

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A liquid pharmaceutical composition comprising (i) ~~an active substance chosen among~~ cetirizine, levocetirizine, ~~and~~ efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and (ii) at least one preservative, wherein the preservative is ~~amount of preservative is in the case of~~ (a) a parahydroxybenzoate ester~~s~~ that is present in an amount of more than 0 and less than 1.5 mg/ml of the composition, ~~and~~ or (b) a ~~in the case of other~~ preservative~~s~~ other than a parahydroxybenzoate ester that is present in an amount ~~is such that it leads to~~ having the same ~~preservative~~ bactericidal effect~~s~~ on the composition as a parahydroxybenzoate ester~~s~~ ~~concentration~~ of concentration of more than 0 and less than 1.5 mg/ml.

2. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein ~~it is an~~ the composition is aqueous ~~composition~~.

3. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the preservative is ~~selected from the group of~~ methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate ~~or propyl parahydroxybenzoate~~, ~~and~~ or a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate.

4. (Currently amended) ~~A~~ The liquid pharmaceutical composition according to claim 3, wherein the preservative~~s~~ is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

5. (Currently amended) ~~A~~ The liquid pharmaceutical composition according to claim ~~1~~4, wherein the ~~pharmaceutical composition contains an~~ amount of p-hydroxybenzoate esters is ~~(methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) selected~~ in the range of 0.0001 and 1.4 mg/ml of the composition.

6. (Currently amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of thimerosal ~~selected~~ in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of chlorhexidine acetate ~~selected~~ in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzylalcohol ~~selected~~ in the range of 0.0001 and 10 mg/ml of the composition.

9. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzalkonium chloride ~~selected~~ in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the active substance is cetirizine.

11. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the active substance is levocetirizine.

12. (Currently Amended) ~~A~~ The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (New) The liquid pharmaceutical composition according to claim 2 comprising levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

14. (New) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (New) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (New) The liquid pharmaceutical composition according to claim 15, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

17. (New) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (New) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1.5 mg/ml of the composition.

19. (New) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (New) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (New) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (New) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (New) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (New) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (New) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (New) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

REMARKS

The applicants have amended claim 1 to include pharmaceutically acceptable salts of ceterizine, levocetirizine, and efletirizine. Support for this amendment can be found, *inter alia*, on p. 2, ll. 30-31 of the specification.

Claim 1 has also been amended to change "preservative effects" to "bactericidal effect." Support for this amendment can be found on page 2, ll. 20-25, of the specification.

Several new claims have been added. Support for claims 13-16 and 18-26 can be found throughout the application and, in particular, Examples 2 and 4. Support for claim 17 can be found on page 3, ll. 3-7.

The remaining amendments merely improve the grammar without changing the scope.

In response to the restriction requirement, the applicants elect the following species:

(i) active substance: levocetirizine

(ii) preservative: mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate

(iii) presence of thimerosal: no (absent)

(iv) presence of chlorhexidine acetate: no (absent)

(v) presence of benyzlalcohol: no (absent)

(vi) presence of benzalkonium chloride: no (absent)/

Claims 1-5, 11, 12 read on the elected species, as do new claims 13-26.

If it is believed that a teleconference will advance prosecution, the examiner is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: March 6, 2008

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	18-Jul-2007
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Michael S. Greenfield/Erika Eklund
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	6	50	300
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**300**

Electronic Acknowledgement Receipt

EFS ID:	2956714
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	06-MAR-2008
Filing Date:	18-JUL-2007
Time Stamp:	10:04:38
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$300
RAM confirmation Number	5585
Deposit Account	132490
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	117461 a632130143b9cbc143f53ef82a89b36ab7292731	no	1
Warnings:					
Information:					
2		06-796_Response.pdf	131719 4b759e81d00b196cec73df7b1bb3fbf070fbca6b	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment - After Non-Final Rejection	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
3	Fee Worksheet (PTO-06)	fee-info.pdf	8172 d5e415ec78e6320c26cf66bd22bc7834ffef7003	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	257352	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☒ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	March 6, 2008	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	March 6, 2008

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/06/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 20	= 6	X $ =		OR	X $50=	300
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	300

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Kim Downing/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 06/04/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	
MAIL DATE	**DELIVERY MODE**
06/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of (i) levocetirizine as the active substance; (ii) a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate as the preservative; (iii-b) thimerosal is absent; (iv-b) chlorhexidine acetate is absent; (v-b) benzylalcohol is absent; and (vi-b) benzylalkonium chloride is absent in the reply filed on 3/6/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The Office action, mailed 2/8/08, is hereby VACATED.

3. The amendment to the claims introduces new claims drawn to distinct inventions. **In addition to the previous species election requirement with the elections made, the following election of a single invention is also required:**

4. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-17, drawn to a liquid pharmaceutical composition.

Group II, claim(s) 18-21, drawn to a method of making a liquid pharmaceutical composition.

Group III, claim(s) 22-26, drawn to a method of treating a patient.

5. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking the inventions is a liquid pharmaceutical composition comprising cetirizine, levocetriizine, efletirizine or a pharmaceutically acceptable salt and a preservative present in an amount equivalent to an amount of a parahydroxybenzoate ester between 0 and 1.5 mg/mL. As pointed out in the previous Lack of Unity Action, Walters (WO 29004/004705 A2; IDS 11/20/2006 reference teaches aqueous (liquid) compositions comprising pharmaceutically active substances (abstract); pharmaceutical agents include cetirizine (p. 7, 4th paragraph; claims 8-9); preservatives such as potassium sorbate and/or sodium benzoate (p. 16, paragraph 7), preservative concentrations include 0.045 g/150 mL (0.3 mg/mL) potassium sorbate and 0.023 g/ 150 mL (0.15 mg/mL) sodium benzoate (both concentrations are well below the equivalent effective concentration of 1.5 mg/mL parahydroxybenzoate esters; p. 20, Example 1). Therefore, since the technical feature linking the inventions has been taught in the prior art, the technical feature does not constitute a “special” technical feature. Accordingly, the inventions are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

6. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

The species remain the same as outlined in the Office Action of 2/8/2008, for which elections have been made.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

7. The claims are deemed to correspond to the species listed above in the following manner:

See previous Office Action

The following claim(s) are generic: see previous Office Action.

8. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

see previous Office Action.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

10. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE OFFICE ACTION MAILED JUNE 4, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office communication mailed June 4, 2008. No fees are believed due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Remarks begin on page 2 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on July 7, 2008.
Date: July 7, 2008 /Michael S. Greenfield/
Michael S. Greenfield

REMARKS

In response to the restriction requirement, the applicants elect Group I, directed to pharmaceutical formulations. The election is made with traverse as to the requirement and the basis therefore.

The applicants reiterate the election of species made in their previous response:

(i) active substance: levoceterizine

(ii) preservative: mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate

(iii) presence of thimerosal: no (absent)

(iv) presence of chlorhexidine acetate: no (absent)

(v) presence of benyzlalcohol: no (absent)

(vi) presence of benzalkonium chloride: no (absent)/

Claims 1-5 and 11 read on the elected species.

If it is believed that a teleconference will advance prosecution, the examiner is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: July 7, 2008

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	3570262
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	07-JUL-2008
Filing Date:	18-JUL-2007
Time Stamp:	10:09:37
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	139954 637968444314 35e691aaac92f0b23bfb69d192e2	no	1

Warnings:	
Information:	

2		06-796_Restriction_Response.pdf	102982 04e0e0fcf4122439848f178b3014c470cf3e1a70	yes	2

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response to Election / Restriction Filed	1	1
Applicant Arguments/Remarks Made in an Amendment	2	2

Warnings:	
Information:	
Total Files Size (in bytes):	242936

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM *(to be used for all correspondence after initial filing)*		
	Application Number	10/599,451
	Filing Date	September 28, 2006
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

No fees are believed due. However, please charge any underpayments and credit any overpayments to Deposit Account No. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	July 7, 2008	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	July 7, 2008

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 09/25/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	
MAIL DATE	**DELIVERY MODE**
09/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *6-10,14-16 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/2006; 11/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on 7/7/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant's election of (i) levocetirizine as the active substance; (ii) a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate as the preservative; (iii-b) thimerosal is absent; (iv-b) chlorhexidine acetate is absent; (v-b) benzylalcohol is absent; and (vi-b) benzylalkonium chloride is absent, with the identification that claims 1-5 and 11 read on the elected species in the reply filed on 3/6/2008 and 7/7/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 18-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/7/2008.

4. Claims 6-10 and 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/7/2008.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5, 11-13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites “certirizine, levocetirizine, efletirizine, **or** a pharmaceutically acceptable salt of certirizine, levocertirizine **or** efletirizine”. Because of the construction using two occurrences of “or”, it is not clear whether 1) one active compound selected from certirizine, levocetirizine, **or** efletirizine (or a salt form of one of these compounds) is required, or whether 2) all three of these compounds (certirizine, levocetirizine, **and** efletirizine) are required to be present (if non-salt forms are selected) in the composition of the instant claims.

For prior art purposes, considering the levocetirizine specie election made, it is assumed that applicant’s intention was that only one active compound is required in the composition of the claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-5, 11-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dietrich et al. (US 2004/0058896 A1; 2004 Mar; priority 2001).

Detrich teaches preparations for an active ingredient (abstract); active ingredients include the antiallergic compound levocetirizine (paragraph 0062); solutions and suspensions are taught that preferably use water as solvent or dispersant (aqueous composition; paragraph 0438); solutions and suspensions may include suitable excipients, preferably added are preservatives, selected from species that include methyl 4-hydroxybenzoate (methyl parahydroxybenzoate) and propyl 4-hydroxybenzoate (propyl parahydroxybenzoate), preservatives are normally used at amounts of 0.1-4% by weight (about 1-40 mg/mL) based on the solution or suspension ready for use (paragraph 0439). Deitrich does not teach the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate elected, and it might be argued that one of ordinary skill in the art would have to pick and choose to arrive at the elected composition. It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare an aqueous liquid composition with levocetirizine as the active ingredient, where a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate are used as preservatives and to optimize the amounts used and ratio of the two preservatives, which would give the elected compositions of the instant claims. The motivation to combine both preservatives would have been combination of two art-recognized suitable compounds for the purpose of preservatives in liquid compositions. The motivation to optimize the amounts would have been the routine optimization of conditions of limiting bacterial growth and stabilizing the active agent at the lowest preservative cost. The liquid compositions obviated by Dietrich would have been in a suitable form for oral use.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 10/599,451	Applicant(s)/Patent Under Reexamination FANARA ET AL.	
	Examiner TIMOTHY P. THOMAS	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2004/0058896	03-2004	Dietrich et al.	514/171
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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BIB DATA SHEET

CONFIRMATION NO. 9142

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/599,451	07/18/2007	514	1614	06-796

APPLICANTS

Domenico Fanara, Wanze, BELGIUM;
Jean Scouvart, Brussels, BELGIUM;
Claire Poulain, Brussels, BELGIUM;
Michel Deleers, Linkebeek, BELGIUM;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP05/07340 07/06/2005

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 04016519.3 07/14/2004

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/21/2007

Foreign Priority claimed	☑ Yes ☐ No	☐ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☑ Yes ☐ No		BELGIUM	0	12	1
Verified and Acknowledged	/TIMOTHY P THOMAS/ Examiner's Signature	Initials				

ADDRESS

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606
UNITED STATES

TITLE

Pharmaceutical Composition Of Piperazine Derivatives

FILING FEE RECEIVED		
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	06-796

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5504113	A	1996-04-02	Lucero et al.	
	2	6319927	B1	2001-11-20	Martin	
	3	6432961	B1	2002-08-13	De Longueville et al.	

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	1	2004004705	WO	A	2004-01-15	Shannon Biotechnology		☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	06-796

	2	0605203	EP	A	1994-07-06	Senju Pharma Co.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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Examiner Signature	/Timothy Thomas/	Date Considered	09/18/2008

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	TBA
Examiner Name	TBA
Attorney Docket Number	06-796

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	3	6432961	B1	2002-08-13	De Longueville Marc et al.	

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	1	WO 2004/004705	WO	A	2004-01-15	Shannon Biotechnology Ltd.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	TBA
	Examiner Name	TBA
	Attorney Docket Number	06-796

	2	EP 0 605 203	EP	A	1994-07-06	Senju Pharma Co.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Database WPI, Section Ch, Week 198551, Derwent Publications Ltd., London, GB; Class A96, AN 1985-319295, XP002309643, & JP 60 204712 A (SS Pharmaceutical KK), 16 October 1985 (1985-10-16) *abstract*	☐

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Examiner Signature	/Timothy Thomas/	Date Considered	09/18/2008

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN	9/18/2008	
PubChem	9/18/2008	
PubMed	9/18/2008	
WEST	9/18/2008	
IDS references	9/18/2008	
PALM Inventor Name Search	9/18/2008	

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/TIMOTHY P THOMAS/ Examiner.Art Unit 1614	

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Search	Most Recent Queries	Time	Result
#17	Search propyl parahydroxybenzoate	16:33:05	1
#16	Search methyl parahydroxybenzoate	16:26:51	1
#8	Search levocetirizine	16:20:06	2

Clear History

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Search	Most Recent Queries	Time	Result
#15	Search levocetirizine preservative	16:13:32	0
#12	Search levocetirizine	16:10:46	153
#11	Search levocetirizine (methyl paraben)	16:10:23	0
#10	Search "levocetirizine"[NM] methyl paraben	16:10:06	0
#9	Search "levocetirizine"[NM]	16:09:44	95
#7	Search plk1	12:53:08	389

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=> d his

     (FILE 'HOME' ENTERED AT 15:33:23 ON 18 SEP 2008)

     FILE 'CAPLUS' ENTERED AT 15:33:54 ON 18 SEP 2008
                E US2007-599451/APPS
L1            1 S E3
                SEL L1 RN 1-

     FILE 'REGISTRY' ENTERED AT 15:34:55 ON 18 SEP 2008
L2           10 S E1-E10
                E LEVOCETIRIZINE/CN
L3            1 S E3
                E METHYL PARAHYDROXYBENZOATE/CN
                E "BENZOIC ACID, 4-HYDROXY-, METHYL ESTER"/CN
L4            1 S E3
                E "BENZOIC ACID, 4-HYDROXY-, PROPYL ESTER"/CN
L5            1 S E3

     FILE 'CAPLUS' ENTERED AT 15:41:21 ON 18 SEP 2008
L6          170 S L3
L7         7374 S L4
L8         4063 S L5
L9            4 S L6 AND L7 AND L8
L10           0 S L9 AND PD<20040714
L11           1 S L9 AND PD<20050706

     FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 15:43:58 ON 18 SEP 2008
L12          65 S L3
L13        2204 S L4
L14        1149 S L5
L15           1 S L12 AND L13 AND L14

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED AT
     15:46:11 ON 18 SEP 2008
L16        7485 S L3 OR LEVOCETIRIZINE OR "(-)-CETIRIZINE" OR "(R)-CETIRIZINE"
L17        3001 S L4 OR (METHYL PARAHYDROXYBENZOATE) OR "METHYL 4-HYDROXYBENZOA
L18        1813 S L5 OR (PROPYL PARAHYDROXYBENZOATE) OR "PROPYL 4-HYDROXYBENZOA
L19           2 S L16 AND L17 AND L18
L20           1 S L19 AND PD<20040714
```

WEST Search History for Application 10599451

Creation Date: 2008091818:15

Query	DB	Op.	Plur.	Thes.
levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE
(methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE
(propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or (Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl 4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE
(levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8)) and ((methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester)) and ((propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE

(Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl 4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester))				
(levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8) and (methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester) and (propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or (Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl 4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester)) and (@pd<20040714 or @ad<20040714 or @rlad<20040714)	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE
(levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8) and (methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester) and (propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or (Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE

4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester) and (@pd<20040714 or @ad<20040714 or @rlad<20040714)) and (levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8)) same (((methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester)) or ((propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or (Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl 4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester)))				
(levocetirizine or ((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8) and (methyl parahydroxybenzoate) or (Methyl paraben) or (methyl 4-hydroxybenzoate) or Aseptoform or Methylben or METHYLPARABEN or Preserval or Maseptol or Methaben or Metoxyde or Metaben or Nipagin or (Methyl 4-hydroxybenzoate) or (Methyl p-hydroxybenzoate) or methylparaben or (Methyl p-oxybenzoate) or (Methyl p-hydroxybenzoate) or (4-(Methoxycarbonyl)phenol) or (Benzoic acid, 4-hydroxy-, methyl ester) or (4-Hydroxybenzoic acid methyl ester) and (propyl parahydroxybenzoate) or (Propyl paraben) or PROPYLPARABEN or Nipazol or Propylparasept or Parasept or Paseptol or Propagin or Nipasol or Paraben or (Betacide P) or (Nipasol P) or (Chemacide pk) or (Chemocide pk) or (Propyl Parasept) or (Aseptoform P) or (Propyl Butex) or (Preserval P) or (Propyl Chemosept) or (Betacine P) or (Protaben P) or (Tegosept P) or (Propyl aseptoform) or (Bonomold OP) or (Nipagin P) or (Nipasol M) or (Solbrol P) or (Propyl chemsept) or (Propyl 4-hydroxybenzoate) or (Pulvis conservans) or (p-Hydroxypropyl benzoate) or (Propyl p-hydroxybenzoate) or (4-Hydroxybenzoic acid propyl ester) or (p-Hydroxybenzoic acid propyl ester) and (@pd<20040714 or @ad<20040714 or @rlad<20040714)) and (levocetirizine or	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE

((2-(2-(4-((R)-(4-chlorophenyl)-phenylmethyl)piperazin-1-yl)ethoxy)acetic acid)) or Xusal or Xyzal or ((-)-Cetirizine) or ((R)-Cetirizine) or Xazal or (Acetic acid, (2-(4-((R)-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)-) or (2-(4-((R-p-Chloro-alpha-phenylbenzyl)-1-piperazinyl)ethoxy)acetic acid) or (130018-77-8)) .ti,ab,clm.				
US-5504113-$.DID. OR US-6319927-$.DID. OR US-6432961-$.DID. OR WO-2004004705-$.DID. OR EP-0605203-$.DID. OR US-19853192951-$.DID. OR JP-60204712-$.DID. OR US-1331018-$.DID.	PGPB, USPT, USOC, EPAB, JPAB, DWPI	ADJ	YES	ASSIGNEE
US-5504113-$.DID. OR US-6319927-$.DID. OR US-6432961-$.DID. OR US-1331018-$.DID.	PGPB, USPT	ADJ	YES	ASSIGNEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE OFFICE ACTION MAILED SEPTEMBER 25, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office communication mailed September 25, 2008. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A liquid pharmaceutical composition comprising (i) ~~cetirizine,~~ levocetirizine~~, efletirizine,~~ or a pharmaceutically acceptable salt of ~~cetirizine~~, levocetirizine~~, or efletirizine~~, and (ii) at least one preservative, wherein the preservative is ~~(a) a parahydroxybenzoate ester that is present in an amount of more than 0 and less than 1.5 mg/ml of the composition, or (b) a preservative other than a parahydroxybenzoate ester that is present in an amount having the same bactericidal effect on the composition as a parahydroxybenzoate ester of concentration of more than 0 and less than 1.5 mg/ml.~~ a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.5 mg/ml of the composition.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Currently amended) The liquid pharmaceutical composition according to claim [[4]] 1, wherein the amount of p-hydroxybenzoate esters is in the range of 0.0001 and [[1.4]] 1.5 mg/ml of the composition.

6. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of thimerosal in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of chlorhexidine acetate in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzylalcohol in the range of 0.0001 and 10 mg/ml of the composition.

9. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzalkonium chloride in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the active substance is cetirizine.

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously Presented) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1.5 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

REMARKS

Claims 1-26 are pending in this case. Claims 18-26 are withdrawn as directed to the non-elected Group II and Group III inventions. Claims 6-10 are withdrawn as directed to non-elected species.

The limitations of claims 4 and 11 have been incorporated into claim 1, and claims 4 and 11 have been canceled accordingly. Claims 3, 13, and 16 have been canceled as redundant in view of the amendment to claim 1. Claim 5 has been amended to depend from claim 1, and to correct a typographical error. Support for this amendment is found in the specification as originally filed at page 4, line 25-28. The claims remaining under consideration are 1, 2, 5, 12, 14, 15, and 17. In the prior response, it was stated that the elected species was covered by claims 1-5 and 11. As the elected species is also covered by claims 12, 14, 15, and 17, it is requested that those claims also be considered at this time.

Oath/Declaration

The examiner's objection to the Declaration submitted in this application is respectfully not understood. The Declaration has two alterations on the second page, one to inventor Claire Poulain's citizenship and the other to her address. In both cases, the inventor's dated signature appears immediately adjacent to the alterations. Thus, the date "28 June 07" and her signature "C Poulain" appear three times on that page: once in the space for the Inventor's signature, once next to the corrected citizenship, and once next to the corrected address. Applicants respectfully request the Examiner to explain what else, if anything, is required.

Claim rejection -- 35 USC 112

The claims were rejected as indefinite with respect to the use of "or" in two separate instances in claim 1. This language has been deleted from amended claim 1, thereby overcoming this ground of rejection.

Claim rejection -- 35 USC 103

The present invention is generally directed to a liquid pharmaceutical composition comprising an active ingredient and a preservative. Pursuant to the amendments herein, the

present claims are directed to the liquid composition wherein the active ingredient is levocetirizine or a pharmaceutically acceptable salt thereof, and the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, the mixture being present in an mount of more than 0 and less than 1.5 mg/ml of the composition. The amendments find support in the specification at least at page 3, lines 3-13; page 4, lines 3-5; and page 4, lines 25-28.

The claims stand rejected as obvious over Deitrich, (US 2004/0058896 A1). Dietrich is directed to a pharmaceutical compositions in which a coated pellet of an active ingredient can retain a desired functionality, even when subjected to further processing. In particular, Dietrich is directed to a preparation made of coated pellets of active ingredients in which the functionalities of the pellet coatings are maintained when the pellets are processed to dosage forms, such as by being shaped into tablets with excipients (Dietrich paras. [0002]-[0003]). Dietrich teaches (para. [0004]) that this can be accomplished by a preparation in which an active ingredient is essentially uniformly dispersed in an excipient matrix composed of one or more excipients selected from the group of fatty alcohol, triglyceride, partial glyceride and fatty acid ester. The composition of Dietrich is not limited to any particular active ingredient; in fact, Dietrich's list of possible active ingredients spans page 2, paragraph [0013] – page 18, paragraph [0401] of the reference. Hundreds of compounds are listed. Levocetirizine is one of the active ingredients listed, but it is not included in any of the examples or otherwise singled out. Preservatives are discussed only at paragraph [0439]. Nothing in that discussion suggests to one skilled in the art to use as a preservative a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight as presently claimed.

Dietrich's discussion of preservatives is part of a broader discussion of general excipients, also including flavorings, buffers, and emulsifiers, and the general amounts of each that can be used in the formed tablets. With regard to preservatives, Dietrich says, "The proportion depends on the preservative used and is normally from 0.1 to 4% by weight based on the solution or suspension ready for use." This is not a teaching of the use of the specific preservatives, in the specific proportions, with the particular active ingredient, as set forth in the amended claims. Indeed, Dietrich's broad disclosure teaches the opposite of the claimed invention, namely, that the choice of preservatives and their quantities is not critical. By

contrast, one aspect of the present invention is based on the discovery that the selection of the particular combination of preservatives and their proportion is indeed critical to the long term stability of this particular active ingredient.

One skilled in the art, searching for a solution to the problem of the stability of levocetirizine would not have turned to Dietrich, which teaches how to protect the functionalities of pellet coatings when the pellets are compressed or otherwise processed into tablets, or used in other pharmaceutical preparations. There is no motivation in the reference to choose levocetirizine as the active ingredient, as required in the amended claims, from among Dietrich's long list of possible active ingredients, or to use the particular preservatives in the particular proportions as claimed in the present application.

Even if one skilled in the art had read the Dietrich reference, he would not have had the idea to use a reduced amount of preservatives in order to obtain a levocetirizine composition stable over a long period of time. (specification, page 2, lines 11-15) It is respectfully submitted that the claims as amended are not obvious over the Dietrich reference.

The applicants' selection of the particular preservatives and amounts is not merely a routine selection by one of ordinary skill in the art based on the teachings of Dietrich. These particular preservatives and amounts lead to a result that is not suggested by the prior art, i.e., enhanced stability of the active ingredient, levocetirizine. Dietrich provides no reason to make the particular invention now being claimed, nor does Dietrich provide any teachings from which one of ordinary skill in the art could have reasonably predicted the results.

For all of the foregoing reasons, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection. Further, should claim 1 as amended be found to be allowable, it is respectfully requested that withdrawn species claims 6-9 be considered as well.

Respectfully submitted,

Date: November 19, 2008

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

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300 South Wacker Drive
Chicago, IL 60606-6709

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	4318330
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	19-NOV-2008
Filing Date:	18-JUL-2007
Time Stamp:	16:19:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	06-796-Response_toOA.pdf	690415 c0a34a4ad6c89bba40c66a098aa957ddb852f867	no	7

Warnings:	
Information:	

Total Files Size (in bytes):	690415

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/19/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Ruth Graden/

PTO/SB/08a (05-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5419898	A	1995-05-30	Ikejiri	
	2	6258814	A	2001-07-10	Martin	
	3	5368852	A	1994-11-29	Umemoto et al.	
	4	6436924	A	2002-08-20	Poppe et al.	
	5	7198800	A	2007-04-03	Ko	
	6	7157464	A	2007-01-02	Pennell et al.	
	7	7094429	A	2006-08-22	Kiel et al.	
	8	4525358	A	1985-06-25	Baltes et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	9	4728509	A	1988-03-01	Shimizu et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2005/107711	WO	A2	2005-11-17	Biolipox AB		☐
	2	2004/050094	WO	A1	2004-06-17	UCB, S.A.		☐
	3	2002/047689	WO	A2	2002-06-20	UCB, S.A.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

If you wish to add additional non-patent literature document citation information please click the Add button			
EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Michael S. Greenfield/	Date (YYYY-MM-DD)	2008-12-18
Name/Print	Michael S. Greenfield	Registration Number	37142

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	4471381
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	18-DEC-2008
Filing Date:	18-JUL-2007
Time Stamp:	15:11:56
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	125927 c5cd100111e10abfcc1dc0d6f319e110f4d76065	no	1

Warnings:	
Information:	

2	Foreign Reference	06-796_FR1.pdf	1760250 b13e44fee7c5e287eb67acf41c03f0c20d175f5a	no	46
Warnings:					
Information:					
3	Foreign Reference	06-796_FR2.pdf	714287 35737603ca69b0ca6d0e8e9aa1ba80761f7ffc37	no	14
Warnings:					
Information:					
4	Foreign Reference	06-796_FR3.pdf	534970 5f6a7ef91f6ec75e77d3f55799fc862d10e2dfeb	no	10
Warnings:					
Information:					
5		06-796_IDS.pdf	884977 6d7993679189143d16cc3c5306daed391da954a6	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Information Disclosure Statement (IDS) Filed (SB/08)	1	3
	Information Disclosure Statement Letter	4	5

Warnings:	
Information:	
Total Files Size (in bytes):	4020411

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):
  Copy of three (3) cited references.

Remarks

No fees are believed due. However, please charge any underpayments and credit any overpayments to Deposit Account No. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	December 18, 2008	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	December 18, 2008

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/107711 A2

(51) International Patent Classification[7]: A61K 9/127, 9/00, 31/495, A61P 37/08

(21) International Application Number: PCT/GB2005/001758

(22) International Filing Date: 6 May 2005 (06.05.2005)

(25) Filing Language: English

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(30) Priority Data:
10/842,433 11 May 2004 (11.05.2004) US

(71) Applicant *(for all designated States except US, UZ)*: **BIOLIPOX AB** [SE/SE]; P.O. Box 6280, SE-102 34 Stockholm (SE).

(71) Applicant *(for UZ only)*: **MCNEENEY, Stephen, Phillip** [GB/GB]; Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PERESWETOFF-MORATH, Lena** [SE/SE]; Biolipox AB, P.O. Box 6280, SE-102 34 Stockholm (SE). **CARLSSON, Anders** [SE/SE]; MediGelium AB, S:t Göransgatan 80, SE-112 38 Stockholm (SE).

(74) Agent: **MCNEENEY, Stephen**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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

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

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND COMPOSITION FOR TREATING RHINITIS

(57) Abstract: There is provided pharmaceutical compositions for the treatment of rhinitis by, for example, nasal or ocular administration comprising zwitterionic cetirizine, a polar lipid liposome and a pharmaceutical-acceptable aqueous carrier. The compositions are preferably homogeneous in their nature.

WO 2005/107711 A2

METHOD AND COMPOSITION FOR TREATING RHINITIS

Field of the Invention

This invention relates to a method for treating rhinitis, and to a corresponding pharmaceutical composition.

Background and Prior Art

Allergic and non-allergic rhinitis are common disorders affecting about 30% of the population. Rhinitis has a considerable impact on quality of life. In fact, rhinitis is regarded to affect the quality of life more so than, e.g., asthma.

Hay fever and perennial allergic rhinitis are characterised by sneezing, rhinorrhea, nasal congestion, pruritus, conjunctivitis and pharyngitis. In perennial rhinitis, chronic nasal obstruction is often prominent and may extend to eustachian tube obstruction.

Oral or local antihistamines are first line treatments, and nasal steroids second line treatments for rhinitis. For most patients, topical corticosteroids and long acting antihistamine agents provide significant relief of symptoms. Antihistamines may also affect non-immunologically (non-IgE) mediated hypersensitivity reactions such as non-allergic rhinitis, exercise induced asthma, cold urticaria, and non-specific bronchial hyperreactivity.

Cetirizine dihydrochloride, [2-{4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl}ethoxy]acetic acid is an orally and locally active, potent, long acting peripheral histamine H_1 receptor antagonist. Cetirizine is one of the most widely used second generation antihistamines for the treatment of rhino-conjunctivitis and urticaria. It is effective, well tolerated and safe when used orally in a dose of 10 mg daily. Sedation and dry mouth do however occur as side effects in orally treated patients. Cetirizine is also approved in children for the treatment of rhinitis.

The main clinical affects of antihistamines include reduced sneezing and rhinorrhea. However, reduction of nasal blockage appears to be less responsive.

Local administration of antihistamines (such as azelastine and levocabastine) has advantages, including rapid onset of action and fewer side effects. At present, however, cetirizine dihydrochloride is not an approved medicine for local administration, although it has been administered in that manner in clinical trials.

In one trial (Francillon C, Pécoud A. *Effect of nasal spray of cetirizine in a nasal provocation test with allergen.* J Allergy Clin. Immunol. 1993:91, Suppl. 2:258 (abstract)), cetirizine nasal spray was found to reduce symptoms and increase nasal peak flow after an allergen challenge. Further, in exercise-induced asthma, a good protective effect was seen when cetirizine mist was administered to the lung with a nebulizer (Ghosh SK, De Vos C, McIlroy I, Patel KR. *Effect of cetirizine on exercise induced asthma*, Thorax 1991 Apr; **46(4)**, 242-4).

Some effect was seen on symptoms when cetirizine (presumably as the di-hydrochloride) was given as a nasal spray in patients with perennial allergic rhinitis. Concentrations of 0.625, 1.25, and 2.5 mg/mL of cetirizine were sprayed three times a day for two weeks (Clement P, Roovers MH, Francillon C, Dodion P. *Dose-ranging, placebo-controlled study of cetirizine nasal spray in adults with perennial allergic rhinitis*, Allergy 1994 Sep; **49(8)**, 668-72). The most common side effects were related to nasal events, although no difference in incidence between the placebo and the cetirizine-treated groups was seen. However, the authors of this article speculated therein that local irritation had an adverse effect on treatment efficacy.

Indeed, due to the irritation of the nasal mucosa by cetirizine, it has been found to be necessary to decrease its immediate exposure in nasal administration. In European Patent No. EP 605 203 B1, it has been reported that this can be achieved by providing cetirizine in form of a composition containing cyclodextrin.

Liposomes (also known as lipid vesicles) are colloidal particles that are prepared from polar lipid molecules derived either from natural sources or chemical synthesis. Such spherical, closed structures composed of curved lipid bilayers, are typically used to entrap drugs, which are often cytotoxic, in order to reduce toxicity and/or increase efficacy. Liposome-entrapped drug preparations are often provided in a dry (e.g. freeze-dried) form, which is subsequently reconstituted with an aqueous solution immediately prior to administration. This is done in order to minimise the possibility of leakage of e.g. cytotoxic drug into aqueous solution and thereby reducing the entrapping effect of the liposome.

Liposomes have also been employed to encapsulate various drug compounds for delivery *via* the nasal route, in order to improve bioavailability or as an adjuvant. Drugs that may be mentioned include tetanus toxoid vaccine, insulin, desmopressin and diphenhydramine hydrochloride (see Türker *et al*, *Review Article: Nasal Route and Drug Delivery Systems*, Pharm. World Sci., 2004; **26**, 137-142 and the references cited therein), as well as ciprofloxacin, CM3 and salbutamol (see Desai *et al*, *A Facile Method of Delivery of Liposomes by Nebulization*, J. Control. Release, 2002; **84**, 69-78).

Liposome-entrapped cetirizine has also been administered topically to evaluate peripheral antihistaminic activity and systemic absorption in a rabbit model (Elzainy *et al*, *Cetirizine from Topical Phosphatidylcholine-Hydrogenated Liposomes*, The AAPS Journal, 2004; **6**, 1-7. See also Drug Development and Industrial Pharmacy, 2005; **31**, 281-291).

The lipophilic behaviour of the cationic (wherein the anion is chloride), zwitterionic, and anionic forms of cetirizine in buffered aqueous phosphatidylcholine liposome systems containing from about 1 to 33.5 mg/mL of phospholipid has also been studied (Plemper van Balen G *et al.*, *Lipophilicity behaviour of the zwitterionic antihistamine cetirizine in phosphatidylcholine liposomes/water systems*, Pharm. Res. 2001; **18**, 694-701). The aim with the study, in which separate solutions of PBS-diluted egg phosphatidylcholine liposomes were poured into separate compartments of dialysis cells, was to gain

insight into the mechanism of interaction of the various electrical species of cetirizine and other drugs with liposomal membranes. The zwitterionic form of cetirizine, which dominates in the pH range of from about pH 4 to about pH 7, and even from about pH 3 to about pH 8, was considered by the authors of this article to be prevented from entry into the liposomal membrane by rendering the formation of lipophilic folded conformers of cetirizine more difficult. In this respect, cetirizine was not entrapped in liposomal membranes for delivery of drug to patients.

To the applicant's knowledge there is no prior disclosure or suggestion in the art of a homogeneous pharmaceutical composition comprising zwitterionic cetirizine, a polar lipid liposome and a pharmaceutical acceptable aqueous carrier.

Surprisingly, we have found that the irritation normally associated with (e.g. nasal) administration of cetirizine may be reduced by way of use of just such a composition.

According to the invention, there is provided pharmaceutical compositions suitable for the treatment of rhinitis by, for example, nasal or ocular administration comprising zwitterionic cetirizine, a polar lipid liposome and a pharmaceutical-acceptable aqueous carrier, which compositions are referred to hereinafter as "the compositions of the invention".

The skilled person will appreciate that zwitterionic cetirizine is employed in compositions of the invention in a pharmacologically-effective amount (*vide infra*). The term "pharmacologically-effective amount" refers to an amount of cetirizine, which is capable of conferring the desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient. Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

By "pharmaceutical compositions" we include compositions that are suitable for use in direct administration to mammals, and especially humans. In this respect,

the term is intended to encompass formulations that include only components that are regarded in the art as suitable for administration to mammalian, and especially human, patients. In the context of the present invention, the term may also mean that the compositions of the invention are in a form of a liquid that is ready-to-use, directly from the shelf, and not a formulation in which drug is encapsulated inside liposomes requiring reconstitution shortly prior to administration in order to avoid leakage of drug from liposomes into an aqueous carrier.

The compositions of the invention are preferably homogeneous. By "homogenous" we include not only that the compositions of the invention comprise liposomes dispersed evenly throughout the aqueous carrier, but further that the active ingredient is distributed throughout the whole composition in a substantially similar concentration in the relevant aqueous medium, whether that medium is located inside or outside of the liposomal structures. By "substantially similar", we include that the concentration may vary by about ±50%, such as about ±40%, preferably about ±30%, more preferably about ±20% and particularly about ±10% (when comparing concentrations inside and outside of the liposomal structures) at room temperature and atmospheric pressure. Drug concentration profiles may be measured by standard techniques known to the skilled person, such as ^{31}P-NMR. For example, a standard *in situ* probing technique, or a technique that involves separation of the liposomal fraction from the free aqueous carrier and measurement of the amount/concentration of drug associated with each fraction may be employed. Separation may be accomplished by centrifugation, dialysis, ultrafiltration, or gel filtration.

It is preferred that the compositions of the invention further include a pharmaceutically-acceptable buffer capable of providing a pH of from about pH 4 (e.g. 4.0) to about pH 8 (e.g. 8.0), preferably from about pH 5 (e.g. 5.0) to about pH 7 (e.g. 7.0). Appropriate buffers include those that will not interfere with the formation of liposomes, such as a phosphate (e.g. disodium phosphate, dipotassium phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate or phosphoric acid plus base), citrate (e.g. sodium citrate or citric acid plus base), or acetate buffer (e.g. sodium acetate or acetic acid plus base), which is

capable of maintaining a pH within the above-specified ranges. Buffers may be employed in an amount that is suitable to provide for the above-mentioned effects and such will be appreciated by the skilled person without recourse to inventive input. Appropriate quantities are for example in the range of about 1 mg/mL to about 30 mg/mL.

Any pharmaceutically-acceptable salt of cetirizine as well as the free base form thereof may be used in the manufacture of compositions of the invention. Preferred salts include chloride salts, hydrochloride (e.g. dihydrochloride) salts and, more particularly, nitrate salts of cetirizine, most preferably cetirizine dinitrate.

The amount of cetirizine or salt thereof that may be employed in preparation of compositions of the invention may be determined by the physician, or the skilled person, in relation to what will be most suitable for an individual patient. This is likely to vary with the severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. It is preferred however that the compositions of the invention comprise cetirizine or a salt thereof in an amount of from about 1 mg/mL to about 30 (e.g. about 25, such as about 23) mg/mL calculated on the zwitterionic form, preferably in an amount of from about 5.5 mg/mL to about 22 mg/mL. A further preferred range is between about 6 mg/mL and about 15 mg/mL, such as about 8 mg/mL to about 12 mg/mL.

In such a case, the total amount of active ingredient that may be present may be sufficient to provide a daily dose of drug per unit dosage that is in the range about 4 mg to about 20 mg, such as about 5 mg to about 15 mg, more preferably about 7 mg to about 12 mg and most preferably about 8 mg to about 10 mg. The skilled person will appreciate that compositions of the invention may be dosed once or more times daily in one or more administrations in order to provide the aforementioned daily dose.

The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The term "liposome" will be well understood by those skilled in the art to include a structure consisting of one or more concentric spheres of polar lipid bilayers separated by water or aqueous buffer compartments.

Liposomes may be prepared by various methods using solvents, reduced pressure, two-phase systems, freeze drying, sonication etc. described, for instance, in *Liposome Drug Delivery Systems*, Betageri G V et al., Technomic Publishing AG, Basel, Switzerland, 1993, the relevant disclosures in which document are hereby incorporated by reference.

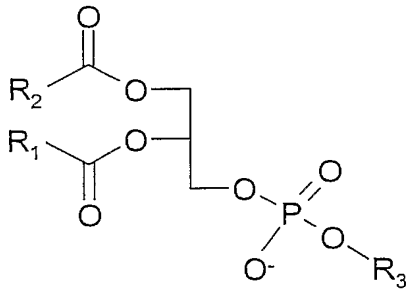
The term "polar lipid" will be well understood by the skilled person to include any lipid with a polar head-group and two fatty acid residues, which is capable of forming liposomes.

Polar lipids, such as those described hereinafter, may be of a natural and/or a synthetic/semi-synthetic origin. Mixtures of natural and synthetic/semi-synthetic polar lipids may also be employed in compositions of the invention.

Polar lipids that may be employed in compositions of the invention may thus be based on, for example, phospholipids, and in particular phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidylserine (PS), or mixtures thereof.

Phospholipids that may be employed in compositions of the invention comprise polar and non-polar groups linked to a backbone entity carrying hydroxyl groups, such as glycerol.

Phospholipids may also be represented by the general formula I



I

wherein R_1 and R_2 independently represent a saturated or unsaturated (e.g. alkenyl), branched or straight chain alkyl group having between 7 and 23 carbon atoms, preferably between 11 and 19 carbon atoms; and R_3 represents an amide or ester bonding group, such as

$-CH_2-CH(OH)-CH_2OH$ (phosphatidylglycerol),

$-CH_2-CH_2-N(CH_3)_3$ (phosphatidylcholine),

$-CH_2-CH_2-NH_2$ (phosphatidylethanolamine),

-H (phosphatidic acid), or

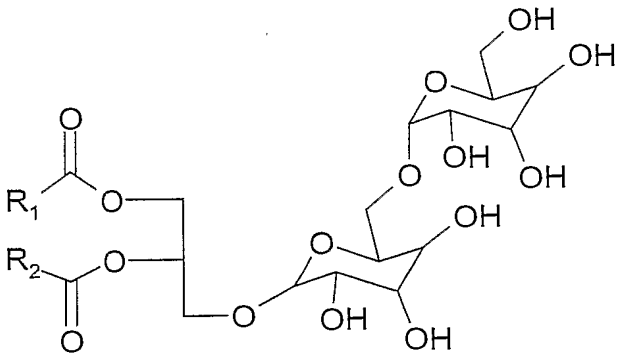
$-CH_2-CH(NH_2)-COOH$ (phosphatidylserine).

The phospholipid may be of natural origin. Natural phospholipids are preferably membrane lipids derived from various sources of both vegetable (e.g. rapeseed, sunflower, etc., or, preferably, soybean) and animal origin (e.g. egg yolk, bovine milk, etc.). Phospholipids from soybean, a major source of vegetable phospholipids, are normally obtained from the by-products (i.e. lecithins) in the refining of crude soybean oil by the degumming process. The lecithins are further processed and purified using other physical unit operations, such as fractionation and/or chromatography. Other phospholipids may be obtained, for example, by pressing various suitable seeds and grains, followed by solvent extraction and then further processing as described above. Phospholipids of natural origin that may be mentioned include for example those that are available under the tradenames Lipoid S75, Lipoid S100 and Lipoid S75-3N (Lipoid GmbH, Germany), which are all blends of several different phospholipids that are found in soybean.

The phospholipid may alternatively be of synthetic or semi-synthetic origin (i.e. prepared by chemical synthesis). For example, a multi-step chemical synthetic approach may be used in order to obtain the key phospholipid intermediates, 1,2-diacylglycerol, from (*S*)-1,2-isopropylideneglycerol, the latter providing the glycerol backbone that is characteristic of phospholipids. 1,2-Diacetylated phospholipids may then be obtained when the corresponding polar head group is attached *via* chemical synthesis to the 1,2-diacylglycerol intermediate. Generally, however, the origin of glycerol and the fatty acids used in the various steps may be of both natural and synthetic origin. Synthetic and/or semi-synthetic phospholipids that may be mentioned include dilaurylphosphatidylcholine (DLPC), dimyristolphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), dilaurylphosphatidylglycerol (DLPG), dimyristolphosphatidylglycerol (DMPG), dioleoylphosphatidylcholine (DOPC) and dioleoylphosphatidylglycerol (DOPG).

The polar lipid may alternatively comprise or, more preferably, consist of a glycolipid. In the context of the present invention, the term "glycolipid" designates a compound containing one or more monosaccharide residues bound by a glycosidic linkage to a hydrophobic moiety such as an acylglycerol, a sphingoid or a ceramide (N-acylsphingoid).

A glycolipid may be a glycoglycerolipid. In the context of the present invention, the term "glycoglycerolipid" designates a glycolipid containing one or more glycerol residues. According to a preferred aspect of the invention, the glycoglycerolipid comprises, or consists of, galactoglycerolipid, more preferably a digalactosyldiacylglycerol of the general formula II,



II

wherein R_1 and R_2 are as hereinbefore defined.

The glycolipid may alternatively be a glycosphingolipid. In the context of the present invention, the term "glycosphingolipid" designates a lipid containing at least one monosaccharide residue and either a sphingoid or a ceramide. The term may thus comprise neutral glycophingolipids, such as mono- and oligoglycosylsphingoids as well as oligo- and, more preferably, monoglycosylceramides. The term additionally comprises acidic glycosphingolipids such as sialoglycosphingolipids, uronoglycosphingolipids, sulfoglycosphingolipids, phosphoglycosphingolipids, and phosphonoglycosphingolipids. The glycosphingolipid can be ceramide, monohexosylceramide, dihexosylceramide, sphingomyelin, lysosphingomyelin, sphingosine, or a mixture thereof. Preferably the glycosphingolipid is sphingomyelin or products derived therefrom. The sphingomyelin content is preferably established by chromatographic methods. Sphingomyelin may be extracted from milk, preferably bovine milk, brain, egg yolk or erythrocytes from animal blood, preferably sheep. For the avoidance of doubt, synthetic and semi-synthetic sphingolipids are comprised by the invention.

The glycolipid may alternatively be a glycophosphatidylinositol. In the context of the present invention, the term "glycophosphatidylinositol" designates a glycolipid containing saccharides glycosidically linked to the inositol moiety of phosphatidylinositols.

Preferred glycolipids include digalactosyldiacylglycerol (DGDG).

Preferred polar lipids (such as phospholipids) are those that swell to a measurable degree in water and/or those which are capable of spontaneous liposome formation.

If the polar (e.g. phospho-) lipid does not swell spontaneously in water, the skilled person will appreciate that it is nevertheless possible to obtain liposomes by adding a more polar, swellable (e.g. phospho-) lipid, such as an anionic (e.g. phospho-) lipid (e.g. phosphatidylglycerol).

Liposome formation may be performed at above about 0°C (e.g. room temperature) if the phase transition temperature of the acyl chains (chain melting; gel-to-liquid crystals) is below the freezing point of water.

Whichever polar lipid substance (or combination thereof) is used, suitable total amounts/concentrations of lipid(s) that may be employed in preparation of a composition of the invention are in the range of about 10 mg/mL to about 120 mg/mL. Compositions of the invention that may be mentioned include those in which, when the polar lipid comprises phospholipid (whether in combination with another lipid or otherwise), the amount of phospholipid(s) in the composition is from about 10 (e.g. about 17, such as about 20) mg/mL to about 120 mg/mL, more preferably from about 25 (e.g. about 35) mg to about 100 (e.g. about 70, such about 50, e.g. about 40) mg/mL.

Compositions of the invention may also comprise an antioxidant, such as α-tocopherol, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, citric acid, fumaric acid, malic acid, monothioglycerol, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, potassium metabisulfite, sodium sulfite, tartaric acid or vitamin E.

According to the invention a chelating agent may be used to reduce the metal ion catalysed oxidation of phospholipid and/or cetirizine. Examples of useful chelating agents are ethylenediaminetetraacetic acid (EDTA),

ethylenediaminetriacetic acid and diethylenetriaminepentaacetic acid (DTPA). It is also possible to use other agents that protect the composition of the invention and, in particular, any unsaturated fatty acid residues that may be present therein, from oxidation.

The composition of the invention can comprise one or more preservatives. Examples of common preservatives for liquid pharmaceutical compositions are benzalkonium chloride, benzoic acid, butylated hydroxyanisole, butylparaben, chlorbutanol, ethylparaben, methylparaben, propylparaben, phenoxyethanol or phenylethyl alcohol.

In order to retain the composition of the invention at its application site it may also comprise viscosity-increasing agent such as, for instance, hydrophilic polymers like polyethyleneglycol, or crosslinked polyvinylpyrrolidone and/or cellulose derivatives such as hydroxypropylmethyl cellulose. Viscosity increasing agents may also function as protective colloids to physically stabilise the composition of the invention prior to administration.

Compositions of the invention may also comprise flavourings (e.g. lemon, menthol or peppermint powder) and/or sweeteners (e.g. neohesperidin).

Compositions of the invention may also comprise tonicity-modifying agents, such as sodium chloride, potassium chloride, glycerol, glucose, dextrose, sucrose, mannitol, etc.

Optional additives, including buffering agents, preservatives, viscosity-increasing agents, antioxidants, tonicity-modifying agents and chelating agents should be selected, in terms of their identity and the amounts employed, keeping in mind that their detrimental effect on liposome stability should be kept at a minimum. For a given agent this can be ascertained by simple experiments, which are well within the understanding of the skilled person. Suitable amounts of such ingredients are however in the range about 0.01 mg/mL to about 10 mg/mL.

There is also provided a process for preparing compositions of the invention. We have surprisingly found that liposomes may be prepared by direct swelling of the polar lipids in an aqueous medium without the addition of any other excipients such as charged lipids and/or surfactants etc., which are normally required.

5

According to a further aspect of the invention, there is provided a process for preparing a composition of the invention, which process comprises:

(a) providing a polar lipid or a mixture of polar lipids that is/are swellable in aqueous media;

10 (b) providing an aqueous solution of cetirizine;

(c) adding the polar lipid or mixture to the aqueous solution with stirring, thereby forming a cetirizine liposome preparation;

(d) optionally adjusting the pH of the preparation to a desired value within the range of from about pH 4 (e.g. 4.0) to about pH 8 (e.g. 8.0), preferably from about

15 pH 5 (e.g. 5.0) to about pH 7 (e.g. 7.0), by adding an acid or a base (e.g. hydrochloric acid and/or sodum hydroxide at an appropriate concentration (e.g. 1M));

(e) optionally adding buffer solution or, more preferably, water or saline to the preparation to obtain a desired final batch volume; and

20 (f) homogenising the preparation to obtain said pharmaceutical composition.

Solutions/liquids may be purged with nitrogen or argon at a suitable stage in the above process, if and as appropriate.

25 In the context of the present invention, a lipid may be said to be swellable in aqueous media if, when placed in contact with such a medium, it swells to a measurable degree.

Buffers may preferably be added to the aqueous solution of drug (and/or drug may

30 be added to an aqueous buffer solution) prior to the addition of lipid. This notwithstanding, the person skilled in the art will be aware of the inherent buffering effect of zwitterionic cetirizine.

The formation of the liposomes of the invention may be facilitated by the spontaneous swelling of the polar lipid in water forming a lamellar liquid crystalline phase having a maximum water content of about 35% by weight or higher depending on the nature of the polar lipid. Depending on the lipid or lipid mixture used and other conditions, spontaneous formation of liposomes may be achieved when excess water is added to this lamellar phase. If spontaneous formation is not achieved, the formation of liposomes may be accomplished by the mechanical dispersion step (i.e. the homogenisation step (f) of the above process) of the lamellar liquid-crystalline phase in excess water.

Homogenisation/dispersion methods include vigorous mechanical mixing, for instance by means of an Ultra Turrax® (Jankel & Kühnke, Germany). Shaking, vortexing and rolling may also be performed as part of the homogenisation step of the above process.

A homogeneous size distribution of the liposomes of the invention may be desirable and may be obtained by extrusion through a membrane filter, such as one made of polycarbonate, with a pore size of about 100 nm. Membrane filters may be procured from Avestin Inc., Canada.

A reduced average liposome size and narrowed liposome size distribution may preferably also be obtained when the liposomal dispersion is subjected to high-pressure homogenisation with a suitable homogeniser (Rannie APV, type 7.30 VH, Rannie AS, Denmark) at, for example, between about 300 bar and about 1000 bar, such as between about 400 bar and about 900 bar, e.g. about 500 to about 800 bar for between about 4 and about 8 (e.g. 7, such as 6) cycles.

Surprisingly, we have found that the presence of cetirizine results in a reduction of liposome size. Smaller liposomes are generally advantageous because they are more stable physically and, due to their higher surface area/volume ratio, are more easily resorbed by the mucosa.

We prefer that the diameter of liposomes in compositions of the invention is less than about 200 nm (e.g. between about 40 to about 100 nm), as measured by, for example, laser diffraction or dynamic light scattering, e.g. as described hereinafter.

Furthermore, the above-mentioned process for the preparation of compositions of the invention does not normally require conventional treatment with organic solvents such as chloroform or dichloromethane. However, if two or more membrane lipids are used it may be appropriate and/or necessary to treat them with organic solvent prior to the addition of the aqueous solvent. For example, the lipids may be dissolved in a volatile solvent or solvent mixture, such as chloroform or chloroform/methanol. The solution may then be deposited on the surfaces of a round-bottomed flask as the solvent is removed by rotary evaporation under reduced pressure. An excess volume of aqueous buffer containing the drug may then be added to the dry thin film of lipids, which may then be allowed to swell to form liposomes.

The compositions of the invention are useful in the treatment of any indication for which cetirizine is known to be indicated, including rhinitis. The term "rhinitis" will be understood to include any irritation and/or inflammation of the nose, whether allergic or non-allergic, including seasonal rhinitis (e.g. caused by outdoor agents such as pollen; hay fever) and/or perennial rhinitis (e.g. caused by house dust mites, indoor mold etc), as well as the symptoms thereof.

According to a further aspect of the invention, there is provided a method for the treatment of rhinitis comprising the (e.g. nasal) administration of a pharmacologically-effective amount of a composition of the invention to a person suffering from or susceptible to that disorder.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment, as well as the symptomatic treatment, the prophylaxis, or the diagnosis, of a condition.

The compositions of the invention may be administered by way of a nasal spray, nasal drops and/or eye drops. It is also possible to administer compositions of the invention as a fine mist to the lungs by nebulization. For nasal administration, any state-of-the-art device suitable for producing sprays of aqueous liposomal dispersions may be used.

Wherever the word "about" is employed herein in the context of dimensions (e.g. pH values, sizes, temperatures, pressures, etc.) and amounts (e.g. amounts, weights and/or concentrations of individual constituents in a composition or a component of a composition, proportions of drug inside/outside the liposomal structures, absolute doses of active ingredient, etc.), it will be appreciated that such variables are approximate and as such may vary by ± 10%, for example ± 5% and preferably ± 2% (e.g. ± 1%) from the numbers specified herein.

The compositions of the invention, and the above-mentioned process that may be employed for their preparation, have the advantages that are mentioned hereinbefore. In particular, compositions of the invention may reduce the incidence of inconvenient side-effects (and in particular irritation) that are normally observed with e.g. nasally-administered cetirizine formulations.

Compositions of the invention are easy to manufacture and enable the production of liposomal-based formulations that are in a ready-to-use form, avoiding the need for reconstitution prior to administration.

Compositions of the invention may also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in foods or pharmaceuticals or of like regulatory status.

Compositions of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile than, and/or have other useful pharmacological, physical,

or chemical properties over, pharmaceutical compositions known in the prior art, whether for use in the treatment of rhinitis or otherwise.

The invention is illustrated by way of the following examples.

Example 1

Table 1

Batch formula

Cetirizine dinitrate*	22.2 g
Phospholipid (from soybean**)	70.0 g
Disodium phosphate, dihydrate; Na_2HPO_4 $2H_2O$	21.3 g
Potassium dihydrogenphosphate; KH_2PO_4	11.0 g
1M Hydrochloric acid and/or 1M sodium hydroxide	to pH 7.0
Water for injection	to 2.0 L

*) White solid, crystallized from THF/acetonitrile/water 2:1:0.28. Obtained from commercially available cetirizine dihydrochloride via neutralisation of the free base with nitric acid. **) Lipoid S75, Lipoid GmbH, Germany

General procedure. For weights and volumes reference is made to Table 1 above. A buffer solution was prepared by dissolving the buffering agents disodium phosphate dihydrate (Na_2HPO_4 $2H_2O$) and potassium dihydrogen phosphate (KH_2PO_4) in 1600 mL water (80% of the total batch volume) in a 2000 mL volumetric flask. The weighed amount of active agent was added to the buffer solution and dissolved by stirring with a magnetic stirrer, followed by addition of 100 mL of aqueous 1M sodium hydroxide. The phospholipid was separately weighed and added to the cetirizine solution. Stirring was continued until a well dispersed suspension had been formed, the pH of which was adjusted to pH 7.0 ± 0.1 with 1.0 M NaOH or 1.0 M HCl. The volume of the preparation was then brought to the final batch volume of 2000 mL. The preparation was transferred to a 5 L glass vessel provided with an Ultra Turrax® T25 homogeniser (Jankel & Kühnke, Germany). Homogenisation was carried out at 22000 rpm for 3 x 2

minutes interrupted by 10 minute settling periods. 10 mL aliquots of the thus obtained composition were removed from the stirred dispersion and transferred to glass vials onto which spray heads (VP7 or VP7D; Valois S.A., France) were either crimped on or attached by screw fitting after filling. The stirred composition as well as the composition aliquots in the vials were protected from light.

Ultrasonication was found to further reduce mean particle size. In this method, the vials with the homogenised compositions were placed in an ultrasonication bath and sonicated for 2 x 10 minutes, whereupon the samples had an almost clear appearance in comparison with the opaque composition afforded by Ultra-Turrax® homogenisation.

The aforementioned particle size reduction methods are compared in Table 2. Particle size distribution was determined by laser diffraction (Mastersizer 2000, Malvern Instrument, UK). A Fraunhofer theory based method was used to calculate the particle size of the high speed homogenised sample whereas a MIE (2.50/0.001) theory based method was used for calculation of the particle size of the sample additionally subjected to sonication.

Table 2

Particle size reduction

Treatment	Mean particle size (nm)
High speed homogenisation	940
High speed homogenisation + ultrasonication	162

Example 2

Table 3

Composition

Cetirizine dinitrate	2.22 g
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	7.00 g
Citric acid, anhydrous	3.84 g
Sodium hydroxide, solid	1.67 g
Ascorbic acid	0.20 g
EDTA sodium	0.20 g
HCl, 1 M and/or NaOH, 1 M	to pH 5.0
Water for injection	to 200 mL

General procedure. For weights and volumes reference is made to Table 3. A buffer solution was prepared by dissolving anhydrous citric acid and solid sodium hydroxide in 160 mL water (80% of the total batch volume) in a 200 mL volumetric flask. The weighed amount of active agent was added and dissolved by stirring with a magnetic stirrer. The phospholipid was separately weighed and added to the cetirizine solution. Stirring was continued until a well dispersed suspension had been formed, the pH of which was adjusted to pH 5.0 ± 0.1 with 1.0 M NaOH and/or 1.0 M HCl. The volume of the preparation was then brought to the final batch volume of 200 mL. The preparation was transferred to a high pressure homogeniser (Rannie APV, type 7.30 VH, Rannie AS, Denmark) and homogenised at 500-800 bar for 5 cycles. Aliquots of the thus obtained composition were removed from the collecting vessel and transferred to glass vials.

Example 3

In Table 4, a high pressure homogenation particle size reduction method, as described in Example 2, is compared with high speed homogenisation (Ultra Turrax® T25 homogeniser; Jankel & Kühnke, Germany), as described in Example

1. The composition employed was that of Example 1. Particle size distribution was determined by dynamic light scattering (Zetasizer 4, Malvern Instruments, UK) at an angle of 90° and at room temperature, using a ZET5104 sizing cell and auto:CONTIN analysis mode.

Table 4

Particle size reduction

Treatment	Cetirizine (mg/mL)	Z average mean (nm)
High speed homogenisation	11.1	282
High pressure homogenisation at 500 bar	11.1	77
High pressure homogenisation at 800 bar	11.1	50
High pressure homogenisation at 500 bar	0	130
High pressure homogenisation at 800 bar	0	121

The methods used for preparing these exemplary batch compositions were adapted for preparing the following additional examples.

Example 4

Cetirizine dinitrate	5.6 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	35.0 mg
Disodium phosphate dihydrate; Na_2HPO_4 H_2O	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	to pH 7.0
Water for injection	to 1 mL

Example 5

Cetirizine dinitrate	22.2 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	35.0 mg
Disodium phosphate dihydrate; Na_2HPO_4 H_2O	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	to pH 7.0
Water for injection	to 1 mL

Example 6

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	70.0 mg
Disodium phosphate dihydrate; Na_2HPO_4 H_2O	10.7
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	to pH 7.0
Water for injection	to 1 mL

Example 7

Cetirizine dinitrate	11.1 mg
Phospholipid (dioleoylphoshatidylcholine*)	35.0
Disodium phosphate, dihydrate; Na_2HPO_4 $2H_2O$	10.7
Potassium dihydrogen phosphate; KH_2PO_4	5.5
1 M HCl and/or 1 M sodium hydroxide	to pH 7.0
Water for injection	to 1 mL

*DOPC, Larodan Fine Chemicals, Sweden

Example 8

Cetirizine dinitrate	11.1 mg
Phospholipid (dioleoylphosphatidylglycerol*)	35.0 mg
Disodium phosphate, dihydrate; Na_2HPO_4 $2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M sodium hydroxide	to pH 7.0
Water for injection	to 1 mL

*DOPG, Avanti Polar Lipids, AL, USA

Example 9

Cetirizine dinitrate	11.1 mg
Galactolipid (digalactosyldiacylglycerol*)	35.0 mg
Disodium phosphate, dihydrate; Na_2HPO_4 $2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M sodium hydroxide	to pH 7.0
Water for injection	to 1 mL

*DGDG, Larodan Fine Chemicals, Sweden

Example 10

Nasal Irritation Test in a Dog Model

Cetirizine dinitrate (5.6, 11.1 and 22.2 mg/mL, respectively, in the compositions of Examples 1, 4 and 5; shaken rather than high speed or high pressure homogenised) was administered twice daily for 14 days to four male beagle dogs per group (5-6 months old, weighing 10.1 – 14.2 kg). Clinical signs and body weights were monitored throughout the study. A necropsy was performed, and the nasal cavity was collected and processed (fixated, decalcified and stained with haematoxylin and eosin). Four sections from the nasal cavity were evaluated microscopically, covering squamous, ciliated respiratory, and olfactory epithelium. No treatment-related clinical signs were observed during the administration period. The mean body weight gain over the administration period

was unremarkable. The macroscopic and microscopic examination of the nasal cavity and the nasal mucosa preparations did not reveal any signs of mucosal irritation or other change.

Example 11

Ocular Irritation Test in a Rabbit Model

The potential irritating properties of the compositions of the invention was also assessed in an eye irritation test in three white (albino), female New Zealand rabbits per treatment weighing between 2.8 to 3.4 kg. The concentrations investigated were 5.6, 11.1 and 22.2 mg/mL in the composition of Example 1. 0.1 mL of the composition was placed in the left eye of each rabbit. The right eye served as untreated control. The eyes were examined prior to treatment and at 1, 24, 48, and 72 h after treatment. The ocular reaction to treatment was graded according to a subjective numerical scoring system. Signs of conjunctival irritation (redness) were observed in two rabbits in the group receiving the composition containing 22.2 mg/mL cetirizine dinitrate. In the first rabbit, a score 2 (diffuse, crimson colour, individual vessels not easily discernable) on a scale graded 0 to 3 was noted one hour after treatment. In the second rabbit, a score 1 (some hyperaemic blood vessels) on a four grade scale was noted at 24 h. In both cases the redness was not present at subsequent observations, and was thus considered reversible. No other signs of eye irritation were observed in any of the animals.

Example 12

Nasal irritation test

A single dose (110 µL in each nostril) of cetirizine dinitrate (11.1 mg/mL) was administered to five healthy volunteers at four sessions in one of four formulations (I – IV; see Table 5 for details) in each session. Formulations I, II, and III are formulations of the examples above whereas reference formulation IV was not a formulation of the invention. The test was performed to investigate the reduction of irritation by liposome formulation as compared to plain buffer solution. Also the influence of particle size and the ratio phospholipid to cetirizine was studied.

Table 5

Cetirizine Dinitrate Formulations Used in Testing Nasal Irritation

Formulation	Composition	mg Phospholipid per mL Vehicle	Features*
I	Example 1	35	High speed homogenised
II	Example 1	35	High speed homogenised + ultrasonicated
III	Example 6	70	High speed homogenised + ultrasonicated
IV	Reference	nil; phosphate buffer	Plain buffered aqueous solution

*Refer to Table 2

Nasal symptom score were assessed at 1, 10, 30 minutes post administration. The nasal symptom score included the following variables: nasal congestion, rhinorrhea, itching/sneezing, burning/pain, and taste. These symptoms were qualified by the subjects according to a no – mild – moderate – severe symptom scale (0 - 3). The results are reported as total score, adding all five subjects scores (maximum score of 15).

The phospholipid formulations were better tolerated than the plain buffer solution. Smaller liposomes seem to be of some advantage. The mild discomfort reported by all subjects at 1 minute had practically disappeared at 10 min for the two formulations (II and III) that had reduced particle size by sonication. In contrast, the initial mild discomfort reported for formulation I persisted at 10 minutes. Increasing the ratio of phospholipid to cetirizine did not further improve the performance of the formulation.

Table 6

Nasal irritation test in healthy volunteers

1 minute post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	0	3	1	6.5	1	11.5
II	0	1	1	6	0	8
III	0	0	1	5.5	0	6.5
IV	0	6	2	14.5	2	24.5

10 minutes post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	0	1	1	6	4	12
II	0	0	0	2	2	4
III	0	0	1	1	4.5	6.5
IV	0	1	1	8	3	13

30 minutes post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	0	0	1	1	3	5
II	0	0	1	0	0	1
III	0	0	0	1	1	2
IV	0	0	0	1.5	1	2.5

Example 13

Nasal irritation test

A single dose (110 μL in each nostril) of cetirizine dinitrate (11.1 mg/mL) was administered to four healthy volunteers at four sessions in one of four formulations (I – IV; see Table 7 for details) in each session. The test was

performed to investigate the irritative properties of formulations with different membrane lipids of natural and synthetic origin.

Table 7

Cetirizine dinitrate formulations used in testing nasal irritation

Formulation	Composition	Membrane lipid	
I	Example 1	Lipoid S75	Natural
II	Example 7	Dioleoylphoshatidylcholine (DOPC)	Synthetic
III	Example 8	Dioleoylphoshatidylglycerol (DOPG)	Synthetic
IV	Example 9	Digalactosyldiacylglycerol (DGDG)	Natural

Nasal symptom score were assessed at 1, 10, 30 minutes post administration. The nasal symptom score included the following variables: nasal congestion, rhinorrhea, itching/sneezing, burning/pain, and taste. These symptoms were qualified by the subjects according to a no – mild – moderate – severe symptom scale (0 - 3). The results are reported as total score, adding all four subjects scores (maximum score of 12).

The formulations containing DOPC and DOPG were very well tolerated with practically no reports of any kind at 1 minute. At 10 minutes there was still a tendency of better tolerability of these two formulations as compared to the membrane lipids of natural origin.

Table 8

Nasal irritation test in healthy volunteers

1 minute post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	0	1	1	3	2	7
II	0	1	0	1	0	2
III	1	0	1	0	0	1
IV	0	1.5	2	2	4	9.5

10 minutes post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	0	1	0	2	3	6
II	0	0	0	1	2	3
III	0	0.5	0.5	1	2	4
IV	0.5	0.5	0	1	4	6

30 minutes post-administration						
Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
I	1	0	0	0	0	1
II	0	0	0	0	0	0
III	0	0	1	0	1	2
IV	0	0	0	0	0	0

The following examples were also made in accordance with procedures analogous to those described hereinbefore.

Example 14

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 15

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	50.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 16

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
EDTA	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 17

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Benzalkonium chloride	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 18

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Methylparaben	1.8 mg
Propylparaben	0.2 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 19

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 20

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	23.3 mg
Phospholipid (soybean; Lipoid S75-3 N; Lipoid GmbH, Germany)	11.7 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 21

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	11.7 mg
Phospholipid (DMPC; Lipoid GmbH, Germany)	23.3 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 22

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	17.5 mg
Phospholipid (DMPC; Lipoid GmbH, Germany)	17.5 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 23

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	23.3 mg
Phospholipid (DMPC; Lipoid GmbH, Germany)	11.7 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 24

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Hydroxypropylmethylcellulose (Metolose 60SH-50)	1.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 25

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Polyethylene glycol (Macrogol 6000)	1.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 26

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 27

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Hydroxypropylmethylcellulose (Metolose 60SH-50)	10 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 28

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	17.5 mg
Phospholipid (DMPC; Lipoid GmbH, Germany)	17.5 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 29

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	23.3 mg
Phospholipid (DMPC; Lipoid GmbH, Germany)	11.7 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 30

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	23.3 mg
Phospholipid (DMPC; Lipoid GmbH, Germany	11.7 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Polyethylene glycol (Macrogol 6000)	10 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 31

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	29.2 mg
Phospholipid (DMPC; Lipoid GmbH, Germany	5.8 mg
Benzalkonium chloride	0.1 mg
Butylated hydroxytoluene (BHT)	0.01 mg
Povidone	1.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 32

Cetirizine dinitrate	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	23.3 mg
Phospholipid (DMPC; Lipoid GmbH, Germany	11.7 mg
Benzalkonium chloride	1.0 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Hydroxypropylmethylcellulose (Metolose 60SH-50)	5.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 33

Cetirizine dihydrochloride	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Ascorbic acid	1.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 34

Cetirizine dihydrochloride	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
α-Tocopherol	1.0 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

Example 35

Cetirizine dihydrochloride	11.1 mg
Phospholipid (soybean; Lipoid S100; Lipoid GmbH, Germany)	35.0 mg
Butylated hydroxytoluene (BHT)	0.1 mg
Citric acid	19.2 mg
Sodium hydroxide	8.4 mg
1 M HCl and/or 1 M NaOH	to pH 5.5
Water for injection	to 1 mL

5

Claims

1. A pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising zwitterionic cetirizine, a polar lipid liposome and a pharmaceutical-acceptable aqueous carrier.

2. A homogeneous composition as claimed in Claim 1.

3. A composition as claimed in Claim 1 or Claim 2, which further includes a pharmaceutically-acceptable buffer capable of providing a pH of from about pH 4 to about pH 8.

4. A composition as claimed in Claim 3, wherein the pH range is about pH 5 to about pH 7.

5. A composition as claimed in Claim 3 or Claim 4, wherein the buffer is a phosphate, citrate or acetate buffer.

6. A composition as claimed in Claim 5, wherein the buffer is disodium phosphate, dipotassium phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, phosphonic acid plus base, sodium citrate, citric acid plus base, sodium acetate or acetic acid plus base.

7. A composition as claimed in any one of Claims 3 to 6, wherein the quantity of buffer is in the range of about 1 mg/mL to about 30 mg/mL.

8. A composition as claimed in any one of the preceding claims, wherein cetirizine is provided in the form of a salt.

9. A composition as claimed in Claim 8, wherein the salt is a chloride salt, a hydrochloride salt or a nitrate salt.

10. A composition as claimed in Claim 9, wherein the salt is cetirizine dinitrate.

11. A composition as claimed in any one of the preceding claims, wherein the amount of cetirizine or salt employed in preparation of the composition is from about 1 mg/mL to about 30 mg/mL calculated on the zwitterionic form.

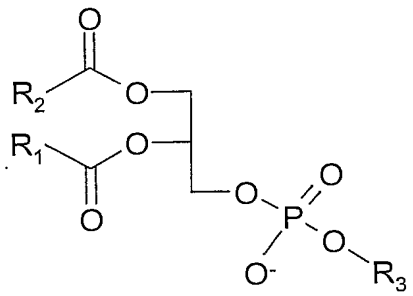
12. A composition as claimed in Claim 11, wherein the amount is from about 5.5 mg/mL to about 22 mg/mL.

13. A composition as claimed in any one of the preceding claims, wherein the polar lipid is of a natural origin, is of a synthetic/semi-synthetic origin, or comprises a mixture of the two.

14. A composition as claimed in any one of the preceding claims, wherein the polar lipid comprises or consists of a phospholipid or a mixture of phospholipids.

15. A composition as claimed in Claim 14, wherein the phospholipid comprises one that is based on phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidic acid, phosphatidylserine or a mixture thereof.

16. A composition as claimed in Claim 14 or Claim 15, wherein the phospholipid comprises one that is represented by the general formula I,



I

wherein R_1 and R_2 independently represent a saturated or unsaturated, branched or straight chain alkyl group having between 7 and 23 carbon atoms and R_3 represents an amide or ester bonding group.

17. A composition as claimed in Claim 16, wherein the amide or ester bonding group is $-CH_2-CH(OH)-CH_2OH$, $-CH_2-CH_2-N(CH_3)_3$, $-CH_2-CH_2-NH_2$, -H or $-CH_2-CH(NH_2)-COOH$.

18. A composition as claimed in any one of Claims 14 to 17, wherein the phospholipid comprises a membrane lipid derived from soybean.

19. A composition as claimed in Claim 18, wherein the phospholipid comprises Lipoid S75, Lipoid S100 and/or Lipoid S75-3N.

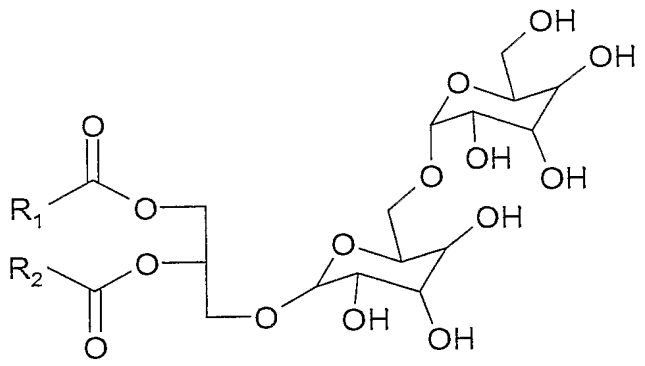
20. A composition as claimed in any one of Claims 14 to 19, wherein the phospholipid comprises dilaurylphosphatidylcholine, dimyristolphosphatidylcholine, dipalmitoylphosphatidylcholine, dilaurylphosphatidylglycerol, dimyristolphosphatidylglycerol, dioleoylphosphatidylcholine or dioleoylphosphatidylglycerol.

21. A composition as claimed in any one of Claims 1 to 13, wherein the polar lipid comprises or consists of a glycolipid or a mixture of glycolipids.

22. A composition as claimed in Claim 21, wherein the glycolipid comprises a glycoglycerolipid.

23. A composition as claimed in Claim 22, wherein the glycoglycerolipid comprises a galactoglycerolipid.

24. A composition as claimed in Claim 22, wherein the glycoglycerolipid comprises a digalactosyldiacylglycerol of the general formula II,



II

wherein R_1 and R_2 are as defined in Claim 16.

25. A composition as claimed in any one of Claims 21 to 24, wherein the glycolipid comprises digalactosyldiacylglycerol.

26. A composition as claimed in Claim 21, wherein the glycolipid comprises a glycosphingolipid.

27. A composition as claimed in Claim 26, wherein the glycosphingolipid comprises a monoglycosylsphingoid, an oligoglycosylsphingoid, an oligoglycosylceramide, a monoglycosylceramide, a sialoglycosphingolipid, a uronoglycosphingolipid, a sulfoglycosphingolipid, a phosphoglycosphingolipid, a phosphonoglycosphingolipid, a ceramide, a monohexosylceramide, a dihexosylceramide, a sphingomyelin, a lysosphingomyelin, a sphingosine or a mixture thereof.

28. A composition as claimed in Claim 27, wherein the glycosphingolipid comprises sphingomyelin or a product derived therefrom.

29. A composition as claimed in Claim 21, wherein the glycolipid comprises a glycophosphatidylinositol.

30. A composition as claimed in any one of the preceding claims, wherein the amount of polar lipid substance that is used is in the range of about 10 mg/mL to about 120 mg/mL.

31. A composition as claimed in any one of Claims 1 to 20 or 30, wherein the amount of phospholipid in the composition is from about 17 mg/mL to about 70 mg/mL.

32. A composition as claimed in Claim 31, wherein the amount is from about 20 mg/mL to about 40 mg/mL.

33. A composition as claimed in any one of the preceding claims, which further comprises an antioxidant.

34. A composition as claimed in Claim 33, wherein the antioxidant is α-tocopherol, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, citric acid, fumaric acid, malic acid, monothioglycerol, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, potassium metabisulfite, sodium sulfite, tartaric acid and/or vitamin E.

35. A composition as claimed in any one of the preceding claims, which further comprises a chelating agent.

36. A composition as claimed in Claim 35, wherein the chelating agent is ethylenediaminetetraacetic acid, ethylenediaminetriacetic acid and/or diethylenetriaminepentaacetic acid.

37. A composition as claimed in any one of the preceding claims, which further comprises a preservative.

38. A composition as claimed in Claim 37, wherein the preservative is benzalkonium chloride, benzoic acid, butylated hydroxyanisole, butylparaben, chlorbutanol, ethylparaben, methylparaben, propylparaben, phenoxyethanol and/or phenylethyl alcohol.

39. A composition as claimed in any one of the preceding claims, which further comprises a viscosity-increasing agent.

40. A composition as claimed in Claim 39, wherein the viscosity-increasing agent is polyethyleneglycol, crosslinked polyvinylpyrrolidone and/or hydroxypropylmethyl cellulose.

41. A composition as claimed in any one of the preceding claims, wherein the diameter of the liposomes is less than about 200 nm.

42. A composition as claimed in Claim 41, wherein the diameter is between about 40 nm and about 100 nm.

43. A process for the preparation of a composition as claimed in any one of the preceding claims, which process comprises:
(a) adding a polar lipid or a mixture of polar lipids that is/are swellable in aqueous media to an aqueous solution of cetirizine with stirring; and
(b) homogenising the preparation.

44. A process as claimed in Claim 43, wherein, prior to the homogenisation step, the pH is adjusted to the desired value by adding an acid or a base.

45. A process as claimed in Claim 43 or Claim 44, wherein, prior to the homogenisation step, water, saline or buffer solution is added to the preparation to obtain a desired final batch volume.

46. A process as claimed in Claim 45 (as dependent on Claim 44), wherein the addition of water, saline or buffer takes place after the pH adjusting step.

47. A process as claimed in any one of Claims 43 to 46, wherein at least one of the solutions/liquids is/are purged with nitrogen and/or argon.

48. A process as claimed in any one of Claims 43 to 47, wherein the aqueous solution of cetirizine is formed either by adding buffer to an aqueous solution of cetirizine or salt thereof, or adding cetirizine or salt thereof to an aqueous buffer solution, prior to the addition of lipid.

49. A process as claimed in any one of Claims 43 to 48, wherein, if a mixture of polar lipids is used, it is pre-treated with organic solvent.

50. A process as claimed in any one of Claims 43 to 49, wherein the homogenisation step (b) comprises vigorous mechanical mixing, high speed homogenisation, shaking, vortexing and/or rolling.

51. A process as claimed in any one of Claims 43 to 50, which comprises an additional liposome size-reduction step.

52. A process as claimed in Claim 51, wherein the size-reduction step comprises extrusion through a membrane filter.

53. A process as claimed in any one of Claims 43 to 49, 51 or 52, wherein the homogenisation step and/or size-reduction step comprises high-pressure homogenisation.

54. A pharmaceutical composition obtainable by a process comprising:
(a) adding a polar lipid or a mixture of polar lipids that is/are swellable in aqueous media to an aqueous solution of cetirizine with stirring; and
(b) homogenising the preparation.

55. A composition as claimed in Claim 54, wherein, in the process, prior to the homogenisation step, the pH is adjusted to the desired value by adding an acid or a base.

56. A composition as claimed in Claim 54 or Claim 55, wherein, in the process, prior to the homogenisation step, water, saline or buffer solution is added to the preparation to obtain a desired final batch volume.

57. A composition as claimed in Claim 56 (as dependent on Claim 55), wherein the addition of water, saline or buffer takes place after the pH adjusting step.

58. A composition as claimed in any one of Claims 54 to 57, wherein, in the process, at least one of the solutions/liquids is/are purged with nitrogen and/or argon.

59. A composition as claimed in any one of Claims 54 to 58, wherein, in the process, the aqueous solution of cetirizine is formed either by adding buffer to an aqueous solution of cetirizine or salt thereof, or adding cetirizine or salt thereof to an aqueous buffer solution, prior to the addition of lipid.

60. A composition as claimed in any one of Claims 54 to 59, wherein, in the process, if a mixture of polar lipids is used, it is pre-treated with organic solvent.

61. A composition as claimed in any one of Claims 54 to 60, wherein, in the process, the homogenisation step (b) comprises vigorous mechanical mixing, high speed homogenisation, shaking, vortexing and/or rolling.

62. A composition as claimed in any one of Claims 54 to 61, which comprises, in the process, an additional liposome size-reduction step.

63. A composition as claimed in Claim 62, wherein the size-reduction step comprises extrusion through a membrane filter.

64. A composition as claimed in any one of Claims 54 to 60, 62 or 63, wherein, in the process, the homogenisation step and/or size-reduction step comprises high-pressure homogenisation.

65. A composition as claimed in any one of Claims 1 to 42, or 54 to 64, for use in medicine.

66. A method for the treatment of rhinitis comprising the administration of a composition as claimed in any one of Claims 1 to 42, or 54 to 64, to a person suffering from or susceptible to that disorder.

67. The use of a composition as claimed in any one of Claims 1 to 42, or 54 to 64, for the manufacture of a medicament for the treatment of rhinitis, which treatment comprises administration of that composition to a person suffering from or susceptible to that disorder.

68. A method as claimed in Claim 66, or a use as claimed in Claim 67, wherein the administration is intranasal.

69. A method as claimed in Claim 66, or a use as claimed in Claim 67, wherein the administration is intraocular.

70. A method as claimed in Claim 66, or a use as claimed in Claim 67, wherein the administration is to the lung.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** USE OF LEVOCETIRIZINE FOR THE TREATMENT OF PERSISTENT ALLERGIC RHINITIS

(57) **Abstract:** The present invention relates to a pharmaceutical use of levocetirizine for the treatment of persistent allergic rhinitis.

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USE OF LEVOCETIRIZINE FOR THE TREATMENT OF PERSISTENT ALLERGIC RHINITIS

The present invention relates to the use of levocetirizine for the preparation of drugs effective for the treatment of the persistent allergic rhinitis.

International patent application 94/06429 describes a method utilising levocetirizine for the treatment of seasonal and perennial allergic rhinitis.

It has now surprisingly been found that levocetirizine possesses therapeutic properties which render it particularly useful in the treatment of persistent allergic rhinitis. These activities are not observed in the dextrocetirizine.

The purpose of the invention concerns the treatment of persistent allergic rhinitis.

The present invention is based on the unexpected recognition that administration of pharmaceutical compositions comprising levocetirizine, or a pharmaceutically acceptable salt thereof to a patient treats the persistent allergic rhinitis.

The present invention encompasses a method for treating persistent allergic rhinitis which comprises administering to a patient a therapeutically effective amount of levocetirizine or a pharmaceutically acceptable salt thereof.

The present invention also encompasses the use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for the treatment of persistent allergic rhinitis.

The present invention relates to the use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for decreasing the symptoms of persistent allergic rhinitis and improving the quality of life.

In another aspect, the present invention relates to a method of treating in a patient persistent allergic rhinitis by administering an effective dose of levocetirizine or a pharmaceutically acceptable salt thereof.

The term "cetirizine" refers to the racemate of [2-[4-[(4 chlorophenyl)phenylmethyl] -1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride salt which is well known as cetirizine dihydrochloride; its levorotatory and dextrorotatory enantiomers are known as levocetirizine and dextrocetirizine. Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent 0 058 146, Great Britain Patent 2.225.320, Great Britain Patent 2.225.321, United States Patent 5,478,941, European Patent application 0 601 028, European Patent Application 0 801 064 and International Patent Application WO 97/37982.

The term "levocetirizine" as used herein means the levorotatory enantiomer of cetirizine. More precisely, it means that the active substance comprises at least 90%

by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis. Each individual optical isomer may be obtained from its racemic mixture by using conventional means such as disclosed in British patent application No. 2,225,321. Additionally, each individual optical isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution, such as disclosed in U.S. Patents No. 4,800,162 and 5,057,427.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also its metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the aminoacid salts. The best results have been obtained with levocetirizine dihydrochloride.

By patient, we understand children, adolescents and adults.

By the term "allergic rhinitis", we understand a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membrane of the nose. Symptoms of allergic rhinitis include rhinorrhea, nasal obstruction, nasal itching, sneezing, ocular pruritis. The term "persistent allergic rhinitis", as used herein, refers to a disease when symptoms last more than 4 days per week and for more than 4 weeks. It is subdivided into mild and moderate-severe rhinitis. It is said "mild" when there are normal sleep, or no impairment of normal daily activities, sport, leisure, normal work and school, or no troublesome symptoms. It is said "moderate-severe" when there are abnormal sleep, or impairment of daily activities, sport, leisure, or problems caused at work or school, or troublesome symptoms.

A therapeutically effective amount of levocetirizine or a pharmaceutically acceptable salt thereof is used to treat or alleviate the effects of persistent allergic rhinitis. The dosage depends essentially on the specific method of administration and on the purpose of the treatment. The size of the individual doses and the administration program can best be determined based on an individual assessment of the relevant case. The methods required to determine the relevant factors are familiar to the expert.

A preferred daily dosage provides from about 0,0005 mg to about 2 mg of levocetirizine or a pharmaceutically acceptable salt thereof, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,001 to about 2 mg per kg of body weight per patient. The best results have been obtained with a daily dosage

from about 0,005 to 1 mg per kg of body weight per patient. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administrated over about a 24 hours time period to reach a total given dosage. Bests results have been obtained with an administration of a compositions of the invention are twice a day for children; and 5 mg once a day for adults. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled person in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

Pharmaceutical compositions used according to the present invention may be administered by any conventional means. The routes of administration include intradermal, transdermal, slow release administration, intramuscular, oral and intranasal routes. Any other convenient route of administration can be used, for example absorption through epithelial or mucocutaneous linings.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologicaly active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention include any conventional therapeutical inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycol and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical composition of the invention can also be formulated for topical application. The composition for topical application can be in the form of an aqueous solution, lotion or jelly, an oily solution or suspension or a fatty or emulsion ointment.

The pharmaceutical composition of the invention can also be used for slow prolonged release with a transdermal therapeutic system in polymer matrix or with an appropriate formulation for oral slow release.

The pharmaceutical compositions according to the present invention may also be administered orally or rectally. They may also be administered by nasal instillation, aerosols or in the form of unguents or creams. The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example, in the form of uncoated or coated tablets, pills, dragees, gelatine capsules, solutions, syrups and the like. For administration by the rectal route, the compositions containing the compounds of the present invention are generally used in the form of suppositories.

The pharmaceutical forms, such as tablets, drops, suppositories and the like, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a disintegration agent, a stabilizing agent and the like. If appropriate, it is also possible to add preservations, sweeteners, coloring agents and the like.

Preferably, the pharmaceutical compositions of the invention is administered in traditional form for oral administration, as film coated tablets, lozenges, dragees, and oral liquid preparation such as syrup.

Best results have been obtained with an oral dosage form, in particular liquid formulations such as syrup for children, and film-coated tablet for adults. For example, patients can receive 2 doses of 0,25 mg/kg (total daily dose : 0,50 mg/kg/day) of an oral solution of levocetirizine dihydrochloride 10 mg/ml per day; one ml of the solution contains 20 drops and one drop of levocetirizine dihydrochloride solution contains 0,5 mg.

As an Example of a composition according to the present invention, the following formulation of a film coated tablet is preferred: levocetirizine dihydrochloride, magnesium stearate, cellulose, lactose and silicon dioxide.

As an Example of a composition according to the present invention, the following formulation of a syrup is preferred: levocetirizine dihydrochloride, methyl- and propylparaben, saccharinum, and purified water.

Pharmaceutical compositions of the invention are useful to treat the persistent allergic rhinitis. These compositions can alleviate the effects of the persistent allergic rhinitis.

Another advantage of the invention is the ability of the process to improve quality of life and all symptoms of persistent allergic rhinitis.

The method of the invention is believed particularly suited to use in patients susceptible to suffer from persistent allergic rhinitis.

Another advantage of the invention is that levocetirizine dihydrochloride has an effect on rhinitis up to 6 months.

It is shown that levocetirizine dihydrochloride has an effect on quality of life up to 6 months.

It is shown that levocetirizine dihydrochloride has an effect on nasal congestion after 3 months. It lasts through 3 months.

The invention is further defined by reference to the following example.

Example

The aim of the study relative to the clinical effect of levocetirizine dihydrochloride was to establish on the intention to treat (ITT population) whether a 6 month levocetirizine dihydrochloride treatment can improve the quality of life and clinical symptoms from adult patients suffering from persistent allergic rhinitis, when compared to placebo. For clinical symptoms, it was considered that a 1 point score reduction is clinically relevant. For health-related quality of life, it was considered that a 0.36 point score reduction is relevant. Secondary parameters of efficacy included different durations of treatment, different symptoms, different quality of life questionnaires, the incidence of co-morbidities suspected to be linked to allergic rhinitis and pharmaco-economic variables. The safety of this long-term treatment with levocetirizine dihydrochloride has also been evaluated.

The target population of this example consisted of adults aged more than 18 years suffering from persistent allergic rhinitis [WHO Initiative on Allergic Rhinitis and its Impact on Asthma (ARIA), 2000, pages S147-S149]. To be enrolled, the subjects needed to have sufficient rhinitis symptoms during the selection period. Excluded were patients with ENT or eye infection during the 2-weeks preceding initial visit.

The study was a prospective, randomized, double blind, parallel group, and placebo-controlled study with levocetirizine dihydrochloride.

The severity of clinical symptoms was rated by the T5SS (sneezing, rhinorrhea, nasal pruritus, ocular pruritus and nasal congestion) evaluated each by a score from 0 to 3. The impact on health related quality of life was measured using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (E. JUNIPER and G.H. GUYATT, Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis, Clinical and Experimental Allergy 1991; 21:77-83; E. JUNIPER, Measuring Health Related Quality of Life in rhinitis, J. Allergy Clin. Immunol. 1997; 99:S742-9).

Study treatment lasted for 6 months. After the treatment period, patients entered a 1-week follow-up period.

The primary end-point for efficacy was a decrease of the T5SS over the first 4 weeks of at least 1 unit of score. The primary end-point for quality of life was a decrease of RQLQ after 4 weeks of at least 0.36 unit of the total score.

Secondary parameters of efficacy included the mean T5SS, the RQLQ and the SF-36 questionnaire at the different time points of the study, and the incidence and the duration of rescue medication over 6 months.

Exploratory parameters of efficacy included the mean of each individual rhinitis score, each RQLQ domain and each scale of the SF-36 questionnaire at the different time points of the study, the Global Evaluation Scale after 4 weeks and 6 months, the incidence of co-morbidities suspected to be linked to allergic rhinitis and the pharmaco-economic direct and indirect costs over 6 months.

At each of the eight visits, diary book entries (T5SS, RQLQ, SF-36, indirect cost pharmaco-economic parameters, concomitant medication, outpatient consultations and adverse events) were verified and transferred into the Clinical Record Form and direct cost pharmaco-economic parameters were recorded. Patients underwent a physical examination, including the measurement of vital signs. At the beginning and at the end of the study they also underwent a safety lab test, including pregnancy test for females, and at Visits 4 and 7, they filled-in a Global evaluation scale.

Adverse events were recorded by the patients on diary cards and discussed with the investigator at each visit. Serious adverse events had to be reported immediately.

Oral tablets of levocetirizine dihydrochloride (5 mg) and matching placebo, similar in appearance, shape and taste were used. The recommended study dosage was 1 tablet per day.

Sample size was based on 40% relative improvement over placebo in the RQLQ questionnaire, assuming an improvement from baseline for placebo of 0.9. For this questionnaire this corresponds to a difference of 0.36 vs. placebo.

The baseline characteristics of the two treatment groups, including demographic data, were comparable.

The study shows that treatment with levocetirizine dihydrochloride improves the symptoms of persistent allergic rhinitis (Difference of T5SS over the first 4 weeks: 1.14, $p < 0.001$; this difference being maintained over the whole study period) and the QOL (Change from baseline of the RQLQ Overall Score at first 4 weeks: 0.48, $p < 0.001$; this difference being maintained over the whole study period). A statistically significant improvement is also observed at all time points for sneezing, rhinorrhea, nasal pruritus and ocular pruritus. In addition, an improvement of nasal

obstruction is observed, which becomes statistically different from 3 months onwards (Difference vs. placebo: 0.15, p = 0.009). Moreover, the long-term administration of levocetirizine did not involve particular safety concerns.

This study provides evidence of activity of levocetirizine in persistent allergic rhinitis. Levocetirizine is shown to be active on nasal obstruction after a long term treatment (equal or more than 3 months).

Table I

Mean T5SS over the first four weeks of treatment

(ITT population)

Treatment	N	Baseline (SD) Mean	Mean (SD)	Adjusted mean[a] (SE)	Diff. vs. placebo[b] (95 % CI)	p-value[c]
Placebo	271	8.90 (2.26)	6.61 (2.47)	6.56 (0.15)		
Lctz 5 mg	276	9.02 (2.28)	5.53 (2.52)	5.43 (0.15)	1.14 [0.75, 1.52]	< 0.001

[a] Mean adjusted for baseline score and country.

[b] Placebo minus levocetirizine dihydrochloride (Lctz) 5mg.

[c] p-value was obtained from an ANCOVA with baseline score as covariate and country and treatment as factors.

In table I it is shown that treatment with levocetirizine dihydrochloride improves the symptoms of persistent allergic rhinitis.

Table II

Change from baseline of the RQLQ Overall Score after first 4 weeks of treatment

(ITT population)

		Baseline	Change			
Treatment	N	Mean (SD)	Mean (SD)	Adjusted Mean[a] (SE)	Diff. vs. placebo[b] (95 % CI)	p-value[c]
Placebo	252	3.06 (0.94)	-0.99 (1.25)	-1.01 (0.07)		
Lctz 5 mg	257	3.04 (0.92)	-1.50 (1.18)	-1.49 (0.07)	0.48 [0.29, 0.67]	< 0.001

[a] Mean adjusted for baseline score and country.

[b] Placebo minus levocetirizine dihydrochloride 5mg.

[c] p-value was obtained from an ANCOVA with baseline score as covariate and country and treatment as factors.

In table II it is shown that treatment with levocetirizine dihydrochloride improves the quality of life.

Table III

Nasal congestion symptoms evaluated over the 24 hours,

over the first week and first 4 weeks, 3, 4.5 and 6 months of treatment

(ITT population)

Period	Treatment	N	Baseline Mean	(SD)	Mean	(SD)	Adjusted Mean[a]	(SE)	Diff. vs. (95 % CI)[b]	p-value[c]
Week 1	Placebo	270	1.85	(0.71)	1.64	(0.77)	1.65	(0.04)		
	Lctz 5 mg	271	1.90	(0.69)	1.61	(0.83)	1.58	(0.04)	0.07 [-0.04; 0.18]	0.203
First 4 weeks	Placebo	271	1.85	(0.71)	1.49	(0.74)	1.48	(0.04)		
	Lctz 5 mg	276	1.91	(0.69)	1.44	(0.78)	1.40	(0.04)	0.08 [-0.02; 0.19]	0.123
3 months	Placebo	270	1.85	(0.71)	1.33	(0.74)	1.31	(0.04)		
	Lctz 5 mg	276	1.91	(0.69)	1.22	(0.78)	1.16	(0.04)	0.15 [0.04; 0.26]	0.009
4.5 months	Placebo	270	1.85	(0.71)	1.29	(0.74)	1.27	(0.04)		
	Lctz 5 mg	276	1.91	(0.69)	1.17	(0.77)	1.11	(0.04)	0.15 [0.04; 0.26]	0.007
6 months	Placebo	270	1.85	(0.71)	1.26	(0.74)	1.24	(0.04)		
	Lctz 5 mg	276	1.91	(0.69)	1.13	(0.76)	1.08	(0.04)	0.16 [0.05;0.27]	0.005

[a] On study Mean adjusted for baseline score and country.

[b] Placebo minus levocetirizine dihydrochloride.

[c] p-value was obtained from an ANCOVA with baseline score as covariate and country and treatment as factors.

In table III it is shown that levocetirizine dihydrochloride is shown to be active on nasal obstruction after a long term treatment.

The following abbreviations are used in the example:

T5SS	Total 5 Symptoms Score
ITT	Intention-to-Treat
N	Number
SD	Standard Deviation
SE	Standard Error of the Mean
Diff.	Difference
vs.	versus
CI	Confidence Interval
P	probability that the observed difference is only by chance
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
ANCOVA	Analysis of Covariance
ENT	Ear-Nose-Throat
SF-36	Medical Outcomes Survey Short Form 36
Lctz	levocetirizine dihydrochloride.

A long duration of effect is noted. The positivity of the trial is due to the lack of tachyphylaxis, i.e there's no "adjustement" of the dosing schedule needed during 6 months. The recommended dosage is effective constantly throughout the trial.

An improvement of quality of life (QoL) is clearly noted during the trial. It is central to ARIA. This is the first time that a drug is able to change the QoL of patients for such a long duration. This is as close as possible to a "disease modifying" effect.

Nasal congestion is treated during the trial. Interestingly, nasal congestion is a symptom relief that appear during the trial, i.e the effect is gradual, this is congruent with the observation that QoL is improving.

It is demonstrated that levocetirizine dihydrochloride is able to treat persistent rhinitis as long as it is administered, but also able to modify daily activities of patients, going beyond the simple symptom relief observed in short duration trials so far.

CLAIMS

1. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the persistent allergic rhinitis.
2. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for decreasing the symptoms of persistent allergic rhinitis and improving the quality of life.
3. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the rhinorrhea.
4. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the nasal obstruction.
5. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the nasal itching.
6. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the sneezing.
7. Use of levocetirizine or a pharmaceutically acceptable salt thereof for the preparation of a medicament intended for treating the ocular pruritis.
8. Use according to any one of claims 1 to claim 7, wherein the salt is the levocetirizine dihydrochloride.
9. Use according to any one of claims 1 to 8, wherein the medicament is adapted for administration of a daily dosage from about 0,0005 mg to about 2 mg of said levocetirizine or said pharmaceutically acceptable salt thereof, per kg of body weight per patient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05491

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495 A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

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

EPO-Internal, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2003	23/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Domingues, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05491

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(54) Title: A METHOD FOR PREVENTING URTICARIA

(57) Abstract: The present invention relates to the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

WO 02/47689 A2

1

A Method for Preventing Urticaria

The present invention relates to a method for preventing, or delaying the onset of urticaria attack with a compound selected from efletirizine, cetirizine, or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention relates to a method for preventing, or delaying the onset of primary urticaria with a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

Urticaria is an inflammatory disease characterized by erythematous, itchy edematous and whealing lesions of the skin or mucous membranes. Individual wheals may be as small as 1-2 mm in diameter, but they can reach several centimeters. Acute urticaria has been defined as episodes lasting for less than 12 weeks particularly 6-12 weeks, chronic urticaria has been defined as episodes lasting beyond 12 weeks.

Different types of urticaria are described such as, but not limited to, acute idiopathic, chronic idiopathic, IgE-mediated , pseudo-allergic, serum-sickness, contact, hereditary angioedema, acquired C1 inhibitor deficiency and physical as well as urticaria vasculitis.

The onset of urticaria attack can be defined as a new flare up of urticaria in a patient, who had already experienced urticaria. Rash or flare up means that an urticaria lesion is already present. The onset of primary urticaria can be defined as the first urticaria attack during a patient's life or an attack at a time when the patient did not otherwise show any presence of urticaria; in this latter case, no urticaria lesions are present at the time of onset.

The term "cetirizine" as used herein refers to 2-[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid.

The term "individual optical isomer of cetirizine" as used herein refers to the levorotatory and the dextrorotatary enantiomers of cetirizine. More precisely, it refers to the active substance comprising at least 90% by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. The dextrorotatory enantiomer of cetirizine is also known as levocetirizine and in the form of its dihydrochloride salt is levorotatory. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis.

Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent No. EP 0 058 146 B1, Great Britain Patents Nos. 2.225.320 and 2.225.321, United States

Patent No. 5,478,941, published European Patent Application Nos. EP 0 601 028 A1 and EP 0 801 064 A1 and published International Patent Application No. WO 97/37982.

The term "efletirizine" as used herein refers to 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid.

Two pseudopolymorphic crystalline forms of efletirizine dihydrochloride, namely anhydrous efletirizine dihydrochloride and efletirizine dihydrochloride monohydrate are described in the European patent No. 1 034 171.

Processes for preparing efletirizine or a pharmaceutically acceptable salt thereof have been described in European Patent 1 034 171, and in the international patent application WO 97/37982.

Unless otherwise mentioned, the invention concerns all forms of efletirizine and cetirizine and pharmaceutically acceptable salts thereof.

Antihistamines are also known for the symptomatic treatment of urticaria and other skin disorders in which histamine plays a role (J. Allergy Clin. Immunol., 1995, 95,759-64).

However, there remains a need for therapeutic methods and pharmaceutical compositions which prevent, or delay the onset of, urticaria attack and/or primary urticaria particularly in infants and/or young children, one of the major groups at risk of developing the disease, because of the relative immaturity of their immune systems and their physiological barriers to allergens.

A first purpose of the invention therefore concerns the primary prevention of primary urticaria.

A second purpose of the invention is the prevention of urticaria attacks in high risk patients, such as patients who have already suffered from urticaria attacks.

A third purpose of the invention is the prevention of primary urticaria in children and particularly in atopic children or children with a direct relative family history of atopy.

A fourth purpose of the invention is the prevention of urticaria attacks in children suffering from atopic dermatitis and/or with a direct relative family history of atopy.

A fifth purpose of the invention is the prevention of acute urticaria attacks.

The present invention is based on the unexpected finding that administration of efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these prevents urticaria attacks especially in infants.

The present invention therefore concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically

acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, primary urticaria in a patient, the said medicament being administered to the patient prophylactically prior to the onset of the urticaria .

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, acute urticaria in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the occurrence or re-occurrence of urticaria in a patient.

In addition the present invention concerns a method for preventing or delaying the onset of urticaria attack which comprises administering to a patient a therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention also concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, urticaria.

In accordance with the invention the selected compound is administered to the patient prior to the onset of the urticaria attack or the primary urticaria (e.g. before any biological or clinical symptoms of urticaria disease occur (primary prevention) or after biological signs of sensitization to an allergen but before the onset of symptoms of an urticaria attack (secondary prevention)).

The present invention also concerns the use of the selected compound for the preparation of a medicament intended for preventing the onset of primary urticaria in a patient, the said medicament being administered to the patient prophylactically after a resolved urticaria attack in order to prevent the re-occurrence of the disease .

It has been shown that the effect of cetirizine in urticaria is two-fold: firstly cetirizine prevents the occurrence of acute urticaria and secondly when acute urticaria occurs the patients, especially children, treated with cetirizine have fewer episodes of acute urticaria than non-treated patients.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also to metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the amino acid salts. Accordingly efletirizine and cetirizine may each be employed as the free acid or in the form of a pharmaceutically acceptable salt. The best results have been obtained with the dihydrochloride salt.

By patient, is to be understood adults, infants and children, in particular young children. Generally, the patients most benefiting from treatment in accordance with the invention are infants or children aged 1 week to 10 years, preferably aged 6 months to 5 years, and more preferably 10 months to 5 years. The best results have been obtained with patients aged 1 to 3.5 years.

Preferably patients treated in accordance with the invention are those not currently affected by urticaria disease and most preferably, those who have never been affected thereby.

A therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these is used to prevent, or delay onset of, an urticaria attack and/or primary urticaria. The dosage employed will depend essentially on the specific method of administration and on the purpose of the prophylaxis. The size of the individual doses and the administration program can best be determined based on an individual assessment of the relevant case. The methods required to determine the relevant factors are familiar to the expert.

A preferred daily dosage for use in accordance with the invention is from about 0,0005 mg to about 2 mg of the selected compound, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,005 to about 2 mg per kg of body weight per patient. The best results are obtained with a daily dosage from about 0,05 to 1 mg per kg of body weight per patient, preferably 0,5 mg. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administered over about a 24 hours time period to reach a total given dosage. Best results are obtained with administration twice a day in two equal doses per day or once a day in retarded release form. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled practitioner, in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

Pharmaceutical compositions used according to the present invention may be administered by any conventional means. The routes of administration include intradermal, transdermal, slow release administration, intramuscular, oral and intranasal routes, fast release, dry syrup. Any other convenient route or form of administration can be used, for example absorption through epithelial or mucocutaneous linings.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologically active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention may include any conventional therapeutically inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycol and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can also be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical composition of the invention can also be formulated for topical application. The composition for topical application can be in the form of an aqueous solution, lotion or jelly, an oily solution or suspension or a fatty or emulsion ointment.

The pharmaceutical composition of the invention can also be used for slow prolonged release with a transdermal therapeutic system in polymer matrix or with an appropriate formulation for oral slow release.

The pharmaceutical compositions according to the present invention may also be administered orally or rectally. They may also be administered by nasal instillation (aerosols) or in the form of unguents or creams. The pharmaceutical compositions

which can be used for oral administration may be solid or liquid, for example, in the form of uncoated or coated tablets, pills, dragees, gelatine capsules, solutions, syrups and the like. For administration by the rectal route, the compositions containing the compounds of the present invention are generally used in the form of suppositories.

The pharmaceutical forms, such as tablets, drops, suppositories and the like, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a disintegration agent, a stabilizing agent and the like. If appropriate, it is also possible to add preservatives, sweeteners, coloring agents and the like.

Preferably, the pharmaceutical composition of the invention is administered in traditional form for oral administration, such as film coated tablets, lozenges, dragees, and oral liquid preparation such as syrup.

Best results are obtained with an oral dosage form, in particular liquid formulations. For example, patients can receive 2 doses of 0,25 mg/kg (total daily dose : 0,50 mg/kg/day) of an oral solution of cetirizine 10 mg/ml per day; one ml of the solution contains 20 drops and one drop of cetirizine solution contains 0,5 mg.

As an example of a composition according to the present invention, the following formulation of a syrup (oral drops) is preferred: cetirizine dihydrochloride, methyl- and propylparaben, saccharinum, and purified water.

As an example of a composition according to the present invention, the following formulation of a film coated tablet is preferred: cetirizine dihydrochloride, magnesium stearate, cellulose, lactose and silicon dioxide.

Pharmaceutical compositions of the invention are useful prophylactically. These compositions can delay or prevent the onset of urticaria attack or delay or prevent the onset of urticaria itself.

The method of the invention is believed particularly suited for use in atopic patients. By atopic patient, is understood a patient predisposed to development of diseases associated with excessive IgE antibody formation.

Another advantage of the invention resides in the ability of the treatment to prevent the onset of urticaria disease, in particular in atopic children, and also in atopic children suffering from atopic dermatitis. Specifically the patients are atopic children suffering from atopic dermatitis and with a positive family history of atopy. For example, early treatment with cetirizine dihydrochloride (initiated between 1 and 2 years of age) decreased from 16 % in the placebo group to 6 % in the treated group the number of children suffering from atopic dermatitis and with a direct relative family history of atopy, who had experienced one or more urticaria episode. Another advantage of the invention resides in the ability of the treatment to prevent acute

urticaria and reduce the number of episodes per child subsequent to its urticaria initiation.

The pharmaceutical composition of the invention may be used to prevent the onset of primary urticaria in patients considered to be at high risk of developing the disease.

The invention is further defined by reference to the following example.

Example

Study on the effect of long-term treatment with the H_1-receptor antagonist cetirizine in the prevention of urticaria in young children with atopic dermatitis.

The study had a prospective, double-blind, parallel-group, placebo-controlled design, 817 children with atopic dermatitis but no asthma or other systemic disorder, who were 12-24 months old at study entry and had at least one allergic parent or sibling, were randomized. The cetirizine dose of 0.25 mg/kg twice daily, or placebo solution similar in appearance, was administered as drops with breakfast and with the evening meal every day for 18 months. After treatment with cetirizine or placebo was discontinued, the study continued in a double-blind manner for an additional 6 months.

Throughout the study, the child's primary caregiver recorded all symptoms, events and medications administered on a diary card, weekly when the child was well, and daily when the child was having symptoms. At 9 regularly scheduled visits : before treatment with cetirizine or placebo, at 1, 3, 6, 9, 12, 15, and 18 months during treatment, and at 24 months (6 months after discontinuation of the study treatment), the information recorded in the diary cards was reviewed and validated with the investigator and entered on the case record form. Before data analysis, the description of the symptom or event was transcribed verbatim from the case record forms and classified according to World Health Organization terminology. Symptoms or events with different WHO preferred terms or different dates of onset were counted as different events. A symptom or event was counted as urticaria when hives, or areas of skin swelling, redness and itching distinct from the child's atopic dermatitis, were reported. The urticaria was considered to be associated with infection if sore throat, pharyngitis, tonsillitis, "cold", upper respiratory tract infection, ear infection, vomiting, diarrhea, gastroenteritis, fever, "flu", or "virus" were reported concurrently with the hives, or within the time frame of 7 days before, or 7 days after the hives appeared.

The Frequency of children with urticaria was compared in the two treatment groups using the Fisher exact test. Use of medications in addition to study medication was compared in the two treatment groups using the x^2 test.

During the 18-month treatment phase, only 23 of the 399 children treated with cetirizine (5.8 %), had one or more urticarial episodes, in contrast to 64 of the 396

children (16.2 %) treated with placebo ($p<0.001$). Also, the children treated with cetirizine had fewer episodes of urticaria per child. During the 6-month follow-up phase, there was no difference with regard to the number of episodes of urticaria in the children previously treated with cetirizine and those previously treated with placebo.

During the 18-month treatment phase with cetirizine or placebo, the child's personal physician, while not encouraged to prescribe additional H_1 receptor antagonists, was allowed to do so if necessary. Fewer children treated with cetirizine (138 of 399, 34.6 %) received additional oral prescription or non-prescription H_1-antagonists in comparison to those treated with placebo (164 of 396, 41.4 %, p= 0.047).

In this study, a relatively high cetirizine dose, approximately twice that recommended world wide for use in children age 2-6 years, was administered. Despite this, cetirizine was free from adverse effects, including central nervous system and cardiovascular system effects. The rationale for twice-daily dosing was that in very young children, cetirizine has a shorter terminal elimination half life and a shorter duration of action as assessed by suppression of the histamine-induced wheal and flare in the skin than it does in older children and adults.

CLAIMS

1. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.
2. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, primary urticaria in a patient.
3. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, acute urticaria in a patient.
4. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the occurrence or re-occurrence of urticaria in a patient.
5. Use according to claim 1, 2, 3 or 4, wherein the selected compound is the cetirizine dihydrochloride.
6. Use according to claim 1, 2, 3, 4 or 5, wherein the patient is an infant or a child.
7. Use according to claim 6, wherein the patient is aged 1 to 3,5 years.
8. Use according to any one of claims 1 to 7, which comprises administering a daily dosage from about 0,0005 mg to about 2 mg of cetirizine or individual optical isomer of cetirizine or pharmaceutically acceptable salt of these, per kg of body weight per patient.
9. Use according to any one of claims 1 to 8, wherein the patient is an atopic patient.
10. Use according to claim 9, wherein the patient suffers from atopic dermatitis or has a direct family history of atopy.

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EXAMINER	
THOMAS, TIMOTHY P	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12-15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12 and 17* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 11/19/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's comments with respect to the Oath/Declaration are noted along with the inventor's signature next to the corrections. The objection to the Oath/Declaration is withdrawn.

3. Applicant's arguments with respect to the rejection of claims 1-2, 5, 12 and 17 under 35 USC 103 have been considered but are moot in view of the new ground(s) of rejection.

Claim Objections

4. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The use of the genus term p-hydroxybenzoate esters in a dependent claim, dependent on the independent claim that is limited to a combination of two species within the genus term broadens the subject matter with respect to the paraben compounds of claim 5.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-2, 5, 12, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is necessitated by the claim amendment

The use of the genus term p-hydroxybenzoate esters in claim 5, dependent on the claim 1 that is limited to a combination of two species within the genus does not make clear whether the genus term is an attempt to broaden the subject matter with respect to the paraben compounds of claim 1 or is a shorthand notation referring to the combination of the two paraben compound species recited in claim 1; therefore it is not clear what the scope of the instant claims is with respect to which paraben compounds are required.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-2, 5, 12, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; IDS 12/18/2008 reference); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578).

This rejection is based on a reference file in the 12/18/2008 IDS.

DeLongueville teaches the use of an individual optical isomer of cetirizine for preparing a medicament (abstract); such optical isomers include levocetirizine, which contains preferably at least 95% by weight of the levocetirizine (p. 1, lines 29, 32-33); pharmaceutical compositions as liquid compositions in the form of a sterile solution miscible with water (p. 5, lines 12-13); carriers and diluents include water (p. 5, lines 21-22); preserving substances are taught (p. 5, line 15); topical application in the form of an aqueous solution (p. 5, line 30-31); solutions for oral administration (p. 6, lines 1-2); drops in the form of a liquid, with added preservatives (p. 6, lines 5, 7, 9); a syrup for oral formulation is preferred that contains methyl- and propylparaben (methyl parahydroxybenzoate and propyl parahydroxybenzoate) and purified water (p. 6, lines 18-20). DeLongueville does not a specific embodiment containing levocetirizine and the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate (although each of these components is taught); or a total amount of methylparaben and propylparaben or their ratio present in the liquid composition.

Doron teaches the antibacterial effects of methyl and propyl paraben against Streptococcus sobrium, which is involved in tooth dacay in the oral cavity, and that antibacterial synergistic effect was found between several combinations of parabens (abstract); at 0.03% (about 0.3 mg/mL) propyl paraben (PP), with increasing amounts of methyl paraben, decreasing amounts of viable bacterial counts were demonstrated (p. 577, Figures 1-2), the ratios vary from 0.015:0.03 (1:2) MP:PP to 0.25:0.3 (8.33:1), or almost 9/1. At the highest ratio in both figures no bacterial counts were recorded

(Figures 1-2; pp. 576-575, bridging paragraph). Additionally, MP had the largest antibacterial effect of the parabens tested (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select levocetirizine with methyl paraben and propyl paraben as preservatives for an aqueous oral formulation and to utilize a large excess of methyl paraben to propyl paraben, and to optimize the ratio and amounts while utilizing the minimum amount that gives satisfactory preservative effect, which would have given the compositions of the claims. The motivation to select levocetirizine would have been the recognized suitability of this compound for conditions responsive to cetirizine; the motivation to utilize and optimize the ratio and amounts would have been the routine optimization of conditions, recognizing synergistic effect is observed and minimizing the required amounts so as to minimize potential side effects of these components.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12/18/2008 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 10/599,451	Applicant(s)/Patent Under Reexamination FANARA ET AL.	
	Examiner TIMOTHY P. THOMAS	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Doron et al.; “Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus”; 2001 International Journal of Antimicrobial Agents; 18: 575-578
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN	9/18/2008	
PubChem	9/18/2008	
PubMed	9/18/2008	
WEST	9/18/2008	
IDS references	9/18/2008	
PALM Inventor Name Search	9/18/2008	
STN	2/20/2009	
EAST	2/20/2009	
PubMed	2/20/2009	
IDS references	2/20/2009	

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/TIMOTHY P THOMAS/ Examiner.Art Unit 1614	

PTO/SB/08a (05-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5419898	A	1995-05-30	Ikejiri	
	2	6258814	A	2001-07-10	Martin	
	3	5368852	A	1994-11-29	Umemoto et al.	
	4	6436924	A	2002-08-20	Poppe et al.	
	5	7198800	A	2007-04-03	Ko	
	6	7157464	A	2007-01-02	Pennell et al.	
	7	7094429	A	2006-08-22	Kiel et al.	
	8	4525358	A	1985-06-25	Baltes et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	9	4728509	A	1988-03-01	Shimizu et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2005/107711	WO	A2	2005-11-17	Biolipox AB		☐
	2	2004/050094	WO	A1	2004-06-17	UCB, S.A.		☐
	3	2002/047689	WO	A2	2002-06-20	UCB, S.A.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

If you wish to add additional non-patent literature document citation information please click the Add button			
EXAMINER SIGNATURE			
Examiner Signature	/Timothy Thomas/	Date Considered	02/20/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

- Search History will be lost after eight hours of inactivity.
- Search numbers may not be continuous; all searches are represented.
- To save search indefinitely, click query # and select Save in My NCBI.
- To combine searches use #search, e.g., #2 AND #3 or click query # for mor options.

Search	Most Recent Queries	Time	Result
#5	Search (methyl paraben) (propyl paraben)	16:43:29	118

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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S2	1	"20020169140"	US-PGPUB; USPAT	OR	ON	2009/02/20 11:47
S3	1	S2 and (cervical dysplasia) and artemisinin	US-PGPUB; USPAT	OR	ON	2009/02/20 11:48
S4	2	2004/0058896	US-PGPUB; USPAT	OR	ON	2009/02/20 15:38
S5	3	"20040058896"	US-PGPUB; USPAT	OR	ON	2009/02/20 15:38
S7	9	US-5419898-$.DID. OR US-6258814-$.DID. OR US-5368852-$.DID. OR US-6436924-$.DID. OR US-7198800-$.DID. OR US-7157464-$.DID. OR US-7094429-$.DID. OR US-4525358-$.DID. OR US-4728509-$.DID.	US-PGPUB; USPAT	OR	ON	2009/02/20 17:32

2/20/2009 6:48:14 PM
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L2              1 S E3
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L3              1 S E3

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L6           4247 S L3
L7              5 S L4 AND L5 AND L6
L8              0 S L7 AND PD<20040714

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                SEL L2 1-
                SEL L3 1-

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     15:48:19 ON 20 FEB 2009
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L16          7700 S L14 OR L15
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L19          5965 S L17-L18
L20          1322 S L3
L21          3715 S E45-E76
L22          3715 S L20-L21
L23             9 S L16 AND L19 AND L22
L24             2 S L23 AND PD<20040714
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE FINAL OFFICE ACTION MAILED FEBRUARY 25, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the final Office Action mailed February 25, 2009. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on April 24, 2009.

Date: April 24, 2009

/Michael S. Greenfield/
Michael S. Greenfield

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) at least one preservative, wherein the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than ~~1.5~~1 mg/ml of the composition.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Currently amended) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 and ~~1.5~~1 mg/ml of the composition.

6. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of thimerosal in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of chlorhexidine acetate in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzylalcohol in the range of 0.0001 and 10 mg/ml of the composition.

9. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzalkonium chloride in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the active substance is cetirizine.

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously Presented) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn-currently amended) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than ~~1.5~~ 1 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

REMARKS

Claims, claim objection, and rejection of claims 1-2, 5, 12, and 17 under 35 USC § 112, second paragraph

Claims 1 and 5 were amended to recited an upper limit on the amount of p-hydroxybenzoate esters of 1 mg/ml. Support for these amendments is found on p. 4, ll. 25-30, of the application.

The claims were objected to and rejected as indefinite for the recitation of "p-hydroxybenzoate esters" in claim 5, the Office alleging that the recitation of this term in dependent claim 5 was seen as broadening the scope of the claim beyond that of independent claim 1 from which claim 5 depends. While the applicants respectfully traverse, in order to clarify claim 5 and expedite prosecution, claim 5 has been amended by inserting the definite article "the" before the recitation of "p-hydroxybenzoate esters." This amendment clarifies that the "p-hydroxybenzoate esters" referred to in claim 5 are the methyl parahydroxybenzoate and propyl parahydroxybenzoate recited in claim 1. It is respectfully submitted that this amendment merely clarifies claim 5 and does not narrow its scope.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of claims 1-2, five, 12, and 17 under 35 USC 103

Claims 1-2, 5, 12, and 17 were rejected as obvious over DeLongueville et al. (WO 02/47689 A2) and Doron et al. The Office relied on DeLongueville for its teaching of cetirizine or an optical isomer (levocetirizine being identified as an optical isomer of cetirizine), liquid pharmaceutical compositions containing them, and a syrup containing cetirizine and methyl- and propylparaben. The Office notes that DeLongueville does not specifically teach an embodiment comprising levocetirizine and a mixture of methyl- and propylparaben nor the total amount of parabens or their ratios. The office relies on Doron for its teachings of the antibacterial effects of methylparaben (MP) and propylparaben (PP) with concentration ratios of [MP]:[PP] up to 8.33:1 and the synergistic antibacterial effects of combinations of parabens. For the following reasons, the applicants respectfully traverse.

The presently amended claims recite liquid levocetirizine compositions comprising [MP]:[PP] = 9:1 with a total urban concentration of [MP] + [PP] < 1 mg/ml. The lowest total

concentration of the combination of MP and PP taught by Doron to be completely antibacterial is 1.55 mg/ml. The applicants respectfully submit that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/ml. This is because those of ordinary skill in the art understand that for pharmaceutical compositions there can be zero tolerance for bacterial growth. There must be 100% certainty that each and every dosage form will be completely bacteria-free. But, following the teachings of Doron, one of ordinary skill in the art would avoid using smaller concentrations (i.e., below 1.5 mg/ml) because they would believe or reasonably expect that concentrations such as those recited in the present claims would render a composition susceptible to bacterial growth. While, as the Office noted, Doron teaches that combinations of parabens have a synergistic effect on planktonic bacteria, in the very same sentence Doron states, "although a complete antibacterial effect is not always achieved." The significance of this statement cannot be over-emphasized because to be safe, useful, and achieve regulatory approval, a complete antibacterial effect must be achieved. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). And acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product.

Doron reports that solutions with [MP] + [PP] < 1.55 mg/ml (all of which, by the way, have a [MP]:[PP] $\leq$ 2) show planktonic bacterial growth. While the same combinations of parabens have complete antibacterial effect at 0.9 mg/ml on immobilized bacteria, Doron expressly states that there is a stronger antibacterial effect on immobilized bacteria compared to planktonic bacteria. So, one of ordinary skill in the art would understand from Doron that higher concentrations of parabens are required for liquid compositions.

In summary, the applicants respectfully submit that one of ordinary skill in the art could not have predicted or had a reasonable expectation that a liquid levocetirizine-containing solution would be completely antibacterial with concentrations of the combination of methyl- and propylparabens of less than 1 mg/ml because,

1. The lowest completely antibacterial concentration of the combination of MP + PP disclosed by Doron is > 1.5 mg/ml, the lower concentrations tested being reported to have bacterial growth;
2. Doron teaches that a complete antibacterial effect of a combination of parabens is not always achieved; and
3. Doron teaches that antibacterial efficacy of parabens is weaker against planktonic bacteria compared to immobilized bacteria.

It is therefore unexpected and nonobvious that compositions according to the claims would have such antibacterial efficacy. The unexpected efficacy of the claimed compositions is manifested in Tables 15-20 of Example 4 of the present application, which show that levocetirizine compositions according to claim 1 with total paraben concentrations ([MP] + [PP]) of from 0.375 mg/ml up to 1.125 mg/ml (and [MP]:[PP] = 9) are free of *Pseudomonas aeruginosa*, *E. coli,* and *Staphylococcus aureus* bacteria 14 and 28 days following inoculation with these bacteria, respectively.[1]

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: April 24, 2009

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

[1] *Candida albicans* and *Aspergillus niger* are fungi.

Electronic Acknowledgement Receipt

EFS ID:	5213830
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	24-APR-2009
Filing Date:	18-JUL-2007
Time Stamp:	13:18:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	118023 c8f02b6c1d682d29a067c5b92b6ba60c1f77dc48	no	1

Warnings:	
Information:	

2		06-796_Response.pdf	145733 b910a96ea50fee94baab4dfccf231577d596a5e7	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment After Final	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	7

Warnings:	
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Total Files Size (in bytes):	263756

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment/Reply
  - ☒ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

No fees are believed due. However, please charge any underpayments and credit any overpayments to Deposit Account No. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	April 24, 2009	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	April 24, 2009

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	300

APPLICATION AS AMENDED – PART II

AMENDMENT	04/24/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 05/11/2009

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
05/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/599,451	**Applicant(s)** FANARA ET AL.	
	Examiner TIMOTHY P. THOMAS	**Art Unit** 1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 April 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *5*.
   Claim(s) rejected: *1,2,5,12 and 17*.
   Claim(s) withdrawn from consideration: *6-10,14,15 and 18-26*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

/Timothy P Thomas/
Examiner, Art Unit 1614

Continuation of 3. NOTE: the limitation of the amount of levocetirizine to less than 1 mg/mL is a new issue that requires further consideration and search.

Continuation of 11. does NOT place the application in condition for allowance because: The rejections and objections of record are maintained for the reasons of record.

Applicants argue a series of arguments based on the claim amendment, which are not relevant, since the claim amendment has not been entered.

With respect to the rejection under 35 USC 103, applicant argues that the lowest completely antibacterial concentration of the combination MP+PP disclosed by Doron is >1.5 mg/mL, the lower concentrations tested being reported to have bacterial growth; that Doron teaches that a complete antibacterial effect of a combination of parabens is not always achieved and antivacterial efficacy of parabens is weaker against planktonic bacteria compared to immobilized bacteria; therefore it is unexpected and nonobvious that compositions according to the claims would have such antibacterial efficacy; unexpected efficacy is disclosed in Tables 15-20 of Example 4 of the present application, which have total paraben concentrations from 0.375 to 1.125 mg/mL and [MP]:[PP] = 9 are free of three bacteria types at 14 and 28 days following inoculation with these bacteria. The unexpected data is noted. However, the unexpected concentrations are not commensurate in scope with the claimed amounts, which range from greater than 0 to less than 1.5 mg/mL, in the independent claim, and only slightly narrowed in claim 5. Therefore the rejection is maintained for embodiments outside of the range for which unexpected results have been demonstrated.

DO NOT ENTER: /TPT/
05/08/2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE FINAL OFFICE ACTION MAILED FEBRUARY 25, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the final Office Action mailed February 25, 2009. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on April 24, 2009.

Date: April 24, 2009

/Michael S. Greenfield/
Michael S. Greenfield

PTO/SB/30 (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995. no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Fanara, Domenico
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

This is a Request for Continued Examination (RCE) under 37 CFR 1 .114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☒ Other After-Final Response filed April 24, 2009.

   b. ☒ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☒ Information Disclosure Statement (IDS)

      iv. ☒ Other Copies of two (2) NPL references.

2. Miscellaneous

   Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a

   a. ☐ period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   The Director is hereby authorized to charge the following fees any underpayment of fees or credit any overpayments to

   a. ☒ Deposit Account No. 13-2490 .

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Michael S. Greenfield/	Date	May 22, 2009
Name (Print/Type)	Michael S. Greenfield	Registration No.	37,942

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature	/Michael S. Greenfield/		
Name (Print/Type)	Michael S. Greenfield	Date	May 22, 2009

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/08a (05-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	1	Handbook of Pharmaceutical Manufacturing Formulations, Par Sarfaraz Niazi, CRC Press, 2004 (5 pages).	☐
	2	Formulation in Pharmacy Practices, 2nd edition, 2001 (2 pages).	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Michael S. Greenfield/	Date (YYYY-MM-DD)	2009-05-22
Name/Print	Michael S. Greenfield	Registration Number	37142

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	18-Jul-2007
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Michael S. Greenfield
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	5377875
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	22-MAY-2009
Filing Date:	18-JUL-2007
Time Stamp:	21:06:03
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	5091
Deposit Account	132490
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal_Letter.pdf	103604 48c944741364b4d761e20f4e813f67a88e0a6096	no	1
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	06-796_RCE.pdf	107956 016caff51eebe9f8480cbddeeada39058e5d40d7	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
3		06-796_IDS.pdf	910730 5991b716086ff0ad8663fd1cbc1b2f1026e1a969	yes	4

Multipart Description/PDF files in .zip description

Document Description	Start	End
Information Disclosure Statement (IDS) Filed (SB/08)	1	2
Transmittal Letter	3	4

Warnings:					
Information:					
4	NPL Documents	06-796_NPL_Reference1.pdf	384981 bd137950b20f5999a390d80df7ec877a9742bdcb	no	5
Warnings:					
Information:					
5	NPL Documents	06-796_NPL_Reference2.pdf	125497 674860e1396cc23f7f49b03c6cdef0150458a498	no	2
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	30239 f2f3a82de7ab46043ba039fe8de8f4e1cbd2312c	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	1663007

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Fanara, Domenico
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):
  Request for Continued Examination (RCE) and copies of two (2) cited NPL references.

Remarks

Please charge the RCE fee and any underpayments to deposit account no. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	May 22, 2009	Reg. No.	37,942

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	May 22, 2009

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/22/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DESHONNE T. MARTINO/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

Entered by RCE on 5-22-09 DS Home 5-27-09

In the Application of:	
Fanara et al.	
Serial No. 10/599,451	Examiner: Timothy P. Thomas
Filing Date: September 28, 2006	Art Unit: 1614
For: Pharmaceutical Composition of Piperazine Derivatives	Confirmation No.: 9142

RESPONSE TO THE FINAL OFFICE ACTION MAILED FEBRUARY 25, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the final Office Action mailed February 25, 2009. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on April 24, 2009.

Date: April 24, 2009

/Michael S. Greenfield/
Michael S. Greenfield

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 07/30/2009

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12,14,15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/2009 has been entered.

Response to Arguments

2. Applicants' arguments, filed 4/29/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments, see p. 5, filed 4/24/2009, with respect to the objection to claim 5 have been fully considered and are persuasive. The objection of claim 5 has been withdrawn.

4. Applicant's arguments, see p. 5, filed 4/24/2009, with respect to the rejection of claims 1-2, 5, 12, and 17 under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. The rejection of claims 1-2, 5, 12, and 17 has been withdrawn.

The claim amendment, when taken with applicant's statement that the "the p-hydroxybenzoate esters" in claim 5 are the methyl parahydroxybenzoate and propyl

parahydroxybenzoate recited in claim 1, is sufficient to demonstrate claim 5 further limits claim 1, and to clarify the subject matter of claims 1, 5 and those that depend on these claims with respect to the required p-hydroxybenzoate ester compounds present.

5. Applicant's arguments, see pp. 5-7, filed 4/24/2009, with respect to the rejection(s) of claim(s) 1-2, 5, 12, and 17 under 35 USC 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as follows.

Applicant's argument that the teaching of Doron taken with DeLongueville does not indicate that the combination of MP and PP would be "completely" antibacterial at total paraben concentrations less than 1 mg/mL is persuasive; when taken with the data disclosed in the instant specification, which demonstrate results that are not expected, the claimed amount of [MP]+[PP] below 1 mg/mL is nonobvious over the combination of references. Doron does not teach an amount below 1.3 mg/ml as having <1% bacteria present, and interpolation of the data does not suggest antibacterial activity for amounts of parabens below below about 1 mg/mL (for the conditions tested); the paraben levels of the instantly claimed amounts have antimicrobial activity disclosed in the instant specification.

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1-2, 5, 12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; IDS 12/18/2008 reference);

Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261); in view of Routledge et al. ("Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19).

DeLongueville teaches the use of an individual optical isomer of cetirizine for preparing a medicament (abstract); such optical isomers include levocetirizine, which contains preferably at least 95% by weight of the levocetirizine (p. 1, lines 29, 32-33); pharmaceutical compositions as liquid compositions in the form of a sterile solution miscible with water (p. 5, lines 12-13); carriers and diluents include water (p. 5, lines 21-22); preserving substances are taught (p. 5, line 15); topical application in the form of an aqueous solution (p. 5, line 30-31); solutions for oral administration (p. 6, lines 1-2); drops in the form of a liquid, with added preservatives (p. 6, lines 5, 7, 9); a syrup for oral formulation is preferred that contains methyl- and propylparaben (methyl parahydroxybenzoate and propyl parahydroxybenzoate) and purified water (p. 6, lines 18-20). DeLongueville does not a specific embodiment containing levocetirizine and the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate (although each of these components is taught); or the total amount of methylparaben and propylparaben or their ratio present in the liquid composition.

Gilliland 1 teaches the effect of temperature on the kill rate of *Escherichia coli* by methyl and propyl parabens was studied (abstract); in the presence of a bactericidal antimicrobial agent the rate of kill of microbes generally increases as the temperature increases (p. 252, 1st paragraph); a comparison of *E. coli* growth is presented in a chemically defined growth medium, which shows positive growth vs. growth in water as the medium, which shows nearly constant levels of *E. coli*, i.e., little or no growth (p. 254, Figure 2); the effect of temperature on the kill rates and rate constants for inocula prepared from exponential and stationary phase E. coli in the presence of 0.12% w/v methyl paraben and 0.012% w/v propyl paraben in the chemical growth medium (a 10/1 ratio, with total [MP]+[PP]=1.32%; p. 254, Table 1; p. 255, Figures 3, 5); the kill rates are reported for both exponential phase and stationary phase cells (p. 254, Table 1, pp. 255, Figures 3-6); reported activation energies for the effect of a series of antimicrobial agents, including phenol, benzyl alcohol and benzalkonium chloride have been reported from 5 different micro-organisms (p. 256, Table 2).

Gilliland 2 teaches antimicrobial effects of methyl and propyl parabens are investigated to determine whether the parabens act synergistically, that combinations of methyl or propyl parabens, at concentrations which slow down or inhibit bacterial growth when used singly produced definite kill, the parabens are therefore synergistic since in combination they produce an effect which is not observed when they are used singly, the effect is not considered true synergism as shown by kinetic results of experiments with a factorial design, which indicated no significant interaction between the two parabens (abstract); combinations of antimicrobial agents are widely used both for

treating diseases and for preserving pharmaceutical systems, the rationale is that by using combinations the activity spectrum may be broadened and the agents involved may act synergistically, although it is difficult to provide clinical evidence for synergy with in vitro systems (p. 258, 1st paragraph); studies utilized a chemically defined medium, to which methyl and propyl esters of p-hydroxybenzoic acid were added (p. 258, 2nd and last paragraphs); control studies employed 0.012 and 0.014 % w/v propyl paraben, for which growth was observed (p. 259, Table 1; p. 261, Figure 4); at 0.12 and 0.14% w/v methyl paraben the number of E.coli cells remained approximately constant, a bacteriostatic effect (p. 260, Figure 3, 2nd paragraph); combinations of 0.12 or 0.14% w/v methyl paraben with 0.012 or 0.014% w/v propyl paraben all resulted in observable kill of *E. coli*, a bactericidal effect of the paraben combination (p. 259, Table 1; p. 260, 2nd & 3rd paragraphs; p. 261, Figure 5). It is noted that the 4 combinations have a MP/PP ratio of 8.6/1 for 0.12% MP + 0.014% PP; a ratio of 10/1 for 0.12% MP + 0.012% PP or 0.14% MP + 0.014% PP; and a ratio of 11.7/1 for 0.14% MP + 0.012% PP. These ratios bracket the claimed ratio of 9/1, rendering the ratio as an obvious variant of the taught ratios.

Routledge teaches that a range of parabens, including methyl- and butylparaben, are weakly estrogenic, the suggestion is made that the safety in use of these chemicals should be reassessed, with particular attention being made to the estimation of the actual levels of systemic exposure of humans exposed to these chemicals, in order to assess the risk of exposure to parabens (abstract); certain synthetic compounds used in a wide range of products can mimic the main natural estrogen, influencing the

expression of estrogen-dependent genes, taken with epidemiological data suggests a progressive decline in human male reproductive health and fertility (p. 12, 1st paragraph); a group of parabens, used extensively in a wide range of products have been studied (p. 12, 2nd paragraph); binding to estrogen receptors is demonstrated for butyl paraben (p. 13, Figure 2); the response of the yeast estrogen screen to propyl and methyl paraben demonstrates that a shifting of about 100-fold higher concentrations of methyl paraben is required as compared to propylparaben in the assay (p. 15, Figure 3); butyl paraben was shown to increase the weight of the uterus in immature rats (p. 15, 3rd paragraph); a discussion of the toxicology of parabens has led to p-hydroxybenzoates being widely permitted in foods in the UK and US at levels of up to 0.1% w/w for MP and PP in food (corresponding to about 1 mg/mL; p. 16, right, 3rd paragraph); maximum levels of parabens in pharmaceutical products seldom exceed 1% w/w, EEC and Danish cosmetic regulations permit the preservation of cosmetic products with MP and PP up to a maximum combined concentration of 0.8% w/w (8m/mL; p. 16, right, 3rd paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the levocetirizine formulations, including oral liquid formulations and eye drops, as taught by DeLongueville with a synergistic ratio of methylparaben and propylparaben; it would have been obvious to utilize the range of ratios taught by Gilliland 2, including the claimed ratio of 9/1, which is within the prior art scope taught; it would also have been obvious to reduce the total amount of MP+PP from the total amounts taught by Gilliland 1 and 2 to a value less than 1%, meeting the claimed total

mixture of paraben amounts, while still giving bacteriocidal preservative effect; accomplished by: 1) reducing defined components in the medium that contribute to microbial growth, such as the growth medium identified by Gilliland 1; and/or 2) including a third preservative agent, such as one of the addition agents taught by Gilliland 1 in Table 2, in combination with the 9/1 ratio of MP/PP; both of these approaches would have resulted in the liquid pharmaceutical compositions within the scope of the instant claims, with the antimicrobial properties demonstrated by applicant. The motivation to utilize MP/PP ratio of 9/1 would have been the clear indication of Gilliland that ratios encompassing this are synergistic in terms of bacterial killing; additionally, utilization of a higher MP/PP ratio, such a 9/1 would employ a significantly smaller amount of PP that binds to estrogen receptors with higher affinity; the motivation to reduce the total [MP]+[PP] to a value less than 1 mg/ml would have been the recognition of Routledge that parabens mimic natural estrogen, and the levels approved in foods of up to 1 mg/mL would be a target concentration to stay below, while still retaining microbicidal activity; the motivation to combine a 9/1 ratio of MP/PP with an additional antimicrobial agent would have been the expectation of additive or even synergistic microbe killing, as well as the potential for a broader spectrum of microbes that are killed by the combination of preservatives.

As pointed out in MPEP 2144.06 (I), “It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…. [T]he idea

of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/

Examiner, Art Unit 1614

Notice of References Cited	Application/Control No. 10/599,451	Applicant(s)/Patent Under Reexamination FANARA ET AL.	
	Examiner TIMOTHY P. THOMAS	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	F	US-			
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	I	US-			
	J	US-			
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FOREIGN PATENT DOCUMENTS

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	N					
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	Q					
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	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Gilliland et al.; "The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257
	V	Gilliland et al. "Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261
	W	Routledge et al.; "Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
STN	9/18/2008	
PubChem	9/18/2008	
PubMed	9/18/2008	
WEST	9/18/2008	
IDS references	9/18/2008	
PALM Inventor Name Search	9/18/2008	
STN	2/20/2009	
EAST	2/20/2009	
PubMed	2/20/2009	
IDS references	2/20/2009	
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PubMed	7/29/2009	
IDS references	7/27/2009	

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

/TIMOTHY P THOMAS/ Examiner.Art Unit 1614	

EAST Search History

EAST Search History (Prior Art)

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EAST Search History

EAST Search History (Prior Art)

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PTO/SB/08a (05-07)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2006-09-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10599451
	Filing Date	2006-09-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	1	Handbook of Pharmaceutical Manufacturing Formulations, Par Sarfaraz Niazi, CRC Press, 2004 (5 pages).	☐
	2	Formulation in Pharmacy Practices, 2nd edition, 2001 (2 pages).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Timothy Thomas/	Date Considered	/Timothy Thomas/

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE NON-FINAL OFFICE ACTION MAILED JULY 30, 2009

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the non-final Office Action mailed July 30, 2009. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on October 23, 2009.

Date: October 23, 2009 /Michael S. Greenfield/
Michael S. Greenfield

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) at least one preservative, wherein the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than ~~1 mg/ml~~ 1.125 mg/ml of the composition.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 and 1 mg/ml of the composition.

6. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of thimerosal in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of chlorhexidine acetate in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzylalcohol in the range of 0.0001 and 10 mg/ml of the composition.

9. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzalkonium chloride in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the active substance is cetirizine.

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously Presented) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn-previously presented) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

27. (New) the liquid pharmaceutical composition according to claim 1, wherein the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate is present in an amount of more than 0 and less than 1 mg/ml of the composition.

REMARKS

Claim 1 has been amended to recite that the upper limit of the amount of parabens is 1.125 mg/ml, and new claim 27 has been added wherein the upper limit is 1 mg/ml (as previously in claim 1). Support for these amendments can be found on page 4, lines 27-30.

Rejection of claims 1-2, 5, 12, and 17 under 35 USC 103

Claims 1-2, 5, 12, and 17 were rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19).

In the previous Office Action response, the applicants noted that Doron et al (2001; Int. J. Antimicrob. Agents; 18: 575-78) taught the lowest total concentration of the combination of MP and PP to be completely antibacterial is 1.55 mg/ml for liquid, planktonic bacterial growth. The examiner agreed that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/ml, as the applicants had argued. One of ordinary skill in the art would have avoided using smaller concentrations (i.e., below 1.5 mg/ml, which includes the upper limit of 1.125 mg/ml of amended claim 1 and new claim 27) because they would believe or reasonably expect that such concentrations (as presently claimed) would render a composition susceptible to bacterial growth. The instant rejection suffers similarly.

Gilliland 1 presents a study of the effect of temperature on the kill rate of *E. coli* by methyl and propyl parabens, providing kinetic data produced from experiments using mixtures of 0.12% w/v methylparaben and 0.012% w/v propylparaben, i.e. at a 10:1 [MP]:[PB] ratio. The total paraben concentration was 0.132% for all reported experiments. The kinetic study revealed first order kill kinetics. No data was presented for total paraben concentrations under 0.132%. The applicants note that the present claims recite total paraben concentration of < 1 mg/ml (0.1 % w/v).

Furthermore, the temperatures tested by Gilliland 1 were between 34 °C and 42 °C (page 254, col. 1), which is well outside the temperature range pharmaceuticals such as recited in the present claims are stored. And, the test was only one inoculation of the medium with *E. coli*, not a continuous inoculation with bacteria and fungi.

In view of the foregoing, nothing in Gilliland 1 would have given one of ordinary skill in the art reason make the presently claimed compositions or to expect the bactericidal results achieved.

Gilliland 2 presents a similar study using four different mixtures of methylparaben and propylparaben. The experiments also employed elevated temperatures (37 °C) for measurement of kill kinetics, and, so, like Gilliland 1, its teachings would have been recognized as of limited value for a pharmaceutical composition such as presently claimed.

But even to the extent that its teachings are applicable, they would *dissuade* the ordinary artisan from the presently claimed composition.

As noted, Gilliland 2 studied kill kinetics of four mixtures of parabens (Table 1, page 259):

(a) 0.12 % methylparaben and 0.012% propylparaben:,
- total paraben 0.132%
- [MB]:[PB] = 10:1

(b) 0.12 % methylparaben and 0.014% propylparaben:
- total paraben 0.136%
- [MB]:[PB] = 8.6:1

(c) 0.14 % methylparaben and 0.012% propylparaben:
- total paraben 0.152%
- [MB]:[PB] = 11.7:1

(d) 0.14 % methylparaben and 0.014% propylparaben:
- total paraben 0.154%
- [MB]:[PB] = 10:1

Gilliland 2 teaches that methylparaben at 0.12% or 0.14% when used alone was bacteriostatic, but not bacteriacidal, And propylparaben at 0.012% or 0.014% when used alone allowed bacterial growth. (page 260, first full paragraph). Gilliland 2 teaches that concentrations below (a) – (d) were not studied because "at lower concentrations the combinations were often only bacteriostatic and consistent kill rate constants could not be calculated." (page 259, fourth paragraph).

The measured rate constant as a function of methylparaben concentration is presented in Fig. 2 of Gilliland 2 (rate constants obtained from Table 1 of Gilliland 2):

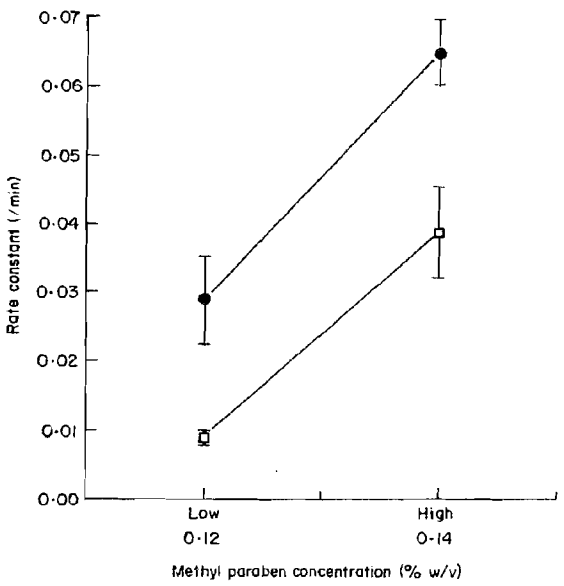

Fig. 2 Results of factorial design experiment to evaluate the effect of methyl and propyl paraben combinations on the kill rate constant of *Escherichia coli*. (Error bars are S.E., $n = 20$.) □, Low propyl paraben; ●, high propyl paraben

- The y-axis is placed at a methylparaben concentration of approximately 0.11%.
  - Positive y-value rate constants correspond to microbial kill.
  - Negative y-value rate constants correspond to microbial growth.

The total concentration of parabens at which there is no bactericidal effect can be readily calculated for [MP]:[PB] = 10:1 by extrapolating the line defined by points (d) and (a) (both having [MP]:[PB] = 10:1) to a rate constant of 0. That line is calculable as follows:

$$\text{slope} = \frac{0.0649 - 0.0091}{0.14 - 0.12} = 2.79$$

and

$$\text{intercept} = \text{rate} - \text{slope} \cdot [\text{MB}] = 0.0649 - 2.79 \cdot 0.14 = -0.3257,$$

yielding the linear equation:

$$\text{rate} = 2.79 \cdot [\text{MB}] - 0.3257.$$

Thus, the rate goes to zero (i.e., the solution loses its bactericidal activity) at

$$[\text{MB}] = \frac{0.3257}{2.79} = 0.1167 \text{ w/v\%}.$$

So, for the ratio [MP]:[PB] = 10:1, the total paraben concentration at which bactericidal activity vanishes is

[MB] + [PB] = (0.1167) + 0.1 (0.1167) = 0.1283 w/v % = 1.283 mg/ml.

And while this is for a ratio [MB]:[PB]=10:1 rather than the claimed 9:1, this clearly suggests that total concentrations below 1 mg/ml for a ratio of 9:1 would be expected not to be bactericidal at this temperature, thus teaching away from the present claims.

Routledge teaches that the GRAS level for parabens is 0.1% w/w. The FDA establishes GRAS (Generally Recognized As Safe) levels for food additives. 27 CFR §170. The agency establishes the level, typically using a 100:1 margin of safety. 27 CFR §170.22. Thus, the GRAS designation and level for parabens is unrelated to the effectiveness of parabens as antimicrobial agents. A principal advantage of being at or under permitted GRAS levels is that the use of the material will not require the food manufacturer to obtain additional pre-market notification review by the FDA under 27 CFR §170.100. Regardless, the FDA routinely subjects pharmaceutical compositions to pre-approval reviews, 21 CFR §314.105(c), so the advantage of coming in under the GRAS level is minimal.

Indeed, as stated in Routledge (page 16, right, 3rd paragraph), maximum levels of parabens in pharmaceutical products seldom exceed 1% w/w, while the Danish cosmetic regulations permit a maximum combined concentration of 0.8% w/w (both levels far exceeding GRAS levels), implying that exceeding GRAS levels is permissible. As an example, the assignee of the present application, UCB Pharma, recently launched an oral solution of a drug effective in the treatment of epilepsy diseases, which solution contains more than 2.5 mg/ml of paraben, greatly exceeding the GRAS level.

Those of ordinary skill in the art recognize that for a liquid pharmaceutical composition to be safe, useful, and achieve regulatory approval, a complete antibacterial effect must be achieved. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). And acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product (21 CFR §314.125(b).

Thus, in balancing the antibacterial requirements against any perceived advantage in achieving GRAS standards, one or ordinary skill in the art would have essentially ignored

Routledge's teachings concerning GRAS in view of Gilliland 2's suggestion that such levels of methyl and propyl parabens would fail to be bactericidal.

In summary, the applicants respectfully submit that one of ordinary skill in the art could not have predicted or had a reasonable expectation that a liquid levocetirizine-containing solution would be completely antibacterial with concentrations of the combination of methyl- and propylparabens of less than 1 mg/ml because,

1. The lowest completely antibacterial concentration of the combination of MP + PP disclosed by Gilliland 1 and Gilliland 2 is > 1.3 mg/ml, with lower concentrations stated to be bacteriostatic and not bactericidal.
2. The contour plot from the 2^2 factorial designed experiment of Gilliland 2 teaches that at total paraben concentrations under about 1.2 mg/ml the preservative mixtures will be ineffective.
3. Routledge teaches that while levels of parabens should be kept at a minimum, both the FDA and Danish authorities recognize that patient safety allows parabens at levels exceeding about 8 – 10 mg/g.

It is therefore unexpected and nonobvious that compositions according to the claims would have antibacterial efficacy observed. The unexpected efficacy of the claimed compositions is manifested in Tables 15-20 of Example 4 of the present application, which show that levocetirizine compositions according to claim 1 with total paraben concentrations ([MP] + [PP]) of from 0.375 mg/ml up to 1.125 mg/ml (and [MP]:[PP] = 9) are free of *Pseudomonas aeruginosa*, *E. coli,* and *Staphylococcus aureus* bacteria 14 and 28 days following inoculation with these bacteria, respectively.[1]

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

[1] *Candida albicans* and *Aspergillus niger* are fungi.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: October 23, 2009

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

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Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	6319258
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	23-OCT-2009
Filing Date:	18-JUL-2007
Time Stamp:	14:55:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796_Transmittal_Letter.pdf	101150 d4ffdb5bc7ed0abc735f915db7800fc36a41bce7	no	1

Warnings:	
Information:	

2		06-796_Response.pdf	184654 7b737409c6c231d70823dbfef77f3fce8ed08599	yes	10

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	10

Warnings:	
Information:	
Total Files Size (in bytes):	285804

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Fanara, Domenico
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

No fees are believed to be due. However, please charge any underpayments to deposit account no. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	October 23, 2009	Reg. No.	37,942

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	October 23, 2009

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/23/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 22	Minus	** 26	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DOROTHY BELL/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 01/05/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
01/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

All Participants:

(1) *TIMOTHY P. THOMAS*.

(2) *Michael Greenfield*.

Status of Application: _____

(3) _____.

(4) _____.

Date of Interview: *30 December 2009*

Time: *9:00 a.m.*

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:
See Continuation Sheet

Claims discussed:
1, 6-8, 14-15, 18, 22

Prior art documents discussed:
Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578)

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Timothy P Thomas/
Examiner, Art Unit 1628

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of rejections discussed: Claims 1-2, 5, 12 and 17, rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; IDS 12/18/2008 reference); Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261); in view of Routledge et al. ("Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19).

Continuation of Substance of Interview including description of the general nature of what was discussed: The reply of record is considered to be persuasive with respect to the prior art rejection of record, based on an unexpected result disclosed in the specification. However, the upper limit of claim 1 has been increased to 1.125 mg/ml. Looking at the Doron reference, which is of record, the reference is suggestive that an amount of just above 0.9% [MP] + [PP] (0.06 + 0.03) would be expected to result in solutions with 0% bacterial growth, based on the data of Figure 1; i.e., 0% bacterial growth would be expected from interpolation of the data at concentrations of just under 1.125 mg/mL. It was proposed that the claim be limited to 1 mg/mL or less as the upper amount, in place of "less than 1.125 mg/mL". Since the basis of overcoming a rejection that would include the Doron reference would be unexpected results, the lowest amount for which there is an unexpected result in the specification is 0.375 mg/mL. It was therefore proposed that the lower limit of claim 1 be 0.375 or greater, in place of the amount of more than 0, currently in claim 1. The range of 0.375 to 1 mg/mL is commensurate in scope to the data for which unexpected results are present in the disclosure.

It was noted that should claim 1 be amended as proposed, and the dependent claims be amended in a corresponding manner, the case would be discussed with supervisors for consideration of whether the claims are patentable. Considering the withdrawn claim components of claims 6-8, each of these compounds are known antimicrobial agents; inclusion of these compounds would no longer lead to an unexpected result when any of the additional compounds are present; i.e., should claim 1 be determined to be allowable, claims 6-8 are not automatically also allowable. Claim 18 would need to contain the limitations of claim 1 to be considered for rejoinder; as would claim 22, should claim 1 be determined to be allowable. .

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 01/15/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
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CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
01/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

All Participants:

(1) *TIMOTHY P. THOMAS*.

(2) *Michael Greenfield*.

Status of Application: *rejected*

(3) _____.

(4) _____.

Date of Interview: *13 January 2010*

Time: *11a.m.*

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:

Claims discussed:
1

Prior art documents discussed:
Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578)

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Timothy P Thomas/
Examiner, Art Unit 1628

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed: Mr. Greenfield had indicated to the Examiner that the limitation of the MP+PP amounts would be authorized to the range of 0.375-1mg/mL, for which the Examiner had indicated a meeting with supervisors would be held, although the claims are still not considered to be patentable, at least because the addition of a third preservative would not provide an unexpected antimicrobial solution. On 1/13/2010, the Examiner informed Mr. Greenfield that problems with the claims that still remain, based on the teaching of Doron, lead to amounts below 1 mg/mL as expected to be antimicrobial, such as when a third antimicrobial agent is present; that the results of the specification are not directly comparable to Doron, which considers other bacteria from what is tested in the specification, and the claims are not commensurate in scope with the data disclosed. Mr. Greenfield was informed that an Office Action with a new rejection that includes Doron would be mailed .

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12,14,15 and 17-27* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12,17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20100113* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 10/23/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection under 35 USC 103 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-2, 5, 12, 17 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; cited in a prior Office Action); Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257; cited in a prior Office Action); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261; cited in a prior Office Action); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578; cited in a prior Office Action); in view of Routledge et al. ("Some Alkyl Hydroxy

Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19; cited in a prior Office Action).

The teachings of DeLongueville, Gilliland 1, Gilliland 2, Doron and Routledge have been outlined on the record, which are repeated here.

DeLongueville teaches the use of an individual optical isomer of cetirizine for preparing a medicament (abstract); such optical isomers include levocetirizine, which contains preferably at least 95% by weight of the levocetirizine (p. 1, lines 29, 32-33); pharmaceutical compositions as liquid compositions in the form of a sterile solution miscible with water (p. 5, lines 12-13); carriers and diluents include water (p. 5, lines 21-22); preserving substances are taught (p. 5, line 15); topical application in the form of an aqueous solution (p. 5, line 30-31); solutions for oral administration (p. 6, lines 1-2); drops in the form of a liquid, with added preservatives (p. 6, lines 5, 7, 9); a syrup for oral formulation is preferred that contains methyl- and propylparaben (methyl parahydroxybenzoate and propyl parahydroxybenzoate) and purified water (p. 6, lines 18-20). DeLongueville does not teach a specific embodiment containing levocetirizine and the required mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate (although each of these components is separately taught); or a total amount of methylparaben and propylparaben or the claimed ratio present in the liquid composition.

Doron teaches the antibacterial effects of methyl and propyl paraben against Streptococcus sobrium, which is involved in tooth dacay in the oral cavity, and that antibacterial synergistic effect was found between several combinations of parabens

(abstract); at 0.03% (about 0.3 mg/mL) propyl paraben (PP), with increasing amounts of methyl paraben, decreasing amounts of viable bacterial counts were demonstrated (p. 577, Figures 1-2), the ratios vary from 0.015:0.03 (1:2) MP:PP to 0.25:0.3 (8.33:1), or almost 9/1. At the highest ratio in both figures no bacterial counts were recorded (Figures 1-2; pp. 576-575, bridging paragraph). Additionally, MP had the largest antibacterial effect of the parabens tested (abstract).

Gilliland 1 teaches the effect of temperature on the kill rate of *Escherichia coli* by methyl and propyl parabens was studied (abstract); in the presence of a bactericidal antimicrobial agent the rate of kill of microbes generally increases as the temperature increases (p. 252, 1st paragraph); a comparison of *E. coli* growth is presented in a chemically defined growth medium, which shows positive growth vs. growth in water as the medium, which shows nearly constant levels of *E. coli*, i.e., little or no growth (p. 254, Figure 2); the effect of temperature on the kill rates and rate constants for inocula prepared from exponential and stationary phase E. coli in the presence of 0.12% w/v methyl paraben and 0.012% w/v propyl paraben in the chemical growth medium (a 10/1 ratio, with total [MP]+[PP]=1.32%; p. 254, Table 1; p. 255, Figures 3, 5); the kill rates are reported for both exponential phase and stationary phase cells (p. 254, Table 1, pp. 255, Figures 3-6); reported activation energies for the effect of a series of antimicrobial agents, including phenol, benzyl alcohol and benzalkonium chloride have been reported from 5 different micro-organisms (p. 256, Table 2).

Gilliland 2 teaches antimicrobial effects of methyl and propyl parabens are investigated to determine whether the parabens act synergistically, that combinations of

methyl or propyl parabens, at concentrations which slow down or inhibit bacterial growth when used singly produced definite kill, the parabens are therefore synergistic since in combination they produce an effect which is not observed when they are used singly, the effect is not considered true synergism as shown by kinetic results of experiments with a factorial design, which indicated no significant interaction between the two parabens (abstract); combinations of antimicrobial agents are widely used both for treating diseases and for preserving pharmaceutical systems, the rationale is that by using combinations the activity spectrum may be broadened and the agents involved may act synergistically, although it is difficult to provide clinical evidence for synergy with in vitro systems (p. 258, 1st paragraph); studies utilized a chemically defined medium, to which methyl and propyl esters of p-hydroxybenzoic acid were added (p. 258, 2nd and last paragraphs); control studies employed 0.012 and 0.014 % w/v propyl paraben, for which growth was observed (p. 259, Table 1; p. 261, Figure 4); at 0.12 and 0.14% w/v methyl paraben the number of E.coli cells remained approximately constant, a bacteriostatic effect (p. 260, Figure 3, 2nd paragraph); combinations of 0.12 or 0.14% w/v methyl paraben with 0.012 or 0.014% w/v propyl paraben all resulted in observable kill of *E. coli*, a bactericidal effect of the paraben combination (p. 259, Table 1; p. 260, 2nd & 3rd paragraphs; p. 261, Figure 5). It is noted that the 4 combinations have a MP/PP ratio of 8.6/1 for 0.12% MP + 0.014% PP; a ratio of 10/1 for 0.12% MP + 0.012% PP or 0.14% MP + 0.014% PP; and a ratio of 11.7/1 for 0.14% MP + 0.012% PP. These ratios bracket the claimed ratio of 9/1, rendering the ratio as an obvious variant of the taught ratios.

Routledge teaches that a range of parabens, including methyl- and butylparaben, are weakly estrogenic, the suggestion is made that the safety in use of these chemicals should be reassessed, with particular attention being made to the estimation of the actual levels of systemic exposure of humans exposed to these chemicals, in order to assess the risk of exposure to parabens (abstract); certain synthetic compounds used in a wide range of products can mimic the main natural estrogen, influencing the expression of estrogen-dependent genes, taken with epidemiological data suggests a progressive decline in human male reproductive health and fertility (p. 12, 1st paragraph); a group of parabens, used extensively in a wide range of products have been studied (p. 12, 2nd paragraph); binding to estrogen receptors is demonstrated for butyl paraben (p. 13, Figure 2); the response of the yeast estrogen screen to propyl and methyl paraben demonstrates that a shifting of about 100-fold higher concentrations of methyl paraben is required as compared to propylparaben in the assay (p. 15, Figure 3); butyl paraben was shown to increase the weight of the uterus in immature rats (p. 15, 3rd paragraph); a discussion of the toxicology of parabens has led to p-hydroxybenzoates being widely permitted in foods in the UK and US at levels of up to 0.1% w/w for MP and PP in food (corresponding to about 1 mg/mL; p. 16, right, 3rd paragraph); maximum levels of parabens in pharmaceutical products seldom exceed 1% w/w, EEC and Danish cosmetic regulations permit the preservation of cosmetic products with MP and PP up to a maximum combined concentration of 0.8% w/w (8mg/mL; p. 16, right, 3rd paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the levocetirizine formulations, including oral liquid formulations and eye drops, as taught by DeLongueville with a synergistic ratio of methylparaben and propylparaben; it would have been obvious to utilize the range of ratios taught by Gilliland 2 including the claimed ratio of 9/1 or to extend the ratios from 8.33:1 taught by Doron to the claimed ratio of 9/1, which is within the Gilliland 2 scope taught or extrapolated from the Doron data; it would also have been obvious to reduce the total amount of MP+PP from the total amounts taught by Gilliland 1 and 2 to a value less than 1%, meeting the claimed total mixture of paraben amounts, while still giving bacteriocidal preservative effect; accomplished by: 1) reducing defined components in the medium that contribute to microbial growth, such as the growth medium identified by Gilliland 1; and/or 2) including a third preservative agent, such as one of the additional agents taught by Gilliland 1 in Table 2, in combination with the 9/1 ratio of MP/PP; both of these approaches would have resulted in the liquid pharmaceutical compositions within the scope of the instant claims, with the antimicrobial properties demonstrated by applicant. The motivation to utilize MP/PP ratio of 9/1 would have been the clear indication of Gilliland that ratios encompassing this are synergistic in terms of bacterial killing and the indication that better killing is observed at higher amounts of MP, relative to PP, illustrated by the killing of the bacterium at the right side of Figures 1 and 2; additionally, utilization of a higher MP/PP ratio, such a 9/1 would employ a significantly smaller amount of PP that binds to estrogen receptors with higher affinity; the motivation to reduce the total [MP]+[PP] to a value less than 1 mg/ml would have been the

recognition of Routledge that parabens mimic natural estrogen, and the levels approved in foods of up to 1 mg/mL would be a target concentration to stay below, while still retaining microbicidal activity; the motivation to combine a 9/1 ratio of MP/PP with an additional antimicrobial agent would have been the expectation of additive or even synergistic microbe killing, as well as the potential for a broader spectrum of microbes that are killed by the combination of preservatives.

As pointed out in MPEP 2144.06 (I), "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…. [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

It is noted that the arguments provided on the record were considered to be persuasive. However, the combination that includes Doron reference is considered to render the instant claims obvious over the references in combination.

Applicant argued that Doron taught the lowest total concentration of the combination of MP and PP to be completely antibacterial is 1.55 mg/ml for liquid, planctonic bacterial growth; that the Examiner agreed that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/mL; that one of ordinary skill in the art would have avoided using smaller concentrations because they would believe or reasonably expect that such concentrations as presently claimed would render a composition susceptible to bacterial growth. While this line of reasoning is persuasive for the combination of

references, when Doron is not included (based on the combination of DeLongueville, Gilliland 1, Gilliland 2, nd Routledge); however, when the data of Doron is also considered, lower amounts even than 1 mg/mL are considered to be obvious. A review of the data of Figure 1 of Doron indicates that reduced growth of the bacteria tested (e.g. immobilized S. sobrinus) is significantly reduced even at the 0.015 w/v MP amount data point, (corresponding to MP+PP of 0.45 mg/mL). This indicates that some reduction in viable bacteria would be expected even at low total amounts, or providing a motivation to include MP and PP even at lower amounts. There is a specific reason to keep the paraben amounts low, below 1 mg/mL, which is based on the recognition of estrogenic activity and the argument for reassessment of safety levels taught by Routledge, that is suggestive of levels lower than the GRAS levels, even though regulations permit higher levels. This motivates a combined amount present of less than 1 mg/mL. It would have been clear to one of ordinary skill in the art that there is still an antimicrobial benefit to use of lower amounts. The data point of Figure 1, at 0.06 w/v% MP (corresponding to 0.9 mg/mL MP + PP, within the claimed range) demonstrates around 1% bacterial growth; this amount of bacterial growth would still provide a benefit to a formulation, rendering a 9/1 ratio where the total of MP+PP as obvious; additionally, the addition of a third active agent would result in further killing at the lower paraben concentrations.

With regard to the argument of an unexpected result of total killing, several points may be made. 1) The comparison of the data in the specification to the Doron data is not a direct comparison; Doron and the data presented in the instant specification test

the growth of different organisms; applying a cutoff point from Doron as unexpected to a completely different set of organisms is an improper comparison to demonstrate a result is unexpected; 2) The combination of MP+PP at a 9/1 ratio where the total amount of the two parabens is less than 1.125, less than 1 mg/ml, or even 0.75 mg/mL would still be expected to be completely antimicrobial when another preservative agent is present with MP and PP, such as one of the Gilliland 1, Table 2 active agents. When a combination of MP+PP and a third antimicrobial agent are used, lower total [MP]+[PP] will be expected to result in an antimicrobial effect. 3) The data argued to be unexpected, disclosed in the specification, are not commensurate in scope with any of the claims under examination, which utilize open language (comprising, permitting even other antimicrobial agents) and are not limited to the amounts of the claimed components in any of the claims under examination; the solutions tested all contain additional ingredients at specific amounts (as disclosed in Table 4) that are not recited in any of the claims.

Applicant's argument that the GRAS level is unrelated to the effectiveness may be the case; however, the argument that lower levels are better, made by Routledge, because of the estrogenic activity of the parabens provides a significant motivation to keep the total amount of parabens lower than the GRAS level; optimization of the conditions and the addition of a third preservative/antimicrobial agent would permit an antimicrobial composition with less than 1% bacterial growth; i.e., one of ordinary skill in the art would not have ignored the Routledge teaching which clearly teaches a potential problem with higher levels of parabens. Such a composition is within the scope of the

instant claims, and <1% growth is not considered unexpected for three antimicrobial agents that include MP and PP at the required amounts.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/

Examiner, Art Unit 1628

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN	9/18/2008	TPT
PubChem	9/18/2008	TPT
PubMed	9/18/2008	TPT
WEST	9/18/2008	TPT
IDS references	9/18/2008	TPT
PALM Inventor Name Search	9/18/2008	TPT
STN	2/20/2009	TPT
EAST	2/20/2009	TPT
PubMed	2/20/2009	TPT
IDS references	2/20/2009	TPT
STN	7/27/2009	TPT
PubChem	7/27/2009	TPT
PubMed	7/27/2009	TPT
EAST	7/27/2009	TPT
EAST	7/27/2009	TPT
PubMed	7/29/2009	TPT
IDS references	7/27/2009	TPT
STN	12/30/2009	TPT

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/TIMOTHY P THOMAS/ Examiner.Art Unit 1628	

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=> d his

     (FILE 'HOME' ENTERED AT 07:39:49 ON 30 DEC 2009)

     FILE 'REGISTRY' ENTERED AT 07:40:13 ON 30 DEC 2009
                E LEVOCETIRIZINE/CN
L1              1 S E3
                E METHYL PARAHYDROXYBENZOATE/CN
                E METHYL PARABEN/CN
                E METHYLPARAHYDROXYBENZOATE/CN
                E METHYLPARABEN/CN
L2              1 S E3
                E PROPYLPARABEN/CN
L3              1 S E3

     FILE 'CAPLUS' ENTERED AT 07:42:24 ON 30 DEC 2009
L4            230 S L1
L5           8364 S L2
L6           4600 S L3
L7              6 S L4 AND L5 AND L6
L8              1 S L7 AND PD<20050706
L9              5 S L7 NOT L8

     FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 07:45:46 ON 30 DEC 2009
L10            81 S L1
L11          2612 S L2
L12          1375 S L3
L13             2 S L10 AND L11 AND L12
L14             0 S L13 AND PD<20050706
```

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Total Number of Pages in This Submission	3
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):
  Response to Examiner's Interview Summary

Remarks

Please charge all necessary fees to maintain the pendency of this application to deposit account no. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Michael S. Greenfield/		
Printed name	Michael S. Greenfield		
Date	February 6, 2010	Reg. No.	37,142

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	/Michael S. Greenfield/		
Typed or printed name	Michael S. Greenfield	Date	February 6, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE EXAMINER-INITIATED INTERVIEW SUMMARY MAILED JANUARY 5, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following remarks in response to the Examiner-Initiated Interview Summary mailed January 5, 2010. No fees are believed to be due, but the Office is nevertheless authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Remarks begin on page 2 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on February 6, 2010.

Date: February 6, 2010

/Michael S. Greenfield/
Michael S. Greenfield

REMARKS

In response to the Examiner-Initiated Interview Summary mailed January 5, 2010, the summary as set forth in the Interview Summary is accurate insofar as it accurately reflects the assertions made by the Examiner during the interview. The Summary accurately reflects the proposed claim amendments and Examiner's reasons for suggesting the claim amendments as conveyed in the Interview. The undersigned took the proposed amendments and reasons therefore under advisement but did not acquiesce to the assertions or authorize amendment of the claims.

The Interview Summary did not indicate that a reply was required, nor did it set a deadline for replying.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: February 6, 2010

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	6964767
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Michael S. Greenfield
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	06-FEB-2010
Filing Date:	18-JUL-2007
Time Stamp:	12:38:13
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06-796-Transmittal.pdf	145599 53356a4f0fdd21d837ed47cd926c0bfc20adcda3	no	1

Warnings:	
Information:	

2	Applicant summary of interview with examiner	06-796-Summary.pdf	83007 dea4dde962377ddf895b4a75e2ac283d88e94b50	no	2

Warnings:	
Information:	
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE NON-FINAL OFFICE ACTION MAILED JANUARY 15, 2010, REQUEST FOR ONE-MONTH EXTENSION OF TIME, AND STATEMENT OF SUBSTANCE OF INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the non-final Office Action mailed January 15, 2010. Applicants request a one-month extension of time. The Office is authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on May 4, 2010.

Date: May 4, 2010

/Sandra B. Weiss/
Sandra B. Weiss

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Previously presented) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) at least one preservative, wherein the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 and 1 mg/ml of the composition.

6. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of thimerosal in the range of 0.0001 and 0.05 mg/ml of the composition.

7. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of chlorhexidine acetate in the range of 0.0001 and 0.05 mg/ml of the composition.

8. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzylalcohol in the range of 0.0001 and 10 mg/ml of the composition.

9. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutical composition contains an amount of benzalkonium chloride in the range of 0.0001 and 0.05 mg/ml of the composition.

10. (Withdrawn) The liquid pharmaceutical composition according to claim 1, wherein the active substance is cetirizine.

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously Presented) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn-previously presented) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

27. (Currently amended) ~~the~~ The liquid pharmaceutical composition according to claim 1, wherein the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate is present in an amount of more than 0 and less than 1 mg/ml of the composition.

REMARKS

Claim 27 is amended herein to correct an error in form.

Statement of the Substance of the Interview

The courtesy of the Examiner's Interview on January 13, 2010 is noted with appreciation. Applicants are in agreement with the Interview Summary provided with this Office Action. It is understood that it is the position of the Office that the claims are not patentable, and would not be patentable if limited to MP + PP in the range of 0.375 – 1 mg/ml, because the composition would be expected to be anti-microbial as when a third anti-microbial agent is present. It is further understood that it is the position of the Office that the claims are not commensurate in scope with the data.

Applicants respectfully disagree with these positions, as explained below.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) and Doron et al. (2001 Int'l J. Antimicrobial Agents 18: 575-578) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19). This rejection is respectfully traversed.

The present invention is based on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6). Thus, applicants herein have made the unexpected finding that a pharmaceutical composition comprising such an active substance and a reduced amount of preservatives is stable, i.e. resistant to microbial contamination, for a long period of time. (id., lines 11-15) Independent claim 1 is directed to a composition comprising levocetirizine, and a preservative, wherein the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition.

Applicants submit that it is wholly unexpected that a levocetirizine composition could be made with both a low concentration of parabens and an MP/PP ratio of 9, and still be resistant to microbial contamination. It is noted that pharmaceutical compositions of other drugs using parabens as preservatives use either much higher concentrations of parabens, or much lower ratios of MP/PP, or both, as shown in the following references, submitted herewith with a Supplemental Information Disclosure Statement.

- U.S. 4,705,683 at col. 3, lines 15-25 and col. 3 line 65 – col. 4 line 8, discloses compositions of cimetidine and ranitidine, respectively, having a combined methyl paraben and propyl paraben of 0.172 g/100 ml or 1.72 mg/ml and a MP/PP ratio of 6.8, both outside the presently claimed values.
- U.S. 6,004,968 discloses pharmaceutical composition of lamivudine and parabens. At col. 4, lines 16-26, the reference discloses that for oral solutions and suspensions, the range of methyl paraben concentration may be 0.096%-0.2% (0.96 mg/mL to 2 mg/mL) and the range of propyl paraben concentration may be 0.01% to 0.02% (0.1 to 0.2 mg/mL), but the preferred ranges are 0.15-0.2% (1.5 mg/mL to 2 mg/mL) for methyl paraben and 0.018-0.019% (0.18 mg/mL to 0.19 mg/mL) for propyl paraben, such that the preferred range for combined parabens and preferred valued for MP/PP are both outside the scope of the present claims. The composition of Example 1 (the only composition disclosed in the reference) has total parabens of 1.6 mg/ml, outside the presently claimed range.
- US 2009/0137645 discloses a famotidine composition in which a first granulate comprising famotidine is mixed with a second granulate comprising parabens. The ratio of MP/PP is 5 (Tables 1-4) well outside the presently claimed range.
- As disclosed at http://www.rxlist.com/levo-dromoran-drug.htm, the commercial drug levo-dromoran is sold in 1 ml ampoules containing the drug plus 1.8 mg methyl paraben and 0.2 mg propyl paraben, for a total of 2.0 mg parabens per ml of solution, well beyond the upper limit of 1.125 mg parabens/ml solution recited in the present claims.
- The treatise Remington the Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749, discloses in Table 39-2 that methyl and propyl parabens are each

typically used in concentrations of 0.1-0.25 w/w%; when combined, these would yield a minimum concentration of 0.2% total parabens, or 2 mg/mL, well beyond the presently claimed range. The table also suggests that the maximum MP/PP ratio would be 2.5, well below the value of 9 recited in the present claims. The use of parabens generally as antimicrobial agents is discussed generally at page 749, left column, under "Esters."

From the foregoing, it may be seen that those skilled in the pharmaceutical arts would not have been led to expect that a liquid pharmaceutical composition comprising levocetirizine could be prepared with a total parabens concentration of no more than 1.125 mg parabens/ml of solution and a methyl paraben to propyl paraben ratio of 9:1, to achieve a composition with the anti-microbial properties required of a pharmaceutical composition. One skilled in the art would have been led to believe that either the overall quantity of parabens would have to be much higher, or the ratio of methyl paraben to propyl paraben would have to be much lower, or both. The quantitative limitations of claim 1 render that claim, and all claims dependent thereon either directly or indirectly, non-obvious over the art of record in this case.

The arguments and remarks set forth in the Response filed October 23, 2009 are incorporated herein by reference.

The present Action restates the rejection from the prior action, then states at page 8: "It is noted that the arguments provided on the record were considered to be persuasive. However, the combination that includes the Doron reference is considered to render the instant claims obvious over the references in combination." The Action notes that Fig. 1 of Doron includes a data point with 0.015 w/v MP, corresponding to MP + PP of 0.45 mg/ml.

This data point does not render the claimed invention obvious for at least four reasons:

- Doron does not relate to the use of parabens as an anti-bacterial preservative for another drug in a pharmaceutical composition. Doron does not teach the use of parabens in combination with any other pharmaceutical. Therefore, one cannot predict from Doron what effect parabens would have when used in combination

with any other pharmaceutical product, or what concentration or ratios of parabens would be effective.

- The data in Fig. 1 of Doron relied on in the Action is the antibacterial effect on **immobilized** *S. sobrinus*. And as the applicants noted in their response to the Office Action mailed February 25, 2009, Doron expressly states that there is a stronger antibacterial effect of a combination of parabens on immobilized bacteria compared to planktonic bacteria. *See* Doron, p. 578, first paragraph, which also states that the effects of individual parabens is similar against planktonic bacteria and immobilized bacteria.

  At least two points follow from this. First, the difference in antibacterial effects of individual parabens versus combinations of parabens against immobilized and planktonic bacteria demonstrate a degree of unpredictability in extrapolating the antibacterial data to new situations.

  Second and moreover, because combinations of parabens are more effective against immobilized bacteria than planktonic bacteria, **the results reported by Doron in Fig. 1 for immobilized bacteria cannot be extrapolated to what one of ordinary skill in the art would expect in a liquid composition as presently claimed (*i.e.* against planktonic bacteria).**

- The ratio of methyl paraben to propyl paraben at the selected data point is 0.5/1, far removed from the 9/1 ratio recited in the present claims. In fact, all the samples in Figs. 1 and 2 of Doron have MP/PP ratios of 0, 0.5, 1, and 2. Nothing in the reference suggests even trying a 9/1 MP/PP ratio, much less that such a ratio would be effective.

- Fig. 1 of Doron shows that at the selected data point the viable bacteria count is greater than 35%, far greater than what would be acceptable for a pharmaceutical product; therefore Doron teaches that 0.45mg/ml is not an effective antimicrobial agent. As the applicants stated in their response to the Office Action mailed February 25, 2009,

  > While, as the Office noted, Doron teaches that combinations of parabens have a synergistic effect on planktonic bacteria, in the very same sentence

> Doron states, "although a complete antibacterial effect is not always achieved." The significance of this statement cannot be over-emphasized because to be safe, useful, and achieve regulatory approval, **a complete antibacterial effect must be achieved**. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). An acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product.

Fig. 1 of Doron shows that the only way to achieve complete eradication of bacteria, as would be required for a pharmaceutical agent, is with methyl paraben of 0.125 w/v% combined with 0.03 w/v% propyl paraben, for a total parabens of 0.155 w/v% or 1.55 mg/ml. Thus Doron teaches that to achieve complete eradication of bacteria both the MP/PP ratio and the total MP + PP content must be well outside scope of the present claims.

- Doron is evaluating various combinations of parabens to serve as antibacterial agents in the oral cavity, which is far different use from serving as a pharmaceutical preservative in a liquid composition, as presently claimed.

The fact that the selected data point "indicates that some reduction in viable bacteria would be expected even at low amounts" does not render the claimed invention obvious, because "some" reduction in bacteria is not the standard for a pharmaceutical composition. The goal for a pharmaceutical composition is substantially complete eradication of bacteria, to protect the pharmaceutical composition from bacterial contamination. The Action provides no scientific basis or reasoning why altering the MP/PP ratio of Doron to that recited in the present claims would be expected to yield a complete antibacterial result. Indeed, Doron suggests to the contrary when it notes that while individual parabens are equally effective against immobilized and planktonic bacteria combinations of parabens are more effective against immobilized bacteria than planktonic bacteria. This suggests that altering the ratio of parabens (at least down to 0) changes the antibacterial effect. One of ordinary skill in the art cannot predict the results of altering the ratio of parabens based on the cited art, so, contrary to the assertions in the Action, the ratio in Doron does not and cannot render a ratio of 9/1 obvious.

One skilled in the art reading Doron would have no reason to recognize that the presence of levocetirizine in the claimed composition unexpectedly allows for the use of a lower concentration of parabens when the parabens are used in the claimed ratio while still achieving essentially complete eradication of bacteria, as recognized by Applicants herein.

To the extent the Action notes at page 9 that a third active agent would result in further killing at the lower paraben concentrations, the applicants respectfully submit that this is irrelevant because it does not detract from the fact that the particular combination of parabens in the recited amounts and ratio surprisingly has an completely antibacterial effect. Because the combination of parabens in the recited amounts and ratio possess an unexpected property (*i.e.* effective antibacterial action when used in combination with levocetirizine), the claimed combination of parabens with levocetirizine must be non-obvious and any composition containing it must be non-obvious too. The optional presence of additional components does not detract from this.

In response to the three points raised on page 10 of the Action:

1) to the extent that Doron is not a direct comparison and therefore a cutoff point from Doron cannot be applied to show that the present results are unexpected, then the fact that it is not a direct comparison also means that the data cannot be used to show that the present results are expected;

2) the possible effects of MP and PP with a third agent are irrelevant because, as noted above, whether a third agent would lead to further antibacterial activity does not detract from the fact that the particular combination of parabens in the recited ratio and amounts has an unexpected antibacterial effect;

3) the unexpected results are shown in the specification at Example 4, pages 12 – 14. The fact that other additional ingredients as set forth in Table 2 are present does not mean that the data is not commensurate in scope with the claims. Table 4 shows the formulations of two compositions, an oral solution and drops. The drops contain a concentration of levocetirizine ten-fold greater than the oral solution. As shown in a comparison of Tables 5 and 6, the drops composition had a significantly greater anti-microbial effect than the oral solution composition with respect to Candida albicans and Aspergillus niger, demonstrating the unexpected antibacterial effect of levocetirizine with respect

to these two innocula. The results shown in these two tables then can be compared with the results shown in Tables 15-20. These show results for "oral solutions ad drops containing levocetirizine according to example 2 but also containing mixtures of" parabens. With all the same ingredients, but with the addition of the recited amount of parabens in a 9:1 ration of MP/PP, these compositions showed superior antimicrobial activity, even with respect to Candida albicans and Aspergillus niger. Thus it is the presence of the parabens in the recited ratio and amounts in combination with levocetirizine that provides the unexpected antimicrobial properties. The other ingredients, present in Example 2 and Example 4, were not responsible for the results achieved in Example 4.

As to Routledge's incentive to use lower levels of parabens due to their estrogenic activity; that incentive fails where such lower levels are shown in Doron to be ineffective. If anything, Routledge demonstrates a long-felt need for a pharmaceutical composition that could achieve substantially complete eradication of bacteria while minimizing the estrogenic effect of the preservatives in the composition. It was heretofore unrecognized that such a need could be met by using such a small quantity of parabens at the 9:1 MP/PP ratio in a levocetirizine composition as presently claimed.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: May 4, 2010

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

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Chicago, IL 60606

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PTO/SB/22 (11-08)
Approved for use through 12/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2009 ***(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)***	Docket Number (Optional) 06-796
Application Number 10/599,451	Filed September 28, 2006
For Pharmaceutical Composition of Piperazine Derivatives	
Art Unit 1614	Examiner Timothy P. Thomas

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☒ One month (37 CFR 1.17(a)(1))	$130	$65	$ 130.00
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☐ Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-2490.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 30,814

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____.

/Sandra B. Weiss/	May 4, 2010
Signature	Date
Sandra B. Weiss	312-913-0001
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-08-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4705683		1987-11-10	Dettmar	
	2	6004968		1999-11-21	Casey et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090137645	A1	2009-05-28	Zhang et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2006-08-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Definition of Levo-Dromoran. Internet document http://www.rxlist.com/levo-dromoran-drug.htm, 1 sheet.	☐
	2	Remington the Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749.	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2006-08-28
	First Named Inventor	Domenico Fanara
	Art Unit	1614
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sandra B. Weiss/	Date (YYYY-MM-DD)	2010-05-04
Name/Print	Sandra B. Weiss	Registration Number	30814

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	18-Jul-2007
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Sandra B. Weiss
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**310**

Electronic Acknowledgement Receipt

EFS ID:	7540090
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	04-MAY-2010
Filing Date:	18-JUL-2007
Time Stamp:	11:19:39
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$310
RAM confirmation Number	14288
Deposit Account	132490
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Miscellaneous Incoming Letter	06-796_Transmittal.pdf	118109 9fcc6313ed007ecd1f1b579231119afe804dedac	no	1
Warnings:					
Information:					
2		06-796_Response.pdf	131958 1b2d7542801dcb786747b573dcddced47460d2b1	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	12	
Warnings:					
Information:					
3	Extension of Time	06-796_Extension.pdf	135662 8146a09f19e846c9cba27bc5b990037f7a7fdbeb	no	1
Warnings:					
Information:					
4		06-796_IDS.pdf	781351 cbced75f1a08a467d19ba3d95e36a33a940b046a	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Information Disclosure Statement (IDS) Filed (SB/08)		1	2	
	Transmittal Letter		3	4	
Warnings:					
Information:					
5	NPL Documents	06-796_NPL1.pdf	60504 680517fcd34ba1bc7a234745737127af43b32ec2	no	1
Warnings:					
Information:					
6	NPL Documents	06-796_NPL2.pdf	1452109 40d6de69a9113e25f386cf8a74a0b610d76a19c1	no	5
Warnings:					

Information:					
7	Fee Worksheet (PTO-875)	fee-info.pdf	31964 b6bfc2990a19310515cbc2f3af9f6f8f19f39fdc	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2711657	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599,451
Filing Date	September 28, 2006
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☒ Fee Attached
- ☒ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below): Copies of two (2) cited references.

Remarks

Please charge any underpayments and/or credit any overpayments to Deposit Account No. 13-2490.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Sandra B. Weiss/		
Printed name	Sandra B. Weiss		
Date	May 4, 2010	Reg. No.	30,814

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being electronically transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature	/Sandra B. Weiss/		
Typed or printed name	Sandra B. Weiss	Date	May 4, 2010

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/04/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANDREA BURDEN/

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/04/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 22	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANDREA BURDEN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 07/27/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
07/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,12,14,15 and 17-27* is/are pending in the application.

4a) Of the above claim(s) *6-10,14,15 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,12,17 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This application contains claims 6-10, 14-15 and 18-26, drawn to an invention nonelected with traverse in the reply filed on 7/7/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments

2. Applicants' arguments, filed 5/4/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 1-2, 5, 12, 17 and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; cited in a prior Office Action); Gilliland et al. (Gilliland 1) (“The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies”; 1992; Journal of Applied Bacteriology; 72: 252-257; cited in a prior Office Action); Gilliland et al. (Gilliland 2) (“Kinetic evaluation of claimed synergistic paraben combinations using a factorial

design"; 1992; Journal of Applied Bacteriology; 72: 258-261; cited in a prior Office Action); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578; cited in a prior Office Action); in view of Routledge et al. ("Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19; cited in a prior Office Action).

The rejection is maintained for the reasons of record.

Applicant argues that the present invention is based on the surprising finding that the active substances, including levocertirizine, possess a preservative effect in aqueous solutions; that an unexpected finding that a pharmaceutical composition comprising the active substance and a reduced amount of preservatives is stable, resistant to microbial contamination, for a long period of time; that it is wholly unexpected that a levocetirizine composition could be made with both a low concentration of parabens and an MP/PP ratio of 9, and still be resistant to microbial contamination, because other drugs using parabens as preservatives use either much higher concentrations of parabens or much lower ratios of MP-PP or both, shown by a series of references: US 4,705,683:US 6,004,968; US2009/0137645; http://www.rxlist.com/levo-dromoran-drug.thm; and pp. 748-749 of Remington's Science and Practice of Pharmacy, 21st Ed. Applicant argues that those skilled in the pharmaceutical arts would not have been led to expect that a liquid pharmaceutical compostion comprising levocetirizine could be prepared with a total parabens concnentration of no more than 1.125 mg parabens/mL of solution and a MP:PP ratio of

9:1. This argument ignores the teachings of record. The fact that others use different ratios of MP/PP or higher amounts of a MP+PP combination or both does not refute the basis for the rejection.

The record indicates: Doron teaches the antibacterial effects of methyl and propyl paraben against Streptococcus sobrium, that antibacterial synergistic effect was found between several combinations of parabens (abstract); at 0.03% (about 0.3 mg/mL) propyl paraben (PP), with increasing amounts of methyl paraben, decreasing amounts of viable bacterial counts were demonstrated (p. 577, Figures 1-2), the ratios vary from 0.015:0.03 (1:2) MP:PP to 0.25:0.3 (8.33:1), or almost 9/1. At the highest ratio in both figures no bacterial counts were recorded (Figures 1-2; pp. 576-575, bridging paragraph). Additionally, MP had the largest antibacterial effect of the parabens tested (abstract). This article demonstrates that MP/PP ratio approaches 9/1, as claimed, rendering obvious the ratio 9/1, with the largest antibacterial effect at the highest ratio reported, rendering obvious the use of lower amounts of the two parabens at the 9/1 ratio. There is no comparative data on the record that compare the taught 8.33:1 ratio with the claimed 9/1 ratio, that might demonstrate the 9/1 ratio has some unexpected property over the Doron ratio taught.

The record further indicates Guililand 2 teaches 4 combinations that have a MP/PP ratio of 8.6/1 for 0.12% MP + 0.014% PP; a ratio of 10/1 for 0.12% MP + 0.012% PP or 0.14% MP + 0.014% PP; and a ratio of 11.7/1 for 0.14% MP + 0.012% PP. These ratios bracket the claimed ratio of 9/1, rendering the ratio as an obvious variant of the taught ratios. With respect to the amounts, the use of lower amounts of a 9/1 ratio

is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guililand 2.

The record indicates Routledge teaches that a range of parabens, including methyl- and butylparaben, are weakly estrogenic, the suggestion is made that the safety in use of these chemicals should be reassessed, with particular attention being made to the estimation of the actual levels of systemic exposure of humans exposed to these chemicals, in order to assess the risk of exposure to parabens (abstract). This reference would have provided further motivation to minimize the levels of parabens to the minimum required in a formulation to provide some measure of antimicrobial growth reduction.

Applicant further argues the arguments previously made are incorporated by reference. All previously made arguments have been addressed in previous Office Actions.

Applicant argues Doron does not teach the use of parabens in combination with another pharmaceutical; therefore one cannot predict from Doron what effect parabens would have when used in combination. There are some expected results, such as greater antimicrobial efficacy at higher ratios of MP/PP, approaching the claimed 9/1 ratio. This permits less of the combination to be used to still achieve the same level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also.

Applicant argues the data in Fig.1 of Doron is the antibacterial effect of immobilized S. sobrinus; that Doron states there is a stronger antibacterial effect of a

combination of parabens on immobilized bacteria compared to planktonic bacteria; that at least tow points follow: first, the difference in antibacterial effects of individual parabens v. combinations of parabens against immobilized and planktonic bacteria demonstrate a degree of unpredictability in extrapolating the antibacterial data to new situations. However, data are demonstrated for both types of bacteria (see Figures 1 & 2, where similar, but not quite the same level of activity is demonstrated for the combinations relevant to the instant claims.

Applicant further argues that, secondly, because combinations of parabens are more effective against immobilized bacteria than planktonic bacteria, the results reported in Figure 1 cannot be extrapolated to what one of ordinary skill in the art would expect in a liquid composition. This is precisely why comparative data is necessary to demonstrate a broad composition claim has unexpected results commensurate in scope with those claims. However, there is still data in Figure 2 that demonstrates zero growth at the highest MP/PP ratio for the planktonic bacteria.

Applicant argues the ratio of MP/PP at the selected data point is 0.5/1, far removed from the 9/1 ratio. The point is that the data demonstrate antimicrobial activity is present at this point, reduced levels of growth are demonstrated. Taken with the 9/1 ratio taught at the higher point, and the ratios of Guililand 2, with the recognition that some type of activity is present that in one sense is considered to be synergistic (see title), renders obvious a 9/1 ratio at the concentrations that would give 0.45 mg/ml or greater. MPEP 2141.03 (I) states:

> "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id*. at ___, 82 USPQ2d at 1396. <

In the instant case the teachings of amounts and ratios of MP and PP in the combination of references render obvious claimed amounts and ratios.

Applicant argues Figure 1 of Doron shows that at the selected data point the viable bacteria count is greater than 35%, far greater that would be acceptable for a pharmaceutical product. This point has not been by evidence. There are conditions, such as when a product is bottled for single use in a sterile amount, that even less of the parabens would be required to add some antimicrobial pressure to the composition. The point is that there is some antimicrobial activity, even at this level, motivating the use of this level in compositions.

Applicant further argues that a complete antibacterial effect must be achieved; arguing antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple exposures to bacterial; an acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product; that Fig. 1 of Doron shows that the only way to achieve complete eradication of bacteria would be for a 0.125 % MP

combined with 0.03% PP, for total parabens of 0.155% or 1.55 mg/mL. It is noted that the claims do not recite any such criteria for bacterial resistance, only the components of a composition are required, that have a pharmaceutical intended use. An antimicrobial effect may be achieved with a lower total amount of parabens, when there is, for example, a sterile solution; a refrigerated solution; or a solution containing a third preservative. Even the lowest level of 0.015 MP still demonstrates a reduction in viable bacterial counts; 0.03 and 0.06% also have reduced and nearly zero levels of viable bacteria in Figure 1. The 0.06% level MP, with 0.03 % PP (at 0.9 mg/ml total paraben), is clearly within the scope of the claimed 1.0 mg/ml total paraben amount of even claim 5. Compositions containing these levels of antimicrobial pressure on a solution would have motivated preparation of the claimed pharmaceutical compositions with total parabens in this range. However, the fact that there appears to be synergy at the higher ratios of MP/PP leads to an expectation that lower total paraben levels are likely to provide a better level of antimicrobial activity with a 9/1 MP/PP ratio.

Applicant argues Doron is evaluating various combinations of parabens to serve as antibacterial agents in the oral cavity, far different use from serving as a pharmaceutical preservative in a liquid composition as presently claimed. The data of Doron provides evidence that would motivate the use of MP and PP in the amounts and ratios of the instant claims, in compositions containing a drug, as claimed.

Applicant argues that “some” level of reduction in bacterial is not the standard for a pharmaceutical composition; the goal is substantially complete eradication of bacteria, to protect that pharmaceutical composition from bacterial contamination; that the Action

provides no scientific basis or reasoning why altering the MP/PP ratio of Doron to that recited in the present claims would be expected to yield a complete antibacterial result. Complete antibacterial result is not a requirement of the instant claims. The reduction of microbial levels would provide a benefit, in some circumstances, such as single doses of a drug that are sealed under sterile conditions, or for a solution intended to be stored in a refrigerator, or when an additional stabilizer is also present.

Applicant argues one skilled in the art upon reading Doron would have no reason to recognize that the presence of levocetirizine in the claimed composition unexpectedly allows for the use of lower concentration of parabens when the parabens are used in the claimed ratio while still achieving essentially complete eradication. This argument is not based on a claim limitation, but on an unexpected result disclosed. It has been previously noted that there is comparative data present in the specification that demonstrates the argued properties. However, the data of the specification are not commensurate in scope with the claims for any claim under examination, which utilize open language, permitting even other antimicrobial agents, some of which are specifically recited in withdrawn claims. The amounts of the tested compositions are not limited to the amounts of the claimed components in any of the claims under examination; the solutions tested all contain additional ingredients at specific amounts (as disclosed in Table 4) that are not recited in any of the claims. MPEP 716.02 (d) states:

716.02(d) Unexpected Results Commensurate in Scope With Claimed Invention [R-2]

> Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)

In the instant case, there are specific components present in the compositions tested; the claims are much broader, using open language, and not reciting all of the components in the tested compositions, let along not reciting them in the amounts they were tested. The claims permit, even withdrawn claims recite, the presence of additional antimicrobial stabilizers. The presence of such a compound would change the level at which antimicrobial activity is present. Applicant is invited to present claims limited to the components of the compositions actually tested in the amounts tested, for which the presence of levoceritizine resulted in lower levels of microbial growth. Favorable consideration would be given to claims so limited.

Applicant argues as to Routledge's incentive to lower levels of parabens due to their estrogenic activity, that fails where such lower levels are shown in Doron to be ineffective. The levels in Doron are not ineffective; they are less effective. Applicant further argues that Routledge demonstrates a long-felt need for a pharmaceutical composition that could achieve substantially complete eradication of bacteria while

minimizing the estrogenic effect of the preservatives in the composition; that it was heretofore unrecognized that such a need could be met by using such a small quantity of parabens at the 9:1 MP/PP ratio in a levocetirizine composition.

With respect to the argument that the claimed subject matter solved a problem that was long standing in the art, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

Conclusion

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-08-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4705683		1987-11-10	Dettmar	
	2	6004968		1999-11-21	Casey et al.	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090137645	A1	2009-05-28	Zhang et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Definition of Levo-Dromoran. Internet document http://www.rxlist.com/levo-dromoran-drug.htm, 1 sheet.	☐
	2	Remington the Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749.	☐

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Examiner Signature	/Timothy Thomas/	Date Considered	07/23/2010

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN	9/18/2008	TPT
PubChem	9/18/2008	TPT
PubMed	9/18/2008	TPT
WEST	9/18/2008	TPT
IDS references	9/18/2008	TPT
PALM Inventor Name Search	9/18/2008	TPT
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PubMed	2/20/2009	TPT
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STN	12/30/2009	TPT
IDS references	7/23/2010	TPT

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/TIMOTHY P THOMAS/ Examiner.Art Unit 1628	

PTO/SB/08a (01-10)
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Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5891913	A	1999-04-06	Novartis Finance Corporation	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0605203	EP	A2	1994-07-06	Senju Pharmaceutical Co., Ltd.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	Filing Date	2007-07-18
	First Named Inventor	Domenico Fanara
	Art Unit	1628
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	1	Communication of a notice of opposition against European Application No. 05758582.0 dated June 29, 2010 listing cited documents.	☐
	2	KIBBE A. H., "Handbook of Pharmaceutical Excipients", 3. edition 2000, American Pharmaceutical Association, pages 340,450; ISBN: 0-917330-96-X	☐
	3	WANG, D.Y., "Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers", Allergy 56 (2001), pages 339-343; ISSN: 0105-4538	☐
	4	Marketing authorization for ZODAC R GTT in Slovakia	☐
	5	Marketing authorization for ZODAC R SIR in Slovakia	☐
	6	Marketing authorization for ZODAC R GTT in Czech Republic	☐
	7	Marketing authorization for ZODAC R SIR in Czech Republic	☐
	8	Summary of product characteristics for ZODAC R GTT	☐
	9	Summary of product characteristics for ZODAC R SIR	☐
	10	Thomson Reuters Newport Premium: Launched Drug Forms Details	☐

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	Attorney Docket Number	06-796

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Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sandra B. Weiss/	Date (YYYY-MM-DD)	2010-08-31
Name/Print	Sandra B. Weiss	Registration Number	30814

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 605 203 A2**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : **93310464.8**

(51) Int. Cl.[5] : **A61K 31/495,** A61K 9/08

(22) Date of filing : **23.12.93**

(30) Priority : **25.12.92 JP 346031/92**

(43) Date of publication of application :
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AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

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Sevenoaks, Kent TN13 1XR (GB)

(54) **Antiallergic composition for ophthalmic or nasal use.**

(57) There is disclosed an antiallergic composition for ophthalmic or nasal use, comprising cetirizine or a salt thereof as an active ingredient. The antiallergic composition may further contain a cyclodextrin compound, as well as a surfactant and/or a water soluble polymer.

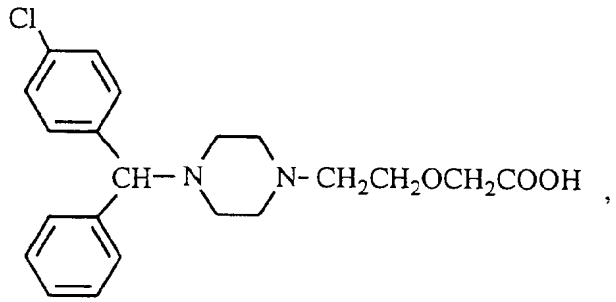
EP 0 605 203 A2

FIELD OF THE INVENTION

The present invention relates to an antiallergic composition for ophthalmic or nasal use, and more particularly, it relates to a cetirizine-containing antiallergic composi tion which is useful for the treatment of allergic diseases in the fields of ophthalmology and otorhinology.

BACKGROUND OF THE INVENTION

Cetirizine is an antiallergic compound of the formula:



the chemical name of which is [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid.

Cetirizine is well known to have an antiallergic effect, for example, by oral administration, and it is particularly useful as an antiallergic agent with significant specificity to histamine (see, e.g., JP-B 63-11353).

In the ophthalmic or nasal allergic diseases, taking the former as an example, systemic symptoms are frequently associated with ophthalmic symptoms, in which case the oral administration of an antiallergic agent is effective for their treatment. There are, however, some cases where no systemic abnormality can be detected even if marked changes are found in the eyes, and in particular, lesions found only in the eyes are not always accompanied by systemic abnormality. In such cases, topical therapy is preferred to systemic therapy because of its safety and effectiveness. This relationship between the systemic and topical symptoms holds true even in the field of otorhinology.

As an ophthalmic solution containing cetirizine, there is disclosed an anti allergic and antihistaminic composition (see, e.g., JP-A 4-9339). This composition comprises an antiallergic agent and an antihistaminic agent capable of exhibiting effective antihistaminic action when used in combination with the antiallergic agent. Cetirizine is exemplified as such an antihistaminic agent that is one of the essential ingredients of the composition.

However, no report has hitherto been made of an effect attained by the ophthalmic application of an antiallergic composition containing cetirizine as only one active ingredient.

Cetiridine has, although it is readily soluble in water, a disadvantage that a solution of cetirizine at low concentrations (below 1 w/v%) may cause the deposition of insoluble matter with the lapse of time, thereby decreasing the stability as an aqueous solution. This seems because cetirizine is one of the diphenylmethane derivatives capable of forming molecular aggregates (see, e.g., Masayuki Nakagaki (ed.), "Bussei-Butsuri (Material Science)," Nankodo, Tokyo, 1986, pp. 238-239). On the other hand, a solution of cetirizine at high concentrations where no insoluble matter will be deposited has strong irritating properties when applied in ophthalmic or nasal use, and it cannot be used as an ophthalmic or nasal solution. For this reason, there have not yet been developed an antiallergic composition for practical use containing cetirizine as the main active ingredi ent, which can be applied as an ophthalmic or nasal solution.

In general, it is difficult in most cases to prepare an ophthalmic or nasal solution with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used.

Cyclodextrin compounds are well known to have a property of taking various drugs into their central portion to form clathrate compounds of these drugs because they are cyclic sugars. Therefore, cyclodextrin compounds have hitherto been used for the purpose of making a solution of various slightly-soluble drugs or improving the stability of drugs. However, when a cyclodextrin compound is blended with a certain drug, it becomes difficult in most cases to exhibit the efficacy of the drug, and this problem is particularly serious for external preparations.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have intensively studied to develop a cetirizine-containing ophthalmic or nasal solution with satisfactory safety and stability, which can overcome the above-described disadvantages of cetirizine and which has no irritating properties to eyes and nasal mucosae. As the result, they have found that the addition of a cyclodextrin compound to an aqueous solution of cetirizine can reduce the deposition of insoluble matter even at low concentrations where molecular aggregates of cetirizine will be found in conventional cases. They have also found that an aqueous solution of cetirizine blended with a cyclodextrin compound can suppress the irritation of cetirizine to eyes or nasal mucosae even at high concentrations where such an irritation will be found in conventional cases, and that such an aqueous solution can maintain a sufficient inhibitory effect on allergic diseases of ocular or nasal portions. Further, they have found that the addition of a surfactant and/or a water-soluble polymer to an aqueous solution of cetirizine blended with a cyclodextrin compound can prevent the association of cetirizine in the aqueous solution for a long period of time. Thus, they have completed the present invention.

That is, the present invention provides an antiallergic composition for oph thalmic or nasal use, characterized in that it comprises cetirizine or a salt thereof as an active ingredient. It may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

The antiallergic composition of the present invention has almost no irritation to eyes and nasal mucosae, and it can be effectively used as a prophylactic and therapeutic agent for allergic diseases in the fields of ophthalmology and otorhinology, such as allergic conjunctivitis (e.g., conjunctival pollinosis), vernal conjunctivitis, uveitis and allergic rhinitis.

DETAILED DESCRIPTION OF THE INVENTION

The antiallergic composition of the present invention contains cetirizine or a salt thereof as an active ingredient. Examples of the salt of cetirizine are inorganic acid salts such as hydrochloride, sulfate, nitrate and phosphate; and organic acid salts such as acetate, citrate, tartrate and maleate.

The antiallergic composition of the present invention may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

Typical examples of the cyclodextrin compound are α-cyclodextrin, β-cycledextrin, γ-cyclodextrin, hydroxypropyl β-cyclodextrin, dimethyl β-cyclodextrin, maltosyl β-cyclodextrin and β-cyclodextrin sulfate. Particularly preferred are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of cetirizine. It is, however, desirable that the amount of cycle dextrin compound is 0.5 to 3.0 times, preferably 1.0 to 2.0 times, as much as the mole of cetirizine.

The surfactants are preferably of the non-ionic type. Typical examples of the non-ionic surfactant are polysorbate 80, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60. These surfactants may be used alone or in combination.

The water-soluble polymer includes cellulose derivatives, vinyl polymers and polyols. Examples of the cellulose derivative are alkylcelluloses such as methylcellulose and carboxymethylcellulose; and hydroxyalkylcelluloses such as hydroxypropylcellulose and hydroxyethylcellulose. Typical examples of the vinyl polymer are polyvinyl pyrrolidone and polyvinyl alcohol. Typical examples of the polyol are a series of macrogol 200 to 6000. These water-soluble polymers may be used alone or in combination.

The amount of surfactant or water-soluble polymer to be used may vary with its kind and the concentration of cetirizine. It is, however, desirable that the amount of surfactant is 0.01 to 1.0 time, preferably 0.05 to 0.5 times, as much as the weight of cetirizine, and the amount of water-soluble polymer is 0.01 to 10.0 times, preferably 0.02 to 5.0 times, as much as the weight of cetirizine.

The antiallergic composition of the present invention can be used within the pH range adopted for ordinary ophthalmic or nasal solutions, and it is usually adjusted to pH 4.0 to 9.0, preferably pH 5.0 to 8.0.

The antiallergic composition of the present invention may further contain any conventional additives in suitable amounts, which are used in ordinary ophthalmic or nasal solutions, e.g., preservatives such as p-hydroxybenzoates, benzalkonium chloride and chlorobutanol; chelating agents such as disodium edetate and sodium citrate; agents for making isotonic solutions, such as sodium chloride, sorbitol and glycerin; buffer agents such as phosphates, boric acid and citrates; and pH controlling agents such as hydrochloric acid, acetic acid and sodium hydroxide. The amount of additive to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic or nasal solutions.

The antiallergic composition of the present invention may further contain any therapeutic ingredients

other than cetirizine in suitable amounts, so long as the excellent advantages attained by the present invention are not deteriorated.

The antiallergic composition of the present invention may have various dosage forms which are pharmaceutically acceptable in the field of ophthalmology or otorhinology, such as solutions, suspensions, emulsions, gels and ointments. It may also be prepared, for example, in aqueous solution form and then lyophilized in powder form, which is reconstructed into an aqueous solution with distilled water at the time of use.

The concentration of cetirizine in the antiallergic composition of the present invention may vary with the administration route and allergic symptoms. It is, however, usually in the range of about 0.01 to 4.0 w/v%, preferably about 0.05 to 2.0 w/v%. For example, when used as an ophthalmic solution for adult patients, the antiallergic composi tion of the present invention is preferably administrated about 3 to 6 times a day in a dose of one to several drops at each time. When used as a nasal solution, the antiallergic corn position of the present invention is preferably atomized and inhaled about 3 to 6 times a day in a dose of 1 to 2 sprays at each time into the nasal cavity with an atomizer.

The present invention will be further illustrated by way of the following test examples and working examples, which are not to be construed to limit thereof.

Test Example 1: Eye irritation test in rabbits

(Method)

Using male Japanese white rabbits without any abnormality in the anterior parts of their eyes (4 groups of 3 rabbits), Composition C, D, E or F prepared in solution form according to the formulation shown in Table 1 was instilled into the right eyes of the rabbits in the corresponding group and only the vehicle into their left eyes 8 times a day at 1-hour intervals in a dose of one drop at each time for 5 days. For evaluation, a macroscopic examination of the anterior parts of the eyes and a corneal fluorescein staining assay were performed before the first instillation on day 1, 30 minutes after the last instillation on each of days 1, 3 and 5 of treatment, and on day 6.

TABLE 1

Ingredient (w/v%)	Compositions									
	A	B	C	D	E	F	G	H	J	K
Active ingredient										
Cetirizine hydrochloride	0.25	0.4	0.5	1.0	1.0	1.0	1.0	1.0	1.0	2.0
Additional ingredients										
α-Cyclodextrin	-	-	-	-	2.1	-	-	-	-	-
β-Cyclodextrin	-	-	-	-	-	2.45	-	-	-	4.9
γ-Cyclodextrin	-	-	-	-	-	-	2.81	-	-	-
Polyvinyl pyrrolidone	-	-	-	-	-	-	-	2.05	-	-
Chlorobutanol	-	-	-	-	-	-	-	-	0.3	-
Vehicle										
Con. glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Boric acid	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

(Results)

In the groups of rabbits topically dosed with Solution C or D, redness was observed on the palpebral conjunctiva and nictitating membrane after the last instillation on day 1. Particularly, in the group of rabbits given Solution D, their symptoms were so severe that individual blood vessels to be clearly observed on the normal palpebral conjunctiva were not definitely discernible. In addition, bulbar conjunctival vasodilation and palpebral conjunctival edema were observed. The redness as mentioned above was still observed even 16 hours after the last administration on day 1 and up to the beginning of instillation on day 2. The observation on day 3 of treatment also found redness of the conjunctiva as in the observation after the last instillation on day 1 but with an increased severity in both groups, indicating that cetirizine has a strong irritating effect on the conjunctiva. In the corneal fluorescein stain assay performed at the completion of instillation treatment, dye spots were observed over the entire corneal area in both groups, indicating that cetirizine also irritates the corneal epithelium. Judging that the rabbit eyes could not tolerate further instillation, the treatment with Solution C or D was discontinued on day 3.

In the group of rabbits given Solution E containing a cyclodextrin compound, slight redness was observed on the palpebral and bulbar conjunctivae after the last instillation on day 1, while very small amounts of discharge were found in some rabbits of the group dosed with Solution F. However, neither the redness nor the eye discharge as found on day 1 was no longer observed on and after day 3. Even in the corneal fluorescein staining assay done at the end of treatment, no change was found from the condition before the treatment and all the findings were invariably within the normal range, clearly indicating that a reduction in ocular irritation can be attained by the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride. The eyes treated with the vehicle showed no sign of irritation caused by the vehicle.

Test Example 2: Toxicity test by instillation into rabbit eyes

(Method)

Using male Japanese white rabbits in good health without any abnormality in the ophthalmological examination (2 groups of 5 rabbits), ophthalmic composition F or K prepared in solution form according to the formulation shown in Table 1 was instilled into both eyes of the rabbits in the corresponding group 8 times a day in a dose of one drop at each time for 28 days. The rabbits were examined for the general condition, food con sumption, body weight and ophthalmological items (macroscopic observation of the anterior part of eyes, observation of the corneal stained spots and fundus oculi, measurement of the intraocular tension) with the lapse of time for 28 days, after which they were subjected to urinalysis, hematological examination, blood chemical examination, autopsy, organ weight measurement, histopathological examination of the eyeball and electron microscopic examination of the cornea.

(Results)

With respect to the instillation of Solution F or K, no abnormality was found in the ophthalmological examination, general condition and other examinations.

Test Example 3: Effect on rat histamine-induced conjunctivitis

(Method)

Male Wistar rats of about 100 g in weight were injected subconjunctivally each with 50 μl of 0.1 w/v% histamine at the upper eyelid. Each of the following test ophthalmic compositions in solution form was instilled into both eyes of the rats in the corresponding group at a dose of 3 μl for each eye 40 and 20 minutes before the histamine injection. The rats were sacrificed one hour after the histamine injection. The palpebral conjunctival edema weight was measured, and the edema inhibition rate was calculated using the edema weight of the physiological saline group as the maximal response. As the test ophthalmic solutions, a solution prepared by dissolving cetirizine hydrochloride in the vehicle (2.0 w/v% conc. glycerin, 0.4 w/v% aqueous boric acid and sodium hydroxide (q.s.); pH 7.0) to have a specified final concentration (hereinafter referred to as CE ophthalmic solution), a solution prepared by dissolving equimolar amounts of cetirizine hydrochloride and either α- or β-cyclodextrin in the vehicle at a specified final concentration (hereinafter referred to as CE + α-CD ophthalmic solution and CE + β-CD ophthalmic solution, respectively) and a solution prepared by dissolving diphenhydramine hydrochloride in the vehicle (hereinafter referred to as DPH ophthalmic solution) were

used.

(Results)

In the rat model of histamine-induced conjunctivitis, cetirizine hydrochloride exhibited an inhibition rate of about 88.8% at the concentration of 0.5 w/v%, indicating that cetirizine hydrochloride has a sufficient antihistaminic effect even when topically used in the field of ophthalmology.

To compare the efficacy against histamine-induced conjunctivitis of cetirizine hydrochloride when formulated with α- or β-cyclodextrin, the cetirizine hydrochloride concentration (mM) of each ophthalmic solution which exhibited a 50% inhibition of the edema (IC_{50}) was determined using the edema rate of the physiological saline-instilled rat group as a control. The IC_{50} values obtained for the test ophthalmic solutions are shown in Table 2.

TABLE 2

Inhibitory Effect of Cetirizine on Histamine-induced Conjunctivitis

Test ophthalmic solution	IC_{50}*
CE	2.05 mM
CE + α-CD	1.97
CE + β-CD	2.76
DPH	120.0

*: The concentration of cetirizine hydrochloride which gives 50% inhibition of histamine-induced rat conjunctivitis.

As shown in Table 2, the IC_{50} value of CE ophthalmic solution was 2.05 mM (about 0.1 w/v%), indicating that cetirizine hydrochloride has an antihistaminic effect to a certain extent even below irritating concentrations. The groups of rats treated with CE or CE + α-CD ophthalmic solution gave substantially equal IC_{50} values, indicating that, in this experimental system, α-cyclodextrin does not substantially affect the efficacy of cetirizine hydrochloride. The IC_{50} value in the group of rats treated with CE + β-CD ophthalmic solution was somewhat higher than that found in the group of rats treated with CE ophthalmic solution (containing cetirizine hydrochloride alone). This fact suggests that the addition of β-cyclodextrin to a composition of cetirizine hydrochloride causes a slight decrease in the efficacy of cetirizine hydrochloride in this experimental system but the degree of decrease is so small that the efficacy of cetirizine hydrochloride can be well maintained.

Test Example 4: Eye irritation test in humans

(Method)

There is some difference in irritation response between the human and animal eyes when an ophthalmic solution is instilled thereinto. In addition, some subjective factors such as a feeling after the use should be considered in case of human eyes. It is, therefore, be concluded that ophthalmic solutions without any irritation to human eyes are more preferred, and any strongly irritative composition cannot be put to practical use. In this regard, Compositions A, B, D, E, F, G, H, J and K in solution form as shown in Table 1 were evaluated for the feeling after their use when instilled into the eyes of human subjects (I, II, III and IV). The results are shown in Table 3.

TABLE 3
Irritation to Human Eyes

Ophthalmic composition	Human subjects			
	I	II	III	IV
A	−	+	−	+
B	+	+	++	++
D	+++	+++	+++	+++
E	−	−	−	−
F	−	−	−	−
G	−	−	−	−
H	+++	++	+++	+++
J	+++	+++	+++	+++
K	−	−	−	−

−: No irritation or discomfort
+: Slight irritation
++: Moderate irritation (pain)
+++: Strong irritation

(Results)

Among the cyclodextrin-free ophthalmic compositions, i.e., Compositions A, B and D in solution form, Solution A containing 0.25 w/v% cetirizine hydrochloride gave slight irritation only to two of four subjects, indicating that the irritation of cetirizine hydrochloride to human eyes is significantly reduced at relatively low concentrations. In contrast, Solutions B and D both having a cetirizine hydrochloride concentration of 0.4 w/v% or more gave irritation to all the subjects, and in particular, Solution D was so much irritative that it has no practical use.

On the other hand, Solutions E, F, G and K each containing α-, β- or γ-cyclodextrin caused no ocular irritation, although their cetirizine hydrochloride concentrations were as high as 1 w/v%. It was, therefore, clear that the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride can reduce the irritation response of eyes to cetirizine hydrochloride and the resulting composition in solution form can be used safely as an ophthalmic solution.

Solution H containing polyvinyl pyrrolidone which caused no ocular irritation but has the property of forming complexes with many different substances, and Solution J containing chlorobutanol which has local anesthetic action and is usually used for reducing the local pain caused by an injection, gave strong ocular irritation, indicating that neither polyvinyl pyrrolidone nor chlorobutanol is suitable as an additional ingredient for the object of the present invention, that is, for suppressing ocular irritation caused by cetirizine or salts thereof.

Test Example 5: Human Nasal Mucosal Irritation Test

(Method)

It can also be said that nasal solutions without any irritation to human noses are more preferred as is true of ophthalmic solutions, and any strongly irritative composi tion cannot be put to practical use. In this regard, Solutions C, D and F were evaluated for the feeling after their use when sprayed into the noses of human subjects (I, II and III). The results are shown in Table 4.

TABLE 4
Irritation to Human Noses

Ophthalmic composition	Human subjects		
	I	II	III
C	–	+	–
D	++	+++	+++
F	–	–	+

–: No irritation or discomfort
+: Slight irritation
++: Moderate irritation (pain)
+++: Strong irritation

(Results)

When Solution C was sprayed into the nose, one of three subjects felt it irritative. When Solution D was applied, all the subjects felt strong irritation which persisted for a fairly long time, indicating that a composition containing only cetirizine hydrochloride in the vehicle is also irritative to nasal mucosae.

On the other hand, Solution F containing β-cyclodextrin gave slight irritation only to one of three subjects, although the cetiridine hydrochloride concentration thereof was the same as that of Solution D giving strong irritation. Moreover, the irritation from Solution F disappeared in a brief time. It is, therefore, clear that the addition of a cycle dextrin compound to a composition of cetirizine or a salt thereof can suppress the irritation to nasal mucosae and such a composition in solution form can be used as a nasal solution.

Test Example 6: Stability Test

(Method)

Compositions A and K shown in Table 5, and Compositions L to N and P to R shown in Table 5 were prepared in solution form. Each of the solutions was filtered through a membrane filter of 0.45 μm mesh, followed by filling into a glass ampoule. These ampoules were stored at room temperature for 6 months, during which they were subjected to macroscopic observation for the presence of insoluble matter with the lapse of time.

TABLE 5

Ingredient (w/v%)	Compositions					
	L	M	N	P	Q	R
Active ingredient						
Cetirizine hydrochloride	0.25	2.0	2.0	2.0	2.0	2.0
Additional ingredients						
β-Cyclodextrin	0.61	4.9	4.9	4.9	4.9	4.9
Hydroxypropylmethylcellulose	-	0.2	-	-	-	-
Polyvinyl alcohol	-	-	0.2	-	-	-
Polysorbate 80	-	-	-	0.2	-	-
Polyvinyl pyrrolidone	-	-	-	-	2.0	-
Macrogol 4000	-	-	-	-	-	1.0
Vehicle						
Conc. glycerin	2.0	2.0	2.0	2.0	2.0	2.0
Boric acid	0.4	0.4	0.4	0.4	0.4	0.4
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0	7.0	7.0

(Results)

The deposition of insoluble matter was observed in the ampoule of Solution A after one day from the beginning of the storage at room temperature. The ampoules of Solution K and L exhibited a slight deposition of insoluble matter after six months. In contrast, no deposition of insoluble matter was found in the ampoules of Solution M, N and P to R even after six months.

It was, therefore, found that the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride can reduce the association of cetirizine and the addition of a surfactant or a water-soluble polymer to a composition of cetirizine hydrochloride and a cyclodextrin compound can prevent the association of cetirizine, thereby making it possible to obtain an antiallergic composition in stable solution form. It was also found that a combination of cetiridine hydrochloride only with a surfactant or a water-soluble polymer cannot prevent the deposition of insoluble matter.

Example 1

An ophthalmic composition was prepared in lyophilized powder form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.5 g
Boric acid	5.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride and boric acid are dissolved in about 80 ml of distilled water, and the solution is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml. The solution thus obtained is sterilized by filtration, and dispensed in 2 ml portions, which are then lyophilized, resulting in an ophthalmic composition. At the time of use, the ophthal mic composition is dissolved in 5 ml of distilled water for injection.

Example 2

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	2.1 g
Boric acid	2.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, α-cyclodextrin and boric acid are dissolved in about 80 ml of distilled water, and the solution is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 3

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	2.1 g
Hydroxypropylmethylcellulose	0.1 g
Boric acid	2.0 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, α-cyclodextrin and boric acid are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 4

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	2.0 g
β-cyclodextrin	4.93 g
Hydroxypropylmethylcellulose	0.2 g
Boric acid	2.5 g
Disodium edetate	0.02 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, β-cyclodextrin, boric acid and disodium edetate are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 5

An ophthalmic composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.3 g
α-cyclodextrin	0.8 g
Polyvinyl alcohol	0.2 g
Sodium acetate	0.1 g
Propylene glycol	2.0 g
Methylparaben	0.2 g
Propylparaben	0.1 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which polyvinyl alcohol, methylparaben and propylparaben are dissolved. After cooling to room temperature, cetirizine hydrochloride, α-cyclodextrin, sodium acetate and propylene glycol are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in an ophthalmic composition.

Example 6

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
β-cyclodextrin	2.47 g
Hydroxypropylmethylcellulose	0.1 g
Boric acid	1.25 g
Disodium edetate	0.01 g
Sodium hydroxide	q.s.
Distilled water	ad 100 ml

About 80 ml of distilled water is heated to about 90°C, in which hydroxy-propylmethylcellulose is uniformly dispersed. The dispersion is stirred in an ice-water bath so that the hydroxypropylmethylcellulose is dissolved. After warming to room temperature, cetirizine hydrochloride, β-cyclodextrin, boric acid and disodium edetate are dissolved in the solution. The solution thus obtained is adjusted to pH 7.0 by the addition of aqueous sodium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 7

A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	0.5 g
Hydroxypropyl β-cyclodextrin	1.6 g
Polyvinyl pyrrolidone	1.0 g
Macrogol 4000	1.0 g
Potassium dihydrogenphosphate	0.1 g
Mannitol	5.1 g
Benzalkonium chloride	0.005 g
Potassium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, hydroxypropyl β-cyclodextrin, polyvinyl pyrrolidone, macrogol 4000, potassium dihydrogenphosphate, mannitol and benzalkonium chloride are dissolved in about 80 ml of distilled water. The solution thus obtained is adjusted to pH 7.5 by the addition of aqueous potassium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Example 8

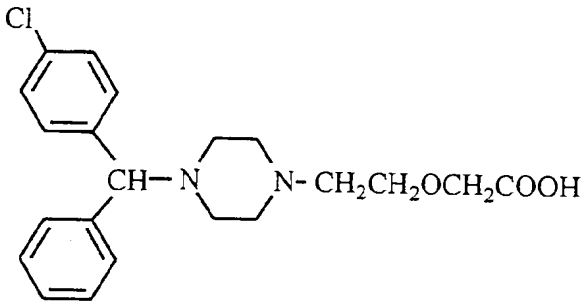
A nasal composition was prepared in solution form according to the following formulation:

Ingredient	Amount
Cetirizine hydrochloride	1.0 g
α-cyclodextrin	1.0 g
β-cyclodextrin	1.5 g
Sodium citrate	0.05 g
Sodium chloride	0.9 g
Potassium hydroxide	q.s.
Distilled water	ad 100 ml

Cetirizine hydrochloride, α-cyclodextrin, β-cyclodextrin, sodium citrate and sodium chloride are dissolved in about 80 ml of distilled water. The solution thus obtained is adjusted to pH 6.5 by the addition of aqueous potassium hydroxide, to which distilled water is further added to have a total volume of 100 ml, resulting in a nasal composition.

Claims

1. An antiallergic composition for ophthalmic or nasal use, comprising a compound of the formula:



or a salt thereof as an active ingredient.

2. An antiallergic composition according to claim 1, further comprising a cyclodextrin compound.

3. An antiallergic composition according to claim 2, wherein said cyclode xtrin compound is selected from the group consisting of α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin.

4. An antiallergic composition according to claim 2, further comprising a surfactant.

5. An antiallergic composition according to claim 2 or 4, further comprising water-soluble polymer.

6. An antiallergic composition according to claim 4, wherein said surfactant is of the non-ionic type.

7. An antiallergic composition according to claim 6, wherein said non-ionic surfactant is selected from the group consisting of polysorbate 80 and polyoxyethylene hydrogenated castor oil.

8. An antiallergic composition according to claim 5, wherein said water soluble polymer is selected from cellulose derivatives, vinyl polymers and polyols.

9. An antiallergic composition according to claim 8, wherein said cellulose derivatives include alkylcelluloses and hydroxyalkylcelluloses.

10. An antiallergic composition according to claim 9, wherein said alkyl celluloses include methylcellulose and

carboxymethylcellulose.

11. An antiallergic composition according to claim 9, wherein said hydroxy-alkylcelluloses include hydroxy-propylmethylcellulose and hydroxyethylcellulose.

12. An antiallergic composition according to claim 8, wherein said vinyl polymers include polyvinyl alcohol and polyvinyl pyrrolidone.

13. An antiallergic composition according to claim 8, wherein said polyols include macrogol 4000.

14. Use of a compound or salt thereof, as defined in claim 1, for the manufacture of an antiallergic medicament for ophthalmic or nasal use.

Electronic Acknowledgement Receipt

EFS ID:	8325942
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	03-SEP-2010
Filing Date:	18-JUL-2007
Time Stamp:	16:26:24
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06_796_Transmittal.pdf	151316 3f612341f0f5bb430f37835c0548581ad32156b2	no	1

Warnings:	
Information:	

2		06_796_IDS.pdf	864136 5c1885ec85c840e07ff09c6fe9c5a771e5463c4b	yes	5

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Information Disclosure Statement (IDS) Filed (SB/08)	1	3
Transmittal Letter	4	5

Warnings:					
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3	Foreign Reference	06_796_EP0605203referece.pdf	603193 4f821c16b37ed880bde2a81126559e9d880c7b0b	no	14
Warnings:					
Information:					
4	NPL Documents	06_796_OppositionNotice.pdf	1406203 34bac85eb7b2c1de30961c3d839b90f3d23ba2b7	no	18
Warnings:					
Information:					
5	NPL Documents	06_796_KibbeReference.pdf	440502 30c0343e6b86e4c44c844d67a8122631972a7209	no	4
Warnings:					
Information:					
6	NPL Documents	06_796_WangReference.pdf	632773 c55ed363135b8ea0ecef59d9716e608817ff8d8a	no	6
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7	NPL Documents	06_796_MarketingZODACGTT_Slovakia.pdf	968117 35a502e4e17999adc6c2cc0d66e7fb5c19dd3473	no	11
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Warnings:					
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13	NPL Documents	06_796_ThomsonReuters.pdf	43834 e24091346fb8014d89e276a5b81936f6ea714809	no	1
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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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PTO/SB/21 (08-08)
Approved for use through 09/30/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/599451
Filing Date	July 18, 2007
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
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- ☐ Reply to Missing Parts/ Incomplete Application
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- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):
  11 cited references

Remarks

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Sandra B. Weiss/		
Printed name	Sandra B. Weiss		
Date	August 31, 2010	Reg. No.	30814

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Signature	/Sandra B. Weiss/		
Typed or printed name	Sandra B. Weiss	Date	August 31, 2010

AFTER FINAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of: Fanara et al.	
Serial No. 10/599,451	Examiner: Timothy P. Thomas
Filing Date: September 28, 2006	Art Unit: 1614
For: Pharmaceutical Composition of Piperazine Derivatives	Confirmation No.: 9142

RESPONSE TO THE OFFICE ACTION MAILED JULY 27, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office Action mailed July 27, 2010. The Office is authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on September 21, 2010.

Date: September 21, 2010

/Sandra B. Weiss/
Sandra B. Weiss

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) ~~at least one preservative, wherein the preservative is~~ a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, wherein said composition is substantially free of bacteria.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 and 1 mg/ml of the composition.

6. (Canceled)

7. (Canceled)

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously Presented) The liquid pharmaceutical composition according to claim 13, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn-previously presented) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

27. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate is present in an amount of more than 0 and less than 1 mg/ml of the composition.

REMARKS

Status of the Claims

Claim 1 is amended herein to recite that the liquid pharmaceutical composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, and that the composition is substantially free of bacteria. This amendment is intended to indicate that no operative quantities of any other preservative components or antibiotic ingredients are present in the composition. Previously withdrawn claims 7-9, which recited the presence of other preservative components, are hereby cancelled. Previously withdrawn claim 10, which recited that the active ingredient is cetirizene, is hereby cancelled.

If the present amendments are found to place claims 1, 2, 5, 12, 14, 15, 17 and 27 in condition for allowance, then the Examiner is authorized to cancel without prejudice previously withdrawn method claims 18-26 by Examiner's amendment, Applicants expressly reserving the right to pursue the subject matter of those claims in one or more continuing or divisional applications.

Supplemental IDS

The corresponding European application is the subject of an Opposition proceeding commenced June 29, 2010. On September 3, 2010, Applicants herein submitted an Information Disclosure Statement citing the references that had been cited in that Opposition. The Opponent had not included a complete copy of reference D3. Applicants herein have since obtained a complete copy, and cited it to the EPO. That more complete copy of the previously cited reference is now submitted herewith with a Supplemental Information Disclosure Statement. As this is simply a more complete copy of a reference that was submitted within the three-month period after being cited in a foreign proceeding, it is respectfully submitted that no additional fee is required for submitting that complete copy now. In any event, the Office is authorized to

charge to Deposit Account 13-2490 any fee that may be deemed to be owed in connection with the submission of this Supplemental IDS.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) and Doron et al. P2001 Int'l J. Antimicrobial Agents 18: 575-578) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19). In light of the foregoing amendments, this rejection is respectfully traversed.

The present invention is based on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6), thereby enabling use of lesser amounts of preservatives, such as parabens. Thus, applicants herein have made the unexpected finding that a pharmaceutical composition comprising such an active substance and a reduced amount of preservatives is stable (i.e., resistant to microbial contamination) for a long period of time. (Id., lines 11-15) Accordingly, independent claim 1 as amended is directed to a composition comprising levocetirizine and a preservative mixture consisting essentially of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 by weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition. That such a low amount of parabens without additional preservatives in a liquid pharmaceutical composition comprising levocetirizine would be sufficiently antimicrobial was unpredictable from the prior art.

It is significant that the present invention is directed to a liquid *pharmaceutical* composition. Depending on the packaging of the composition and the intended pharmaceutical use, such compositions can come into repeated contact with dosing implements that can introduce bacteria. For example, solutions for oral consumption can be packaged in a bottle that can come in repeated contact with a dosing spoon; solutions of eye drops or nose drops will come into repeated contact with a dropper device. Such spoons and droppers can be carriers of bacteria that can then be transferred to the pharmaceutical composition. Thus, it is necessary that the liquid pharmaceutical composition remain free of bacterial contaminants not only up to the time of initial use, but also after the seal on the packaging is opened. Further, such an opened

package must remain free of bacteria over the useful shelf life of the product. (Specification, page 1, line 27 – page 2, line 3) It has been surprisingly found that the composition of the present invention can accomplish this result due to the heretofore unappreciated preservative nature of the levocetirizine itself. This result is even more surprising when one considers that other liquid pharmaceutical compositions use significantly greater amounts of preservatives, as shown by the references submitted with the response of May 4, 2010. Contrary to the Examiner, this argument does not "ignore the teachings of the record." (Action, page 4, line 1) These additional references add to the record, and provide evidence as to what those skilled in the art of pharmaceutical compositions understand to be necessary levels of preservatives.

The Doron reference teaches ratios of MP:PP approaching those recited in the present claims, but at much higher concentration levels than are used in the present invention. Doron relates to an oral rinse solution intended to destroy streptococcus bacteria on oral surfaces. It does not relate to the issues of repeated contact of a dosing implement that can introduce bacteria to the solution, nor does it address the issue of planktonic (non-immobilized) bacteria. The findings of Doron as to preservative levels and ratios effective in an oral rinse against immobilized bacteria do not teach one skilled in the art about preservative levels and ratios effective to maintain an opened pharmaceutical composition free of planktonic bacteria, where that pharmaceutical composition may be subject to repeated contact with dosing implements.

Doron does not teach or suggest that the presently claimed upper limit of 1.125 mg/g total parbens can be effective against planktonic bacteria. It is the claim as a whole that must be considered in the obviousness determination, not whether individual limitations are suggested in the prior art; it is meaningless to consider only the MP:PP ratio as taught in Doron without also considering the overall concentration of preservatives. And the Action recognizes at page 6, lines 1-7 that the data in Fig. 2 of Doron, while showing the same trend for planktonic bacteria as the data in Fig. 1 shows for immobilized bacteria, does not show the same level of anti-bacterial activity as the claimed composition. The Action refers to the data point in Fig. 2 of Doron using 0.125% MP and 0.03% PP, for a total parabens content of 0.155%, or 1.55 mg/ml. This is 37% greater than the maximum of 1.125 mg/ml of the present claims. The fact that the data is Figure 2 demonstrates zero planktonic bacteria growth at the highest MP/PP ratio does not suggest that the substantially lower amount of parabens in the claimed composition is obvious. Rather, that data in Fig. 2 of Doron et al. teaches away form the claimed invention by teaching that greater

amounts of parabens are necessary to achieve zero bacteria growth for a liquid pharmaceutical composition.

Guillard 2 was a study to determine if the effects of MP and PP are synergistic. In these studies, the amount of MP was either 0.12 or 0.14 w/v%, and the amount of PP was either 0.012 or 0.140 w/v%. Thus, the lowest amount of total preservative used was 0.12 + 0.012 = 0.132 w/v%; assuming 1 g/ml of solution, this corresponds to a total *minimum* preservative level of 1.320 mg/ml. This is 17% greater than the 1.125 mg/g *maximum* preservative level recited in the present claims. Moreover, Guillard found that this lowest dosage level did not destroy E.coli, as shown in Fig. 5 at the curve for "L methyl + L propyl." Yet the present invention has shown that a *maximum* dosage level significantly lower than Guillard's *lowest* (and ineffective) dosage level is effective as a preservative for a levocetirizine solution, due to the surprising and heretofore unappreciated preservative effects of the levocetirizne itself.

The statement spanning pages 4-5 of the Action that "With respect to the *amounts*, the use of lower amounts of a 9/1 ratio is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guilland 2" is respectfully traversed. The largest antimicrobial activity achieved by Doron is at an amount of parabens 37% greater than the maximum amount presently claimed; and the minimum amount of parabens used by Guilland 2 is still 17% greater than the maximum amount presently claimed. These references, taken alone or in combination, do not teach or suggest the amount of parabens of independent claim 1.

Nor do these references suggest that the presence of levocetirizene would contribute a preservative effect. The Action states at page 5, "This [greater microbial efficiency at higher ratios of MP/PP] permits less of the combination to be use to still achieve the *same* of level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also." (emphasis added) Even if this unsupported statement were true, the invention herein does not lie in achieving the *same* level of antimicrobial activity, the invention lies in achieving *greater* levels of antimicrobial activity at the recited concentration and MP;PP ratios, due to the presence in the solution of a particular drug, namely, levocetirizene.

To the extent that the Action relies on the showing of "some antimicrobial activity," (Action page 7) the claims have been amended to recite that the pharmaceutical compositions of the present invention are "substantially free of bacteria," such that Doron and Guillard 2 which establish "some" antimicrobial activity do not render the claimed invention obvious.

The Action states at page 8 that there is no limitation in the claim regarding resistance to bacteria. Claim 1 has been amended to recite that the claimed composition is substantially free of bacteria.

The Action states at pages 9-10 that the claims are written in an open form that allows the presence of other antimicrobial agents. Claim 1 has been amended so that the only preservative components are methyl paraben and propyl paraben, in the ratio and total amounts recited in the claim.

As all bases of rejection have been addressed by the foregoing amendments, a Notice of Allowance is requested.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: September 21, 2010

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	8452475
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	21-SEP-2010
Filing Date:	18-JUL-2007
Time Stamp:	12:30:15
Application Type:	U.S. National Stage under 35 USC 371

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06_796_Transmittal2.pdf	150671 9e2a1bf55adc110987c814b390bc7b9833527621	no	1

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2		06_796_Supplemental_IDS.pdf	997611 f461d0ff0463db9bf27ac02d77cddc359eef7599	yes	4

Multipart Description/PDF files in .zip description		
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Miscellaneous Incoming Letter	3	4

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Document Description	**Start**	**End**
Amendment After Final	1	1
Claims	2	4
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TRANSMITTAL FORM

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Filing Date	July 18, 2007
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

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- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
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Firm Name	McDonnell Boehnen Hulbert & Berghoff LLP		
Signature	/Sandra B. Weiss/		
Printed name	Sandra B. Weiss		
Date	September 21, 2010	Reg. No.	30814

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Typed or printed name	Sandra B. Weiss	Date	September 21, 2010

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Application Number	10599451
Filing Date	2007-07-18
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2007-07-18
	First Named Inventor	Domenico Fanara
	Art Unit	1628
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	1	KIBBE, Arthur H., "Handbook of Pharmaceutical Excipients", Third Edition 2000, American Pharmaceutical Association, pages 340-343, 450-453.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	10599451
	Filing Date	2007-07-18
	First Named Inventor	Domenico Fanara
	Art Unit	1628
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sandra B. Weiss/	Date (YYYY-MM-DD)	2010-09-21
Name/Print	Sandra B. Weiss	Registration Number	30814

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/21/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA ANTHONY/

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 09/27/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1628	
MAIL DATE	**DELIVERY MODE**
09/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/599,451	**Applicant(s)** FANARA ET AL.	
	Examiner TIMOTHY P. THOMAS	**Art Unit** 1628	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 September 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,5,12,17 and 27*.
   Claim(s) withdrawn from consideration: *6-10,14,15 and 18-26*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 9/3/2010; 9/21/2010
13. ☒ Other: See Continuation Sheet.

/Timothy P Thomas/
Examiner, Art Unit 1628

Continuation of 3. NOTE: The amended claim limitations of claim 1 are both new limitations that require further consideration and search.

Continuation of 11. does NOT place the application in condition for allowance because:

Claims 1-2, 5, 12, 17 and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over DeLongueville et al. (WO 02/47689 A2; cited in a prior Office Action); Gilliland et al. (Gilliland 1) ("The bactericidal activity of a methyl and propyl parabens combination: isothermal and non-isothermal studies"; 1992; Journal of Applied Bacteriology; 72: 252-257; cited in a prior Office Action); Gilliland et al. (Gilliland 2) ("Kinetic evaluation of claimed synergistic paraben combinations using a factorial design"; 1992; Journal of Applied Bacteriology; 72: 258-261; cited in a prior Office Action); and Doron et al. ("Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus"; 2001 International Journal of Antimicrobial Agents; 18: 575-578; cited in a prior Office Action); in view of Routledge et al. ("Some Alkyl Hydroxy Benzoate Preservatives (Parabens) Are Estrogenic"; 1998; Toxicology and Applied Pharmacology; 153: 12-19; cited in a prior Office Action).

The rejection is maintained for the reasons of record.

Applicant argues that unexpected findings that a pharmaceutical composition comprising levocertizine and a reduced amounts of preservatives, such as parabens is stable, i.e., resistant to microbial contamination, for a long period of time; that the low amount of parabens without additional preservatives in a liquid pharmaceutical composition comprising levocetirizine would be sufficinetly antimicrobial was unpredictable from the prior art. The rejection of record establishes an expectation of antimicrobial activity when the elected components are present. The record indicates that some results for an unexpected result have been disclosed; however, those results are not commensurate in scope with the claims (see discussion in Final Office Action, mailed 7/27/2010).

Applicant further argues surprising results, that levocetirizine itself has the property of a preservative. Even so, preservative activity is expected from the composition, based on the added parabens, known to be preservatives. The demonstration of unexpected results is not commensurate in scope with the instant claims.

Applicant argues that Doron teaches ratios of MP:PP approaching those recited in the present claims, but at a much higher concentration levels than are used in the present invention; that Doron relates to an oral rinse solution intended to destroy streptococcus bacteria on oral surfaces; that it does not relate to the issues of repeated contact of a dosing implement that can introduce bacteria to the solution, nor does it address the issue of planktonic bacteria. The claims do not recited limitations associated with these arguments; only a liquid pharmaceutical composition containing specific ingredients, with some amount and ratio limitations. The record indicates reduced bacterial counts have been demonstrated, even at 0.9 mg/ml total paraben.

Applicant argues that Doron does not teach or suggest that the presently claimed upper limit of 1.125 mg/g total paraben can be effective against planktonic bacteria. Planktonic bacteria is not a limitation recited in the claims; indeed 0.9 mg/ml total paraben has been established as having reduced bacterial counts.

Applicant argues that the data of Figure 2 require 1.55 mg/ml (0.155%) total parabens to achieve zero planktonic bacteria growth; therefore, this data teaches away from the claimed invention. This is not persuasive; lower levels of total parabens, including the value of 0.9, have been established reducing bacterial counts.

Applicant argues that Guillard 2 used the lowest total paraben amount of 0.132 w/v (about 1.32 mg/ml) which is 17% greater than the recited maximum; that the present invention has shown that a maximum dosage level significantly lower than Guillard's lowest and ineffective dosage level is effective as a preservative for levocetirizine solution ,due to the surprising and heretofore unappreciated preservative effects of the levocetirizine itself. It has been acknowledged that there is data present in the specification demonstrating unexpected results over the comparative solutions. However, for the reasons discussed on the record, this data is not commensurate in scope with the instant claims. Doron establishes 0.9 mg/ml total parabens has activity in reducing bacterial counts, rendering this amount obvious in the instant claimed formulations.

Applicant argues that the obviousness that the use of lower amounts of a 9/1 ratio is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guilland 2 would employ amounts of parabens 17-37% greater than the maximum amount presently claimed; that these references do not teach or suggest the amount of parabens required by claim 1. This is not persuasive. 0.9 mg/ml is established to be an amount that reduces bacterial counts, motivating the use of amounts in this range, especially when a 9/1 ratio is clearly synergistic.

Applicant's arguments with respect to amended claim limitations are not relevant, because the claims have not been entered..

Continuation of 13. Other: The 9/21/2010 IDS has not been considered; there no statement required under 37 CFR 1.97 e (1) or (2) and there is no fee, both of which are required after final; see MPEP 609.04(b) (III), which states that both (A) and (B) are required after a final Office Action.

DO NOT ENTER: /TPT/
09/23/2010

AFTER FINAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO THE OFFICE ACTION MAILED JULY 27, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office Action mailed July 27, 2010. The Office is authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on September 21, 2010.

Date: September 21, 2010

/Sandra B. Weiss/
Sandra B. Weiss

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	10599451
Filing Date	2007-07-18
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5891913	A	1999-04-06	Novartis Finance Corporation	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0605203	EP	A2	1994-07-06	Senju Pharmaceutical Co., Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

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	First Named Inventor	Domenico Fanara
	Art Unit	1628
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

	1	Communication of a notice of opposition against European Application No. 05758582.0 dated June 29, 2010 listing cited documents.	☐
	2	KIBBE A. H., "Handbook of Pharmaceutical Excipients", 3. edition 2000, American Pharmaceutical Association, pages 340,450; ISBN: 0-917330-96-X	☐
	3	WANG, D.Y., "Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers", Allergy 56 (2001), pages 339-343; ISSN: 0105-4538	☐
	4	Marketing authorization for ZODAC R GTT in Slovakia	☐
	5	Marketing authorization for ZODAC R SIR in Slovakia	☐
	6	Marketing authorization for ZODAC R GTT in Czech Republic	☐
	7	Marketing authorization for ZODAC R SIR in Czech Republic	☐
	8	Summary of product characteristics for ZODAC R GTT	☐
	9	Summary of product characteristics for ZODAC R SIR	☐
	10	Thomson Reuters Newport Premium: Launched Drug Forms Details	☐

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EXAMINER SIGNATURE			
Examiner Signature	/Timothy Thomas/	Date Considered	09/23/2010

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	10599451
Filing Date	2007-07-18
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

	1	KIBBE, Arthur H., "Handbook of Pharmaceutical Excipients", Third Edition 2000, American Pharmaceutical Association, pages 340-343, 450-453.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Timothy Thomas/	Date Considered	09/23/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	10599451	Filing Date	2007-07-18	Docket Number (if applicable)	06-796	Art Unit	1628
First Named Inventor	Domenico Fanara			Examiner Name	Timothy P. Thomas		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☒ Affidavit(s)/ Declaration(s)
- ☒ Other
  Copy of one (1) cited reference.

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☒ Other
Petition for One (1) Month Extension of Time

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 132490

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature
☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Sandra B. Weiss/	Date (YYYY-MM-DD)	2010-11-29
Name	Sandra B. Weiss	Registration Number	30814

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1628
Filing Date: July 18, 2007	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

AMENDMENT IN RESPONSE TO THE OFFICE ACTION MAILED JULY 27, 2010, SUBMITTED WITH REQUEST FOR CONTINUED EXAMINATION AND REQUEST FOR ONE-MONTH EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please consider the following amendments and remarks in response to the Office Action mailed July 27, 2010, and the Advisory Action mailed September 27, 2010. Submitted herewith are a Request for Continued Examination (RCE), and a request for a one-month extension of time. The Office is authorized to charge any fees necessary to maintain the pendency of this application to Deposit Account, No. 13-2490.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

CERTIFICATE OF TRANSMISSION (37 C.F.R. 1.8)
I hereby certify that this correspondence is being transmitted to the USPTO via the USPTO EFS on November 29, 2010.

Date: November 29, 2010

/Sandra B. Weiss/
Sandra B. Weiss

Amendments to the Claims

The following listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) ~~at least one preservative, wherein the preservative is~~ a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, wherein said composition is substantially free of bacteria.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 and 1 mg/ml of the composition.

6. (Canceled)

7. (Canceled)

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Currently amended) The liquid pharmaceutical composition according to claim ~~13~~ 1, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Withdrawn-previously presented) A method of making a liquid pharmaceutical composition according to claim 1 comprising combining,

a) cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, and

b) parahydroxybenzoate ester in an amount of more than 0 and less than 1 mg/ml of the composition.

19. (Withdrawn) The method according to claim 18, comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

20. (Withdrawn) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Withdrawn) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Withdrawn) In a method of treating a patient with cetirizine, levocetirizine, efletirizine, or a pharmaceutically acceptable salt of cetirizine, levocetirizine, or efletirizine, the improvement comprising administering a liquid composition according to claim 1.

23. (Withdrawn) The method according to claim 23, wherein the liquid composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

24. (Withdrawn) The method according to claim 23, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

25. (Withdrawn) The method according to claim 24, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

26. (Withdrawn) The method according to claim 25, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1 by weight.

27. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate is present in an amount of more than 0 and less than 1 mg/ml of the composition.

28. (New) The composition of claim 1, wherein the composition is in the form of an oral solution comprising 0.50 mg/ml levocetirizine dihydrochloride, 0.675 mg/ml methyl p-hydroxybenzoate, and 0.075 mg/ml propyl p-hydroxybenzoate.

29. (New) The composition of claim 1, wherein the composition is in the form of a solution of oral drops comprising 5.0 mg/ml levocetirizine dihydrochloride, 0.3375 mg/ml methyl p-hydroxybenzoate, and 0.0375 mg/ml propyl p-hydroxybenzoate.

REMARKS

Status of the Claims

Claim 1 is amended herein to recite that the liquid pharmaceutical composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, and that the composition is substantially free of bacteria. This amendment is intended to indicate that no operative quantities of any other preservative components or antibiotic ingredients are present in the composition. Previously withdrawn claims 7-9, which recited the presence of other preservative components, are hereby cancelled. Previously withdrawn claim 10, which recited that the active ingredient is cetirizene, is hereby cancelled.

Claim 14 is amended to correct the dependency.

New claim 28 is directed to the embodiment set forth at page 12, Table 16 of the application as originally filed.

New claim 29 is directed to the embodiment set forth at page 13, Table 18 of the application as originally filed.

If the present amendments are found to place claims 1, 2, 5, 12, 14, 15, 17 and 27 in condition for allowance, then the Examiner is authorized to cancel without prejudice previously withdrawn method claims 18-26 by Examiner's amendment. Applicants expressly reserving the right to pursue the subject matter of those claims in one or more continuing or divisional applications.

Submitted herewith in support of this application is the Declaration of Domenico Fanara Under 37 CFR 1.132. Mr. Fanara is the first-named inventor of the present application.

New Claims

New claims 28 and 29 recite specific levels of levocetirizine, methyl paraben, and propyl paraben. Submitted herewith is experimental evidence demonstrating the unexpected results

achieved by these compositions, namely, that the compositions remain substantially free of bacteria while maintaining levels of parabens substantially below the levels taught by the prior art as being necessary (Decl. ¶¶ 8,9). It is respectfully submitted that these claims are not obvious over the art of record.

Supplemental IDS

Submitted with the Supplemental IDS is a more complete copy of one of the references previously submitted on September 3, 2010.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992, *J. Appl. Bacteriol.*, 72: 252-57); and Gilliland 2 (1992, *J. Appl. Bacteriol.*, 72:258-61) and Doron et al. P2001 *Int'l J. Antimicrobial Agents* 18: 575-578) in view of Routledge (1998; *Toxicol. Appl. Pharmacol.*; 153:12-19). In light of the foregoing amendments and arguments presented below, this rejection is respectfully traversed.

The presently claimed invention is based, at least in part, on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6), thereby enabling use of lesser amounts of preservatives such as parabens. Independent claim 1 as amended is directed to a composition comprising levocetirizine and a preservative mixture consisting essentially of methyl parahydroxybenzoate (methyl paraben, hereinafter "MP") and propyl parahydroxybenzoate (propyl paraben, hereinafter "PP") in a ratio of 9/1 by weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition. Surprisingly, levocetirizine has antimicrobial properties (*Id.* and Decl. ¶ 7), such that the presence of levocetirizine in the composition in combination with the 9:1 MP/PP ratio, allows for the use of low levels of total parabens and essentially no other preservatives, while maintaining the liquid composition substantially free of bacteria. This is particularly important for a liquid pharmaceutical composition, which is susceptible to microbial contamination when the seal on the packaging is opened and the contents are subject to repeated contact with dosing implements. (Specification, page 1, line 27 – page 2, line 3; Decl. ¶ 4)

This result is even more surprising when one considers that other liquid pharmaceutical compositions use significantly greater amounts of preservatives, typically about 2 mg/ml of total parabens, as shown by the references submitted with the response of May 4, 2010, Decl ¶ 5). This argument does not "ignore the teachings of the record" (July 27, 2010 Office Action, page 4, line 1). These additional references provide evidence as to what those skilled in the pharmaceutical arts understand to be necessary levels of preservatives in liquid pharmaceutical compositions. Further, these references are more relevant than the references cited by the Office, because these references each disclose pharmaceutical compositions, while the Gilliland 1, Gilliland 2, and Doron references cited by the Office do not disclose pharmaceutical compositions.

It is respectfully submitted that the present rejection is based on the selection of different parameters out of different references, suggesting without support that it would have been obvious that the combination of these different parameters would have resulted in a liquid pharmaceutical composition substantially free of bacteria. DeLonguevlle, commonly owned by the assignee herein, teaches compositions of cetrizine with methyl-and propyl paraben but does not teach such compositions with levocetirizine and teaches nothing about the ratios and amounts of methyl and propyl paraben. (Decl. ¶11) None of the other references relates to levocetirizine compositions, and none suggests that it is possible to achieve a liquid levocetirizne pharmaceutical composition that is substantially free of bacteria with the preservative concentration recited in the present claims.

Doron describes a study "as a step in optimizing the concentration of parabens as antibacterial agents in the oral cavity" (Doron at 575-576). Doron teaches one composition wherein MP/PP is 4/1 and overall parabens is 1.55 mg/ml, and another composition wherein MP/PP is 8.33/1 and overall parabens is 2.8 mg/ml. These compositions respectively have parabens levels 37% and 248% greater than the maximum parabens level of the present claims. This reference does not suggest that the total parabens in a liquid pharmaceutical composition could be reduced to 1.125 mg/ml or less, and suggests nothing about the effect of the presence of levocetirizine. In fact, this reference teaches away from the present invention by teaching that a higher MP/PP ratio requires greater level of total parabens. (Decl ¶ 14) It is improper to rely on

Doron for its teaching of an MP/PP ratio without also recognizing its teaching regarding total paraben concentration, because the reference must be considered for *all* that it teaches.

With respect to Gilliland 2, the Office cites the following compositions:

MP/PP	Conc., mg/ml
8.6/1	1.34
10/1	1.32
10/1	1.54
11.7/1	1.52

The *minimum* preservative level of 1.320 mg/ml is 17% greater than the 1.125 mg/g *maximum* preservative level recited in the present claims. Moreover, this composition did *not* destroy E.coli, as shown in Fig. 5 at the curve for "L methyl + L propyl." The fact that these compositions bracket the claimed MP/PP ratio of 9/1 does not make the claims as a whole obvious where the claim is based on the combination of the ratio, the concentration level, the presence of levocetirizine, the absence of other preservatives, and the fact that the composition remains substantially free of bacteria.

The statement that "With respect to the *amounts*, the use of lower amounts of a 9/1 ratio is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guilland 2" (July 27, 2010 Action, pp.4-5) is respectfully traversed. The largest antimicrobial activity achieved by Doron is with an amount of parabens 37% greater than the maximum amount presently claimed; and the minimum amount of parabens used by Guilland 2 is still 17% greater than the maximum amount presently claimed. These references, taken alone or in combination, do not teach or suggest the amount of parabens in a pharmaceutical composition as recited in independent claim 1.

The July 27, 2010 Action states at page 5, "This [greater microbial efficiency at higher ratios of MP/PP] permits less of the combination to be used to still achieve the *same* level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also." (emphasis added) Even if this unsupported statement were true, the invention herein does not lie in achieving the *same* level of antimicrobial activity, the invention lies in achieving *greater* levels of antimicrobial activity at the recited concentration and MP/PP

ratios due to the presence in the solution of a particular drug, namely, levocetirizine. Thus, taking the Examiner's assertion as true substantiates the non-obviousness of the presently claimed compositions.

The July 27, 2010 Action states at page 8 that there is no limitation in the claim regarding resistance to bacteria. Claim 1 has been amended to recite that the claimed composition is substantially free of bacteria. Thus, even if Doron and Guillard 2 suggest "some" antimicrobial activity, they do not render the claimed invention obvious because they do not suggest that the compositions disclosed therein will remain substantially free of bacteria. (Decl ¶¶12-15)

The Action states at pages 9-10 that the claims are written in an open form that allows the presence of other antimicrobial agents. Claim 1 has been amended so that the preservative mixture consists essentially of methyl paraben and propyl paraben, thereby excluding functionally significant amounts of other preservatives. Other claims reciting the presence of other preservatives have been cancelled.

It is respectfully submitted that in view of the foregoing claim amendments, the claims are now commensurate in scope with the evidence of unexpected results, as acknowledged by the Office.

As all bases of rejection have been addressed by the foregoing amendments, a Notice of Allowance is requested.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: November 29, 2010

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

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Chicago, IL 60606

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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First Named Inventor	Domenico Fanara
Art Unit	1628
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Attorney Docket Number	06-796

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10599451
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	Attorney Docket Number	06-796

	1	KIBBE, Arthur H., "Handbook of Pharmaceutical Excipients", Third Edition 2000, American Pharmaceutical Association, pages 340-343, 450-453.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1628
	Examiner Name	Timothy P. Thomas
	Attorney Docket Number	06-796

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Sandra B. Weiss/	Date (YYYY-MM-DD)	2010-11-29
Name/Print	Sandra B. Weiss	Registration Number	30814

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/22 (11-08)
Approved for use through 12/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2009 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 06-796
Application Number 10/599,451	Filed July 18, 2007
For Pharmaceutical Composition of Piperazine Derivatives	
Art Unit 1628	Examiner Timothy P. Thomas

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☒ One month (37 CFR 1.17(a)(1))	$130	$65	$ 130.00
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☐ Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-2490.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number 30,814

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____.

/Sandra B. Weiss/ — Signature
November 29, 2010 — Date
Sandra B. Weiss — Typed or printed name
312-913-0001 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P.
Thomas		
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

DECLARATION OF DOMENICO FANARA UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Domenico Fanara, in support of the above-identified patent application, do aver and state as follows:

1. I am the first named inventor of this application.
2. I received a Pharmacy degree from University of Liège Belgium in 1986
3. I have been employed by UCB Pharma SA since 1993 after having spent 6 years in another pharmaceutical company Galephar S.A as head of formulation development.
4. A copy of my CV is attached hereto as Exhibit A that include list of publications
5. Levocetirizine and particularly its dihydrochloride salt are known to be useful as antihistamines. Levocetirizine dihydrochloride is available in solid dosage form. The present invention is directed to a formulation that allows for the availability of levocetirizine and its salts in liquid dosage form.

6. One common problem with liquid pharmaceutical formulations in general is that the presence of water can allow for the growth of microorganisms, particularly after the seal on the product packaging has been broken, and when the contents of the packaging are exposed to dosing implements. Thus, it has become common practice to include preservatives in such formulations to prevent the growth of such microorganisms. Methyl parahydroxybenzoate and propyl parahydroxybenzoate, commonly known as methyl paraben and propyl paraben, respectively (hereinafter "MP" and "PP," together "parabens"), are frequently used for this purpose.

7. The combined parabens in typical pharmaceutical preparations is at least about 2 mg/ml, as shown by an accepted pharmaceutical treatise (see, Remington, The Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749, Ex. B, hereinafter "the Remington treatise").

8. In the course of developing liquid pharmaceutical formulations of levocetirizine and its salts, we were surprised to discover that levocetirizine itself can act as an anti-microbial. This is shown in Tables 5 and 6 of the present application, in which samples of an oral solution and oral drops containing 0.5 and 5.0 mg/ml of levocetirizine hydrochloride, respectively, and which were inoculated with various microbes, were essentially free of bacteria 14, 21, and 28 days after inoculation. The oral drop formulation that contained the higher concentration of the drug also was substantially free of fungal infection 21 and 28 days after inoculation.

9. This result was totally unexpected. Even though levocetirizine and its salts were well characterized, to our knowledge it had not been recognized prior to our invention that levocetirizine has antimicrobial properties. This led to our discovery that liquid pharmaceutical compositions of levocetirizine could be formulated with lower paraben concentrations than previously thought necessary and without additional preservatives.

10. Submitted herewith as Exhibit C are the results of testing of antimicrobial efficacy on several batches of oral drop solution having 5 mg/ml of levocetirizine, 0.3375 mg/ml MP and 0.0375 mg/ml of PP, for an MP/PP ratio

of 9 and a total parabens content of 0.375 mg/ml. The compositions contained no other preservative. The batch sizes varied from 100 L to 1000 L. The testing results confirmed that inoculated test samples of all of the batches were essentially free of both bacteria and fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one fifth of the minimum recommended by the Remington treatise.

11. Submitted herewith as Exhibit D are the results of testing of antimicrobial efficacy on two batches of oral solution containing 0.5 mg/ml of levocetirizine, 0.675 mg/ml MP and 0.075 mg/ml of PP, for an MP/PP ratio of 9 and a total parabens content of 0.750 mg/ml. The compositions contained no other preservative. The batch sizes were each 1000 L. The testing results confirmed that inoculated test samples of both of the batches were essentially free of bacteria and two of three species of fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one half of the minimum recommended by the Remington treatise.

12. I have reviewed the references cited by the U.S. Patent and Trademark Office against this application.

13. WO 02/47680 of DeLongueville et al. relates to earlier work on cetirizine and its optically active isomers, performed by the present assignee. The only mention of any specific preservative is at page 6, lines18-22, which states, "As an example of a composition according to the present invention, the following formulation of a syrup (oral drops) is preferred: cetirizine dihydrochloride, methyl- and propyparaben, saccharinum, and purified water." There is no teaching or suggestion as to the relative amounts of any of these components of the composition. As one skilled in the art, upon reading this disclosure I would understand that the amount of total parabens intended was at least the minimum of 2 mg/ml as set forth in the Remington treatise and as generally understood at that time as being a typical concentration of preservative for a liquid pharmaceutical product.

14. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 252-257 ("Gilliland 1"), reports a study on the effect of temperature on the kill rate of *E. coli* by methyl and propyl parabens. Solutions containing 0.12% MP (1.2 mg/ml) and 0.012% PP (.12 mg/ml) were evaluated at temperatures of 34, 37, 40, and 42°C, which are well beyond the temperatures at which most pharmaceutical compositions are stored. The combined parabens in the tested solutions was 1.32 mg/ml, more than 10% higher than the 1.125 mg/ml maximum parabens concentration of our invention. The longest time period over which measurements were made was 28 hours (Fig. 5) so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage. No pharmaceutical component of any type was included in the formulations evaluated. In a test run in which the temperature of the sample was constantly altered rather than being held at a steady state, the authors found that the viable count of *E. coli* showed variability that was too high to enable adequately precise rate constants to be calculated, such that the method was of little value in that experiment (p. 257). The amount of parabens used in Gilliland 1 is outside the claims of our invention; the experiments of Gilliland were conducted at different temperatures, and for much shorter times than the experiments of our application. For at least these reasons, as one skilled in the art, it is my opinion that Gilliland I would be afforded little weight by those of ordinary skill in the art with respect to its relevance to the present invention and does not teach or suggest a pharmaceutical solution of levocetirizine or one of its salts, and with a combined parabens of no more than 1.125 mg/ml.

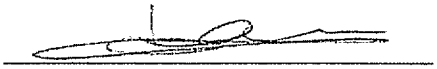
15. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 258-261 ("Gilliland 2"), reports a study on whether methyl and propyl paraben act synergistically. Various solutions were prepared with MP at either 0.12% or 0.14%, and with PP at 0.012% and 0.014%. These concentration levels were selected because at these levels the kill rate was slow enough that the rate constants could be calculated; higher concentrations killed bacteria too quickly for the required sampling to be carried out satisfactorily. (p. 259) To me, as one skilled in the

art, this suggests that the concentrations selected for study were not necessarily optimal for use in a pharmaceutical composition that have to be essentially free of such bacteria. I also note that the time period over which testing was done was about six hours, so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage.

16. Doron discloses compositions that significantly reduce E.coli, but at paraben concentration that are 37% and 248% greater than the concentrations used in our invention. As one skilled in the art, this reference suggests to me that at the MP/PP ratios of Doron, a much greater total concentration of parabens is necessary to achieve a composition that remains substantially free of bacteria than was achieved with our invention.

17. As one skilled in the art, the combination of Doron, DeLongueville, Gilliland I and Gilliland II does not teach or suggest that a pharmaceutical formulation could be prepared that is maintained substantially free of bacteria and having the a total of MP and PP of no greater than 1.125 mg/ml, and no other preservative. Gilliland I and II were thermal and kinetic studies of parabens. The authors indicate that the concentrations chosen were those that facilitated their measurements; there is no suggestion that the concentrations chosen for evaluation in these studies would be suitable for use in actual pharmaceutical compositions.

I hereby state that I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the application or document or any registration resulting therefrom, and I declare that all statements made of my own knowledge are true; and all statements made on information and belief are believed to be true.



Domenico Fanara

Date: 23/11/2010

EXHIBIT A

Domenico Fanara, Ind. Pharm.

Inte

Home Address: Rue Pont de Soleil, 2A,
B-4520 Wanze

Telephone (wk): +32.2.386.20.04
Telephone (hm): +32.85.23.57.69
Mobile : +32.494.578.142
E-mail: domenico.fanara@ucb.com

Current Position: Senior Director
Innovation & Technology Development
UCB Pharma S.A.
B-1420 Braine-l'Alleud.

Date of birth: October 11th, 1963

Expertise: Specific Skills

- Fully familiar with pharmaceutical sciences and drug development.
- Extensive experience in the development of novel technologies for compounds with poor solubility
- Extensive experience in the development of slow release formulations
- Evaluation of external technologies to support own projects
- Program and project management skills including goal setting, planning, budget forecasting and tracking and progress reporting
- Experience in management of development staffs with global footprint.
- Management of budget (OPEX,External,Investment)

Strengths:

- Creativity, focus, and result oriented

General skills:

- Trilingual English, French (mother tongue) Italian
- Fully familiar with the main computer softwares (Word, Excel, PowerPoint, Access, Outlook ...)

Domenico Fanara, Ind. Pharm.

Employment:

April 2010	Senior Director Head of Innovation and Technology Development
2009	Delivery Route R&D Senior Director and Deputy of the head of pharmaceutical Sciences UCB Pharma S.A. (85 FTE's)
2006 -2009	Drug Product R&D Senior Director, UCB Pharma S.A. (135 FTE's)
1995	Manager of Pharmaceutical Development, UCB Pharma
1993	Galenic Development, UCB Pharma
1988	Head of Pharmaceutical Development, SMB – Galephar
1986	Pharmaceutical Development, SMB – Galephar

Current key and past accountabilities:

To support a harmonized consistent approach to new technologies development
To support the development of new tools, new technologies to optimize processes .
To participate in the integration of innovation in the design of the future manufacturing processes (Chemical DS, Chemical DP, Biological DS, Biological DP, analytical Tools).
To develop internal expertise and competences at UCB for these novel technologies

The key requirement of my function is the management of all activities of the Drug Product and Delivery Route Research & Development department in accordance with the Pharmaceutical Sciences mission statements.

The fulfilment of this role will therefore require the active provision of strategic technical guidance for the initiation and management of development projects and for the supply of Drud Product (DP) for early clinical trials. In connection with this, I ensure the management of the department via the effective management of resources (specifically staff, facilities and the relevant budgets).

- To lead pharmaceutical development globally encompassing all projects from the Research to Development transition point through proof of concept transition into DP D&I Department. The DP R&D Department will also be responsible for transferring processes, technology, data and preparing regulatory submissions with its business partner DP DI (Global Technical Operations). (The role has a global remit and must ensure the optimal use of resources across UCB for all projects. This is a line function and I'm a member of the Pharmaceutical Sciences and NonClinical Management Team).

Domenico Fanara, Ind. Pharm.

As deputy of the head of Pharmaceutical Sciences :

- To coordinate Development's activities related to Pre-formulation ,Formulation & Drug Delivery Developments for NBE's and NCE's
- To manage the availability of DP for Clinical trials.
- To obtain and to ensure the coherence between all different Projects, in order to prioritize responsibilities and tasks in the department.
- To ensure full compliance with QA, cGMP or related requirements.
- To strengthen the UCB IP position through innovation.
- I oversee and advice for the development of pre-clinical and clinical formulations and characterization of materials as well as development of manufacturing processes for all products in the portfolio.

I am also responsible for managing the:

- Development of intellectual property fillings with for freedom to operate and potential exclusions.
- Development of extensions for current UCB proprietary drug delivery technologies.

Education:

1989 Industrial Pharmacist
1986 Pharmacist, University of Liège, Belgium
1981 Humanities (applied sciences section), Provincial Institute of secondary Education, Seraing, Belgium.

Other Relevant courses and workshops attended:

2008 Global Leadership program

2008 Leadership and innovation

2007 Internal training on NBE's

2004 – 2005 Leadership and Management – Internal Training

2001 Change management – Internal Training

2000 Management by objectives – Internal Training

1999 UCB Global leadership program – Internal Training

1998 Experimental planification – Internal Training

1998 Goal directed project management – Internal Training

1998 Compression: simple and double layer tablets (Courtoy)

1997 New drug delivery systems (P. Couvreur)

1996 Symposium drug delivery

1995 Pharmaceutical technology: lipidic vehicles (Gattefosse)

1995 Pharmaceutical technology conference (Amsterdam)

1995 First european intensive course on new forms a,nd new routes of administrations or drugs (Coimbra)

1994 GTRV (Paris)

1994 Pharmaceutical technology conference (Barcelona)

1993 Statistic course (ULB)

1993 European congress of biopharmaceutics and pharmacokinetics

1993 – 1995 Experimental work of a PHD Thesis – "Oral drug delivery of peptides" (ULB)

1992 Peptide and protein drug delivery (V. Lee)

1986 Work experience in the pharmaceutical chemistry laboratory of the University of Liège (Prof. Delarge)

1985 Work experience in the clinical biology laboratory of the University of Liège Prof. Heusghem)

Domenico Fanara, Ind. Pharm.

Bibliography (literature & patents)

Literature

Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine.
Source
International Journal of Pharmaceutics. 299(1-2):167-77, 2005 Aug 11.

Correlation of extrusion forces, raw materials and sphere characteristics.
Source
Journal of Pharmacy & Pharmacology. 44(8):676-8, 1992 Aug.

Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces.
Source
Journal of Pharmacy & Pharmacology. 43(11):745-9, 1991 Nov.

Preparation and in vitro/in vivo evaluation of nano-sized crystals for dissolution rate enhancement of UCB-35440-3, a highly-dosed poorly water soluble weak base.
Eur. J. Pharm. & Biopharm, 64, 360-368 (2006)

In vitro transport studies of nifedipine nanoparticules across Caco-2/HT29-5M21 cultures & co-cultures
Eur. J. Pharm. & Biopharm, submitted, (2007)

Patents

Tablet comprising cetirizine and pseudoephedrine
International patent application WO 03/002098 and US Patent 7,014,867

Pharmaceutical compositions for controlled release of active substances
International patent application WO 98/41194 and US Patent 6,699,502

Pseudopolymorphic forms of 2-[2-[4-[Bis (4-fluorophenyl) methyl]-1-piperazinyl]ethoxy]acetic acid dihydrochloride
International patent application WO 99/28310 and US Patent 6,335,331

Tablet comprising efletirizine and pseudoephedrine.
International patent application: WO 2003/059328

Tablet comprising efletirizine
International patent application: WO 2003/057198

Oral formulations for cetirizine and related compounds.
International patent Application: WO 99/01133 and US patent US 6,455,533

Domenico Fanara, Ind. Pharm.

Pharmaceutical compositions for oral administration comprising substituted benzhydrylpiperazines and a cyclodextrin.
US Patent US 6,455,533 - European Patent EP 0 994 710.

Use of pharmaceutical compositions capable of being gelled in periodontology
International patent application WO 56726 and US Patent US 6,818,224

Pharmaceutical compositions capable of being gelled
International patent application WO 99/56725 and US Patent US 6,464,987

Pharmaceutical composition of piperazine derivatives.
International patent application WO 2006/005507

Pharmaceutical compositions comprising Levetiracetam
International patent application WO 2010/006929

Liquid composition of Brivaracetam
International patent application WO 2009/109547

Pharmaceutical compositions comprising 2-oxo-1-pyrrolidine derivatives
International patent application WO 2010/086315

Pharmaceutical compositions comprising Brivaracetam
International patent application WO 2010/089372

Pharmaceutical oral compositions
International patent application WO 2010/057869

Pharmaceutical oral compositions
International patent application WO 2010/057870

Other interests:

Reading, cycling, swimming.

EXHIBIT B

21ST EDITION

Remington

The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
A Wolters Kluwer Company
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AUTHORS

The 133 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by the authors listed on pages xi to xv.

Director

Philip P Gerbino 1995-2005

Twenty-first Edition—2005

Published in the 185th year of the
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1 2 3 4 5 6 7 8 9 10

When a preservative is required, its selection is based upon several considerations, in particular the site of use whether internal, external, or ophthalmic.[13] Several researchers have described various interactions that must be considered when preservatives are selected.[14,15] The major criteria that should be considered in selecting a preservative are as follows: It should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form, inexpensive, and relatively free of taste and odor.

The chosen preservative should be sufficiently stable and soluble to achieve adequate concentration to provide protection. This choice is more critical in two and three phase emulsion systems in which the preservative may be more soluble in the oil phase than in the aqueous phase.[12,16] The pH of the preparation must be considered to ensure that the preservative does not dissociate rendering it ineffective or degrade by acid or base catalyzed hydrolysis. The undissociated moiety or molecular form of a preservative possesses preservative capacity because the ionized form is unable to penetrate microorganisms. The preservative must be compatible with the formulation ingredients and the product container or closure. Finally, the preservative must not impact the safety or comfort of the patient when administered. For instance, preservatives used in ophthalmic preparations must be non-irritating. Chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate are commonly used in these applications.

Although few microorganisms are viable below a pH of 3 or above pH 9, most aqueous pharmaceutical preparations are manufactured within the favorable pH range. Acidic preservatives such as benzoic acid, boric acid, and sorbic acid are less dissociated and more effective in acidic formulations. Similarly, alkaline preservatives are less effective in acidic or neutral conditions and more effective in alkaline formulations. The scientific literature is rife with examples of incompatibilities between preservatives and other pharmaceutical adjuncts.[17–19] Commonly used macromolecules including cellulose derivatives, polyethylene glycol and tragacanth gum have been reported to cause preservative failure due to binding and adsorption.[20,21]

The mode of action by which preservatives interfere with microbial growth, multiplication, and metabolism occurs through one of several mechanisms. Preservatives often alter cell membrane permeability causing leakage of cell constituents (partial lysis), complete lysis, and cytoplasmic leakage and / or coagulation of cytoplasmic constituents (protein precipitation). Other preservatives inhibit cellular metabolism by interference with enzyme systems or cell wall synthesis, oxidation of cellular constituents, or hydrolysis.

Preservatives commonly used in pharmaceutical products are listed in Table 39-2 with typical concentration levels. Preservatives may be grouped into a number of classes depending upon their molecular structure. These basic groups are discussed below.

Alcohols

Ethanol is useful as a preservative when it is used as a solvent; however, it does need a relatively high concentration, somewhat greater than 15%, to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range of 15% to 30%. It is not volatile like ethanol and is used frequently not only in solutions but also in suspensions and emulsions. Chlorobutanol and phenylethyl alcohol are other alcohols used in lower concentrations (about 1%) as preservatives.

Acids

Benzoic acid has a low solubility in water, about 0.34% at 25°C, but the apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Activity depends on the pH of the medium because only the undissociated acid has antimicrobial properties. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[22] It has been reported that antimicrobial activity of benzoic acid is enhanced by the addition of the basic protein protamine.[23] Sorbic acid also has a low solubility in water, 0.3% at 30°C. Suitable concentrations for preservative action are in the range of 0.05% to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. The optimum antibacterial activity is obtained at pH 4.5, and practically no activity is observed above pH 6. Sorbic acid is subject to oxidation, particularly in the presence of light and in aque-

Table 39-2. Common Preservatives Used in Liquid Pharmaceutical Dosage Forms and Their Typical Concentration Levels

ANTIMICROBIAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)	ANTIFUNGAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)
Benzalkonium Chloride	0.002–0.02%	Butyl Paraben	0.1–0.4%
Benzethonium Chloride	0.01–0.02%	Methyl Paraben	0.1–0.25%
Benzyl Alcohol	3.0%	Ethyl Paraben	0.1–0.25%
Bronopol	0.01–0.1%	Propyl Paraben	0.1–0.25%
Cetrimide	0.005%	Benzoic Acid	0.1–0.5%
Cetylpyridinium chloride	0.0005–0.0007%	Potassium sorbate	0.1–0.2%
Chlorhexidine	0.002–0.5%	Sodium Benzoate	0.1–0.2%
Chlorobutanol	0.5%	Sodium Propionate	5–10%
Chlorocresol	0.2%	Sorbic Acid	0.05–0.2%
Chloroxylenol	0.1–0.8%		
Cresol	0.15–0.3%		
Ethyl Alcohol	15–20%		
Glycerin	20–30%		
Hexetidine	0.1%		
Imidurea	0.03–0.5%		
Phenol	0.1–0.5%		
Phenoxyethanol	0.5–1.0%		
Phenylethyl Alcohol	0.25–0.5%		
Phenylmercuric Nitrate	0.002–0.01%		
Propylene Glycol	15–30%		

solutions. Activity against bacteria can be variable because of its limited stability. Thus, sorbic acid is frequently used in combination with other antimicrobial preservatives or glycols in which synergistic effects occur.

Esters

Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl, and butyl derivatives. The water solubility of the parabens decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products, stable over a pH range of 4 to 8, and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore, a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%) or by using parabens in combination with other antimicrobial agents such as imidurea. Activity is reduced in the presence of nonionic surface active agents due to binding. In alkaline solutions, ionization takes place and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary Ammonium Compounds

Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration, 0.002% to 0.02%, depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at room temperature. Because of the cationic nature of this type of preservative, it is incompatible with many anionic compounds such as surfactants and can bind to nonionic surfactants. It is used generally in preparations for external use or those solutions that come in contact with mucous membranes. In ophthalmic preparations, benzalkonium chloride is widely used at a concentration of 0.01–0.02% w/w. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*. A concentration of 0.002–0.02% is used in nasal and otic formulations, sometimes in combination with 0.002–0.005% thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products.

Clearly, when the pharmacist dispenses or compounds liquid preparations, responsibility is assumed, along with the manufacturer, for the maintenance of product stability. General chapter ⟨1191⟩ of the USP describes stability considerations for dispensing, which should be studied in detail.[9] Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated on the manufacturer's label or in the compendium. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, major signs of instability are color change, precipitation, and evidence of microbial or chemical gas formation. Emulsions may cream, but if they break (ie, there is a separation of an oil phase) the product is considered unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred (Ostwald Ripening). Additional details on these topics are provided in the pertinent sections of this chapter.

SOLUTIONS

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid, or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Most solutions are unsaturated with the solute, in other words, the concentration of the solute in the solution is below its solubility limit. The strengths of pharmaceutical solutions are usually expressed in terms of % strength, although for very dilute concentrations expressions of ratio strength are sometimes used. The term % when used without qualification (as with w/v, v/v, or w/w) means % weight-in-volume for solutions or suspensions of solids in liquids; % weight-in-volume for solutions of gases in liquids; % volume-in-volume for solutions of liquids in liquids; and % weight-in-weight for mixtures of solids and semisolids.

Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients, and particle size. For the pharmacist, solutions are more defined by site of administration and composition than by physicochemical definitions. For instance, pharmaceutical solutions may be classified as an *oral solution, nasal solution, ophthalmic solution,* or *topical solution*. These solutions may also be classified based upon their composition. *Syrups* are aqueous solutions containing a sugar; *elixirs* are sweetened hydroalcoholic (combinations of water and ethanol) solutions; *spirits* are solutions of aromatic materials if the solvent is alcoholic or *aromatic waters* if the solvent is aqueous. Depending on their method of preparation and concentration, *tinctures* or *fluid extracts* are solutions prepared by extracting active constituents from crude drugs.

Many pharmaceutical chemicals are only slowly soluble in a given solvent and require an extended time for complete dissolution. To increase the dissolution rate, a pharmacist may employ one or several techniques such as applying heat, reducing the particle size of the solute, utilizing of a solubilizing agent, or subjecting the ingredients to rigorous agitation. In most cases, solutes are more soluble in solvents at elevated temperatures than at room temperature or below due to the endothermic nature of the dissolution process. The pharmacist should ensure that the materials are heat stabile and non-volatile when using heat to facilitate the dissolution rate.

AQUEOUS SOLUTIONS

The narrower definition in this subsection limits the solvent to water and excludes those preparations that are sweet and/or viscid in character and nonaqueous solutions. This section includes those pharmaceutical forms that are designated as *Aromatic Waters, Aqueous Acids, Solutions, Douches, Enemas, Gargles, Mouthwashes, Juices, Nasal Solutions, Otic Solutions,* and *Irrigation Solutions.*

Aromatic Waters

The USP defines Aromatic Waters as clear, saturated aqueous solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances.[9] Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other foreign odors. Aromatic waters may be prepared by distillation or solution of the aromatic substance, with or without the use of a dispersing agent. They are used principally as flavored or perfumed vehicles.

EXHIBIT C

The total paraben concentration fixed at 0.0375 % (m/V) is obtained with 0.3375 mg/ml of methyl parahydroxybenzoate and 0.0375 mg/ml of propyl parahydroxybenzoate.

The antimicrobial efficacy of the preservatives has been tested according to the European Pharmacopoeia 5.1.3 in order to demonstrate that the concentrations of preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate) in Xyzal® 5 mg/ml oral drops are adequate to ensure the long-term protection of the drug product against microbial contamination.

Test for Efficacy of Antimicrobial Preservation

a) Efficacy of antimicrobial preservation at 100 % of the labeled strength of methylparaben (0.3375 mg/ml) and propylparaben (0.0375 mg/ml)

The efficacy of antimicrobial preservation has been tested according to the method of the European Pharmacopoeia on batches 11531, 11532, 03F30, 03K24 and 04B16. Batches 11531, 11532, 03K24 and 04B16 are also used in the stability study (see part 3.2.P.8). The results are summarized hereafter and demonstrate that the drug product complies with the requirements of the Ph. Eur. 5.1.3.

Table 2:5 **Batches Tested**

Batch number	Date of manufacture	Batch size (l)	Place of manufacture	Drug substance batch number	Drug substance batch size
11531	02/2002	100	UCB S.A. Chemin du Foriest B – 1420 Braine-l'Alleud Belgium	C01375-1006 (2001092401)	104 kg
11532	02/2002	100			
03F30	06/2003	100	UCB PHARMA S.p.A. Via Praglia, 15 I-10044 PIANEZZA (Torino) Italy	01G201002	384 kg
03K24	11/2003	1000		03G201006	378 kg
04B16	02/2004	500		03H201008	370 kg

Table 2:6 **Results of the enumerations of batch 11531 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	8.70×10^5	5.00×10^5	3.48×10^5	1.65×10^5	1.26×10^6
0	2.42×10^5	2.40×10^5	3.19×10^5	1.21×10^4	2.12×10^5
After 7 days	< 1	< 1	< 1	< 1	5×10^2
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:7 **Results of the enumerations of batch 11532 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	8.70×10^5	5.00×10^5	3.48×10^5	1.65×10^5	1.26×10^6
0	3.10×10^5	2.91×10^5	3.28×10^5	9.80×10^4	2.78×10^6
After 7 days	< 1	< 1	< 1	< 1	$< 10^3$
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:8 **Results of the enumerations of batch 03F30 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	6.90×10^5	3.85×10^5	4.35×10^5	4.55×10^5	1.56×10^6
0	5.35×10^5	2.85×10^5	3.65×10^5	4.30×10^5	1.38×10^6
After 7 days	< 1	< 1	< 1	< 1	4.50×10^2
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:9 **Results of the enumerations of batch 03K24 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	2.4×10^6	4.1×10^6	2.2×10^6	3.4×10^6	4×10^5
0	1×10^4	1.6×10^5	3.7×10^5	3.2×10^5	5×10^4
After 14 days	0	0	0	0	0
After 28 days	0	0	0	0	0

Table 2:10 **Results of the enumerations of batch 04B16 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	2.1×10^6	2.1×10^6	1.2×10^6	3.1×10^6	4.1×10^6
0	1×10^5	1×10^5	3×10^5	1×10^5	3×10^5
After 14 days	0	0	0	0	0
After 28 days	0	0	0	0	0

b) Efficacy of antimicrobial preservation at *different concentrations* of methylparaben and propylparaben.

The efficacy of antimicrobial preservation has been tested on formulations containing the following concentrations of parabens :

- 0 mg/ml methylparahydroxybenzoate and 0 mg/ml propylparahydroxybenzoate
- 0.3375 mg/ml methylparahydroxybenzoate and 0.0375 mg/ml propylparahydroxybenzoate
- 0.675 mg/ml methylparahydroxybenzoate and 0.075 mg/ml propylparahydroxybenzoate
- 1.0125 mg/ml methylparahydroxybenzoate and 0.1125 mg/ml propylparahydroxybenzoate

The results are summarized hereafter and demonstrate that all formulations are in compliance with the requirements of the Ph. Eur. 5.1.3.

Table 2:11 **Results of the enumerations of batch 11294 0 mg/ml methylparahydroxybenzoate and 0 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.5×10^5	3.1×10^5	1.8×10^5	1.7×10^6
After 7 days	<100	<100	<100	<100	9.0×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:12 **Results of the enumerations of batch 11295 0.3375 mg/ml methylparahydroxybenzoate and 0.0375 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.2×10^5	2.6×10^5	1.7×10^5	1.8×10^6
After 7 days	<100	<100	<100	<100	9.5×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:13 **Results of the enumerations of batch 11296 0.675 mg/ml methylparahydroxybenzoate and 0.075 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.0×10^5	3.0×10^5	1.8×10^5	1.4×10^6
After 7 days	<100	<100	<100	<100	5.4×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:14 **Results of the enumerations of batch 11297 1.0125 mg/ml methylparahydroxybenzoate and 0.1125 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	2.9×10^5	6.9×10^4	2.7×10^5	5.0×10^4	1.5×10^6
After 7 days	<100	100	<100	<100	4.8×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

EXHIBIT D

The total paraben concentration fixed at 0.075 % (m/V) is obtained with 0.675 mg/ml of methyl parahydroxybenzoate and 0.075 mg/ml of propyl parahydroxybenzoate.

The antimicrobial efficacy of the preservatives has been tested according to the European Pharmacopoeia (5.1.3) in order to demonstrate that the concentrations of preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate) in Xyzal 0.5 mg/ml oral solution are adequate to ensure the long-term protection of the drug product against microbial contamination.

Test for Efficacy of Antimicrobial Preservation

The efficacy of antimicrobial preservation has been tested according to the method of the European Pharmacopoeia on batches of Xyzal 0.5 mg/ml oral solution containing increasing concentrations in preservatives (0 %, 0.0375%, 0.075 % and 0.1125 % (m/V)).
The results are summarized hereafter and demonstrate that the drug product containing 0.075 % preservatives complies with the requirements of the Ph. Eur. (5.1.3).

Moreover, the results given in section 3.2.P.8 show the stability of the preservatives activity as supported by the antimicrobial preservatives efficacy test performed at time 0 and towards the end of the shelf life.

Table 2:3 Batches Tested

Batch number	Date of manufacture	Batch size (l)	Place of manufacture	Drug substance batch number	Drug substance batch size (kg)	Preservatives concentration (% m/V)
11298	09/2001	1	UCB S.A. Chemin du Foriest B – 1420 Braine-l'Alleud Belgium	507	11.4 kg	0
11299	09/2001	1		507	11.4 kg	0.0375
11300	09/2001	1		507	11.4 kg	0.075
11301	09/2001	1		507	11.4 kg	0.1125
11434 (02A09)	01/2002	1000	UCB Pharma S.p.A. Via Praglia, 15 I-10044 PIANEZZA (Torino) Italy	C01375 - 1006	104.3 kg	0.075
11435 (02A10)	01/2002	1000		C01375 - 1006	104.3 kg	0.075

Table 2:4 Results of the enumerations of batch 11298 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.8×10^5	3.5×10^5	3.9×10^5	1.6×10^6
After 7 days	150	< 100	< 100	2.8×10^4	1.0×10^6
After 14 days	< 1	< 1	< 1	1.4×10^4	4.8×10^5
After 21 days	< 1	< 1	< 1	2.6×10^2	2.2×10^5
After 28 days	< 1	< 1	< 1	6.2×10^3	5.3×10^5

Table 2:5 Results of the enumerations of batch 11299 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.7×10^5	1.3×10^5	2.8×10^5	3.8×10^5	1.6×10^6
After 7 days	< 100	< 100	< 100	2.0×10^4	1.1×10^6
After 14 days	< 1	< 1	< 1	1.7×10^4	1.6×10^5
After 21 days	< 1	< 1	< 1	30	7.0×10^3
After 28 days	< 1	< 1	< 1	< 1	< 100

Table 2:6 Results of the enumerations of batch 11300 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.5×10^5	1.6×10^5	2.4×10^5	3.4×10^5	1.6×10^6
After 7 days	< 100	< 100	< 100	4.3×10^3	1.3×10^6
After 14 days	< 1	< 1	< 1	5.5×10^2	1.4×10^4
After 21 days	< 1	< 1	< 1	< 1	4.0×10^2
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:7 Results of the enumerations of batch 11301 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.9×10^5	1.2×10^5	3.0×10^5	3.5×10^5	1.4×10^6
After 7 days	< 100	< 100	< 100	2.0×10^5	8.9×10^5
After 14 days	< 1	< 1	< 1	< 10	< 1000
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:8 Results of the enumerations of batch 11434 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	1.04×10^5	3.44×10^5	5.65×10^5	9.35×10^5	1.98×10^6
0	4.25×10^4	2.48×10^5	3.85×10^5	5.70×10^5	1.90×10^6
After 7 days	< 100	< 100	< 100	2.85×10^4	8.00×10^4
After 14 days	< 1	< 1	< 1	50	4.65×10^4
After 21 days	< 1	< 1	< 1	< 1	50
After 28 days	< 1	< 1	< 1	< 1	100

Table 2:9 Results of the enumerations of batch 11435 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	1.04×10^5	3.44×10^5	5.65×10^5	9.35×10^5	1.98×10^6
0	4.00×10^4	2.70×10^5	3.70×10^5	5.60×10^5	2.18×10^6
After 7 days	< 100	< 100	< 100	< 100	2.36×10^6
After 14 days	< 1	< 1	< 1	< 1	6.50×10^3
After 21 days	< 1	< 1	< 1	< 1	< 100
After 28 days	< 1	< 1	< 1	< 1	10

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	18-Jul-2007
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Sandra B. Weiss
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**940**

Electronic Acknowledgement Receipt

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Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
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1	Request for Continued Examination (RCE)	06-796-RCE.pdf	1202867 74db1aaa0c8a60eea9cf21a5b2dd594b47e09dcf	no	3
Warnings:					
Information:					
2		06-796-Response.pdf	151737 001b8a0d54c5e93e8866a34be1ec67e0a4b5ec68	yes	9

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	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	9

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4	NPL Documents	06-796_NPL.pdf	2164777 01d134334fbd586f60300fdc7641115f50d07193	no	5
Warnings:					
Information:					
5	Extension of Time	06-796-Extension_of_Time.pdf	133628 9df1176ba366cd20ac0c32d69d443b4589829496	no	1
Warnings:					
Information:					
6	Rule 130, 131 or 132 Affidavits	06-796-Declaration.pdf	4811801 802ea6cbd1636c7d9f37135a2303b36f7002bca5	no	28
Warnings:					
Information:					

7	Fee Worksheet (PTO-875)	fee-info.pdf	32217 5971d0b98bcc230ec2d79eef947459c2a79be212	no	2

Warnings:	
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/599,451	07/18/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/29/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 26	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TIFFIANY n. TABB/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 09/09/2013

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
RODRIGUEZ, RAYNA B	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
09/09/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	RAYNA B. RODRIGUEZ	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) *RAYNA B. RODRIGUEZ*. (3) *Sandra Weiss*.

(2) *Timothy P. Thomas*. (4)_____.

Date of Interview: *04 September 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1 and 15*.

Identification of prior art discussed: *Remington's The Science and Practice of Pharmacy; 2005 - Exhibit B submitted with declaration and Guilland 1 and 2 previously cited*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Timothy P Thomas/ Primary Examiner, Art Unit 1628	/RAYNA B RODRIGUEZ/ Examiner, Art Unit 1628

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Examiner contacted Sandra Weiss to discuss possible allowable subject matter. Examiner noted that the Declarant states that combined parabens in typical pharmaceutical preparations is at least about 2 mg/ml as shown by Remington. Examiner noted that this argument is not found persuasive. Remington discloses that parabens are common preservatives used in liquid pharmaceutical dosage forms and their typical concentration levels range from about 0.1% and up. Assuming a density of the composition of 1; 0.1% is equivalent to about 1mg/ml. Furthermore, the cited art of record (Guilliand 2) teaches that methyl paraben and propyl paraben have synergistic effects when in combination. This teaching combined with the lower limit taught by Remington, one would expect that MP/PP in a dose of about 1 mg/ml and slightly below would be expected to be antimicrobial in view of the prior art. However, based on the art of record, one of ordinary skill would not expect that amounts of MP/PP much less than 1 mg/ml would be effective. A review of the data provided in the Declaration demonstrate that compositions containing levocetrizine and MP/PP with ratio of 9/1 and total concentration of 0.675 mg/ml and 0.375 have antimicrobial effects. This is deemed to be surprising and unexpected. Examiner noted that one of ordinary skill in the art would not expect to have antimicrobial effects at these concentrations based on the art of record, however based on the art of record the upper limit of MP/PP amount of 1 mg/ml in claim 5 and 1.125 mg/mg in claim 1 would not be unexpected. The upper limit of claim 15 of 0.75 mg/ml is also considered to be unobvious in view of the prior art. Examiner suggests incorporating the upper limit of claim 15 (i.e. 0.75 mg/ml) as the upper limit in claim 1 to make the instant claims allowable. The examiner can do this by Examiner's Amendment and send out a Notice of Allowance.

Examiner noted that Applicant demonstrate that levocetrizine has unexpected antimicrobial effects; however addition of amounts of MP/PP of about 1 mg/ml would be expected to be antimicrobial in view of the prior art. Examiner proposed that if the applicant could present data that demonstrated the criticality of the upper limit of less than 1.125 mg/ml (as instantly claimed in claim 1), this may support allowability of the entire claimed range of claim 1 as instantly claimed. Examiner proposed an experiment that may support this would be test 1.125 mg/ml MP/PP in a 9/1 ratio alone as the control and then addition of the active agent. If the addition of the active agent works better than the preservative alone, this would support that the instant claimed range has unexpected properties.

The attorney said that she would speak to the client about the Examiner's proposal and get back to the Examiner by the end of next week (9/13/2013) with an answer. Attorney noted that if the client would like to pursue the full scope of claim 1 and provide further evidence, they would require an office action be sent in order to preserve the client's rights in view of PTA.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P. Thomas
Serial No. 10/599,451	)	
	)	Art Unit: 1628
Filing Date: July 18, 2007	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

RESPONSE TO EXAMINER-INITIATED INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is in response to the paper entitled "Examiner-Initiated Interview Summary," mailed September 9, 2013, and relating to the interview initiated by Examiners Thomas and Rodriguez for this case on September 4, 2013 with applicants' undersigned representative.

Applicants agree with all the statements in the Summary, except that the Summary omits a description of a second set of experiments proposed by the Examiners in that Interview that might provide further evidence of unexpected results. In addition to the set of experiments described in the Summary, during the Interview the Examiners proposed a set of experiments wherein a set of samples would be prepared of methyl paraben and propyl paraben in a ratio of 9:1, and at a series of concentration levels as recited in the various claims. The samples would be inoculated with microbes, to determine which of these concentration levels does not kill microbes, i.e., to determine the bacteriostatic threshold. If a composition at that threshold with added levocetirizine was then found to have microbicidal properties, that would be considered evidence of unexpected properties to support patentability at that concentration level.

On September 10, 2013, the undersigned applicants' representative telephoned Examiner Thomas to discuss this proposed second set of experiments. Examiner Thomas confirmed that

the second set of proposed experiments would still be of interest, with patentability depending on the experimental results.

Applicants acknowledge with appreciation the careful consideration given to this case by Examiners Thomas and Rodriguez, and their suggestions as to how to achieve allowability. Applicants also thank the Examiners for their time and for the courtesies extended during the interviews of September 4 and September 10, 2013.

Respectfully submitted,

Date: September 11, 2013

/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

Electronic Acknowledgement Receipt

EFS ID:	16821774
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	11-SEP-2013
Filing Date:	18-JUL-2007
Time Stamp:	14:07:04
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	06_796_Response.pdf	64434 d3c513f770a7de8383d780fc4338b24f96a710fe	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	64434

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

20306 7590 09/27/2013

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
RODRIGUEZ, RAYNA B	
ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 09/27/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

TITLE OF INVENTION: Pharmaceutical Composition Of Piperazine Derivatives

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	12/27/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20306 7590 09/27/2013
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

TITLE OF INVENTION: Pharmaceutical Composition Of Piperazine Derivatives

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	12/27/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
RODRIGUEZ, RAYNA B	1628	514-252120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

20306 7590 09/27/2013

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
RODRIGUEZ, RAYNA B	

ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 09/27/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 832 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 832 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	RAYNA B. RODRIGUEZ	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) *RAYNA B. RODRIGUEZ*. (3) *Sandra Weiss*.

(2) *Timothy P. Thomas*. (4)_____.

Date of Interview: *10 September 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,5 and 18-27*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Sandra Weiss left a message stating that her client agreed to the proposed amendment to amend claim 1 to limit the upper limit of the preservative mixture to 0.75 mg/ml by Examiner's Amendment. Examiner contacted Ms. Weiss to confirm the appropriate language of claim 1 and to discuss the withdrawn claims. Examiner noted that previously withdrawn claim 18, and claims 19-21, which incorporate all the limitations of claim 18, are drawn a method of making a pharmaceutical composition according to claim 1, and lists choices that are outside the scope of claim 1. Examiner suggested cancelling claim 18. Examiner noted that claim 19 would be allowable if rewritten in independent form with the ratio of claim 20. Claim 20 is drawn to a salt of levocetirizine and claim 21 is drawn to a hydrochloride salt of levocetirizine. These limitations would further limit base claim 19, and would also be deemed allowable. Examiner noted that previously withdrawn claim 22, and claims 23-26, which incorporate the limitations of base claim 22, are drawn to a method of treating a patient comprising administering a composition according to claim 1, but list choices of active that are outside of the scope of claim 1. Furthermore, claim 22 is drawn to a method of treating a patient, and does not limit the treatment to a particular patient population. Examiner noted that these claims would raise issues under 112(a), because the instant claims as written are not enabled for the treatment of every possible patient population. Examiner suggested cancelling claims 22-26. Examiner noted that claim 27 does not further limit claim 1, from which it depends. Examiner suggested cancelling claim 27 .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/R. B. R./ Examiner, Art Unit 1628	

Notice of Allowability	Application No. 10/599,451	Applicant(s) FANARA ET AL.	
	Examiner RAYNA B. RODRIGUEZ	Art Unit 1628	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *11/29/2010*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1, 2, 5, 12, 14, 15, 17, 19-21, 28 and 29*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☒ All b) ☐ Some *c) ☐ None of the:
   1. ☒ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Timothy P Thomas/ Primary Examiner, Art Unit 1628	/R. B. R./ Examiner, Art Unit 1628

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

1. Claim 1 is directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(b), claims 19-21, directed to the process of making or using the allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, **the restriction requirement between groups I, claims** 1, 2, 5, 12, 14, 15, 17, 28 and 29, and group II**, claims 19-21, as set forth in the Office action mailed on June 4, 2008 is hereby withdrawn**. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

EXAMINER'S AMENDMENT

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Sandra Weiss on September 10, 2013.

The application has been amended as follows:

The claims are amended as follows:

1. (Currently amended) A liquid pharmaceutical composition comprising (i) levocetirizine or a pharmaceutically acceptable salt of levocetirizine, and (ii) a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and ~~less than 1.125~~ up to 0.75 mg/ml of the composition, wherein said composition is substantially free of bacteria.

2. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is aqueous.

3. (Canceled)

4. (Canceled)

5. (Currently amended) The liquid pharmaceutical composition according to claim 1, wherein the amount of the p-hydroxybenzoate esters is in the range of 0.0001 ~~and 1~~ to 0.75 mg/ml of the composition.

6. (Canceled)

7. (Canceled)

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the composition is in the form of oral solutions, nasal drops, eye drops or ear drops.

13. (Canceled)

14. (Previously presented) The liquid pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

15. (Previously Presented) The liquid pharmaceutical composition according to claim 14, wherein the hydrochloride salt of levocetirizine is present in amount of 0.5 mg/ml and the mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate is present in amount of 0.75 mg/ml.

16. (Canceled)

17. (Previously presented) The liquid pharmaceutical composition according to claim 1, which composition comprises levocetirizine or a pharmaceutically acceptable salt that is at least 95% by weight of the levorotatory enantiomer of cetirizine.

18. (Canceled)

19. (Currently amended) A method of making a liquid pharmaceutical composition according to claim 1 ~~The method according to claim 18,~~ comprising mixing levocetirizine or a pharmaceutically acceptable salt thereof with a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

20. (Previously presented) The method according to claim 19, comprising mixing a pharmaceutically acceptable salt of levocetirizine with a mixture of methyl p-hydroxybenzoate and propyl p- hydroxybenzoate, wherein the methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are present in a ratio of 9:1.

21. (Previously presented) The method according to claim 20, wherein the pharmaceutically acceptable salt of levocetirizine is a hydrochloride salt.

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Previously presented) The composition of claim 1, wherein the composition is in the form of an oral solution comprising 0.50 mg/ml levocetirizine dihydrochloride, 0.675 mg/ml methyl p- hydroxybenzoate, and 0.075 mg/ml propyl p-hydroxybenzoate.

29. (Previously presented) The composition of claim 1, wherein the composition is in the form of a solution of oral drops comprising 5.0 mg/ml levocetirizine dihydrochloride, 0.3375 mg/ml methyl p- hydroxybenzoate, and 0.0375 mg/ml propyl p-hydroxybenzoate.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance:

As set forth in the Interview Summary for the interview conducted September 4, 2013, Remington (provided with the declaration) discloses that parabens are common preservatives used in liquid pharmaceutical dosage forms and their typical concentration levels range from about 0.1% and up. Assuming a density of the composition of 1; 0.1% is equivalent to about 1 mg/ml. Furthermore, the cited art of record (Guilliand 2) teaches that methyl paraben and propyl paraben have synergistic effects when in combination. This teaching combined with the lower limit taught by Remington, one would expect that MP/PP in a dose of about 1 mg/ml and slightly below would be expected to be antimicrobial in view of the prior art. However, based on the art of record, one of ordinary skill would not expect that amounts of MP/PP much less than 1 mg/ml would be effective. A review of the data provided in the Declaration

demonstrates that compositions containing levocetrizine and MP/PP with ratio of 9/1 and total concentration of 0.675 mg/ml and 0.375 have antimicrobial effects. This is deemed to be surprising and unexpected. The upper limit of claim 15 of 0.75 mg/ml is also considered to be unobvious in view of the prior art. The instant amendment is sufficient to overcome the obviousness rejection of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1, 2, 5, 12, 14, 15, 17, 19-21, 28 and 29 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RAYNA B. RODRIGUEZ whose telephone number is (571)272-7088. The examiner can normally be reached on 8am-5:00pm, Monday - Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/R. B. R./
Examiner, Art Unit 1628

/Timothy P Thomas/
Primary Examiner, Art Unit 1628

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/599,451	FANARA ET AL.	
	Examiner	Art Unit	
	RAYNA B. RODRIGUEZ	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) *RAYNA B. RODRIGUEZ*. (3) *Sandra Weiss*.

(2) *Timothy P. Thomas*. (4)_____.

Date of Interview: *10 September 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,5 and 18-27*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

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☐ Attachment

/R. B. R./ Examiner, Art Unit 1628	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	Art Unit
	TIMOTHY P THOMAS	1614

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN	9/18/2008	TPT
PubChem	9/18/2008	TPT
PubMed	9/18/2008	TPT
WEST	9/18/2008	TPT
IDS references	9/18/2008	TPT
PALM Inventor Name Search	9/18/2008	TPT
STN	2/20/2009	TPT
EAST	2/20/2009	TPT
PubMed	2/20/2009	TPT
IDS references	2/20/2009	TPT
STN	7/27/2009	TPT
PubChem	7/27/2009	TPT
PubMed	7/27/2009	TPT
EAST	7/27/2009	TPT
EAST	7/27/2009	TPT
PubMed	7/29/2009	TPT
IDS references	7/27/2009	TPT
STN	12/30/2009	TPT

/TIMOTHY P THOMAS/ Examiner.Art Unit 1628	

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
IDS references	7/23/2010	TPT
Inventor Search, EAST, STN, IDS references	9/10/2013	RBR

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
514	252.12	9/10/2013	RBR

/TIMOTHY P THOMAS/ Examiner.Art Unit 1628	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	0	levocetirizine and hydoxybenzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/09/10 16:57
S1	35	((DOMENICO) near2 (FANARA)).INV.	US-PGPUB; USPAT	OR	ON	2013/09/10 14:36
S2	8	S1 and levocetirizine	US-PGPUB; USPAT	OR	ON	2013/09/10 14:38
S3	1	((JEAN) near2 (SCOUVART)).INV.	US-PGPUB; USPAT	OR	ON	2013/09/10 14:40
S4	2	((CLAIRE) near2 (POULAIN)).INV.	US-PGPUB; USPAT	OR	ON	2013/09/10 14:40
S5	32	((MICHEL) near2 (DELEERS)).INV.	US-PGPUB; USPAT	OR	ON	2013/09/10 14:40
S6	7	S5 not S1	US-PGPUB; USPAT	OR	ON	2013/09/10 14:41
S7	0	S6 and levocetirizine	US-PGPUB; USPAT	OR	ON	2013/09/10 14:41
S8	8	S5 and levocetirizine	US-PGPUB; USPAT	OR	ON	2013/09/10 14:41
S9	0	S8 not S2	US-PGPUB; USPAT	OR	ON	2013/09/10 14:42

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	1417	(514/252.12).CCLS.	US-PGPUB; USPAT; UPAD	OR	OFF	2013/09/10 16:46
L3	5	l2 and levocetirizine	US-PGPUB; USPAT; UPAD	OR	ON	2013/09/10 16:48
L4	165	l2 and hydroxybenzoate	US-PGPUB; USPAT; UPAD	OR	ON	2013/09/10 16:49
L5	0	levocetirizine and hydoxybenzoate	US-PGPUB; USPAT; UPAD	OR	ON	2013/09/10 16:57

9/10/2013 4:57:59 PM

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	**Art Unit**
	RAYNA B RODRIGUEZ	1628

CPC		
Symbol	**Type**	**Version**
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CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**
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/RAYNA B RODRIGUEZ/ Examiner.Art Unit 1628	09/10/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/TIMOTHY THOMAS/ Primary Examiner.Art Unit 1628	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	**Art Unit**
	RAYNA B RODRIGUEZ	1628

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	252.12	A	6	1	K	31 / 48 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

/RAYNA B RODRIGUEZ/ Examiner.Art Unit 1628	09/10/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/TIMOTHY THOMAS/ Primary Examiner.Art Unit 1628	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10599451	FANARA ET AL.
	Examiner	**Art Unit**
	RAYNA B RODRIGUEZ	1628

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	7	17												
2	2	-	18												
-	3	8	19												
-	4	9	20												
3	5	10	21												
-	6	-	22												
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4	12	11	28												
-	13	12	29												
5	14														
6	15														
-	16														

/RAYNA B RODRIGUEZ/ Examiner.Art Unit 1628	09/10/2013	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	12	
/TIMOTHY THOMAS/ Primary Examiner.Art Unit 1628	09/23/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2007-07-18
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.R./

Receipt date: 11/29/2010	Application Number	10599451	10599451 - GAU: 1628
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-18	
	First Named Inventor	Domenico Fanara	
	Art Unit	1628	
	Examiner Name	Timothy P. Thomas	
	Attorney Docket Number	06-796	

	1	KIBBE, Arthur H., "Handbook of Pharmaceutical Excipients", Third Edition 2000, American Pharmaceutical Association, pages 340-343, 450-453.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Rayna Rodriguez/	Date Considered	09/10/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.R./

STN Express Query Summary

(FILE 'HOME' ENTERED AT 17:01:43 ON 10 SEP 2013)

FILE 'REGISTRY' ENTERED AT 17:02:11 ON 10 SEP 2013

E LEVOCETIRIZINE/CN

L1 1 SEA SPE=ON ABB=ON PLU=ON LEVOCETIRIZINE/CN

L2 3 SEA SPE=ON ABB=ON PLU=ON (LEVOCETIRIZINE/CN OR "LEVOCETIRIZINE DIHYDROCHLORIDE"/CN OR "LEVOCETIRIZINE HYDROCHLORIDE"/CN)

D

SEL CN

L3 3 SEA SPE=ON ABB=ON PLU=ON ("(-)-CETIRIZINE"/CN OR "(R)-(-)-CETIRIZINE HYDROCHLORIDE"/CN OR "(R)-CETIRIZINE DIHYDROCHLORIDE"/CN OR "(R)-CETIRIZINE"/CN OR "ACETIC ACID, (2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-"/CN OR "ACETIC ACID, (2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, DIHYDROCHLORIDE"/CN OR "ACETIC ACID, (2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, MONOHYDROCHLORIDE"/CN OR "ACETIC ACID, (2-(4-((4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, (R)-"/CN OR "ACETIC ACID, (2-(4-((4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, DIHYDROCHLORIDE, (R)-"/CN OR "ACETIC ACID, 2-(2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-"/CN OR "ACETIC ACID, 2-(2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, HYDROCHLORIDE (1:1)"/CN OR "ACETIC ACID, 2-(2-(4-((R)-(4-CHLOROPHENYL)PHENYLMETHYL)-1-PIPERAZINYL)ETHOXY)-, HYDROCHLORIDE (1:2)"/CN OR ALLERCET/CN OR "LEVOCETIRIZINE DIHYDROCHLORIDE"/CN OR "LEVOCETIRIZINE HYDROCHLORIDE"/CN OR LEVOCETIRIZINE/CN OR LEZYNCET/CN OR "UCB 28556"/CN OR XUSAL/CN OR XYZAL/CN OR XYZALL/CN)

FILE 'CAPLUS, MARPAT, REGISTRY' ENTERED AT 17:03:11 ON 10 SEP 2013

L4 567 SEA SPE=ON ABB=ON PLU=ON L3

L5 18568 SEA SPE=ON ABB=ON PLU=ON HYDROXYBENZOATE

L6 0 SEA SPE=ON ABB=ON PLU=ON L4 (L) L5

FILE 'CAPLUS' ENTERED AT 17:03:53 ON 10 SEP 2013

FILE 'CAPLUS, USPATFULL' ENTERED AT 17:04:00 ON 10 SEP 2013

L7 10 SEA SPE=ON ABB=ON PLU=ON L3 AND L5

L8 0 SEA SPE=ON ABB=ON PLU=ON L7 AND PD<20040714

L9 0 SEA SPE=ON ABB=ON PLU=ON L7 AND PD<20050706

D IBIB ABS HIT 1-10 L7

L10 33 SEA SPE=ON ABB=ON PLU=ON L3 AND ANTIMICROBIAL

L11 3 SEA SPE=ON ABB=ON PLU=ON L10 AND PD<20040714

D IBIB ABS HIT 1-3

FILE HOME

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 SEP 2013 HIGHEST RN 1450791-93-1

DICTIONARY FILE UPDATES: 9 SEP 2013 HIGHEST RN 1450791-93-1

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 4, 2013

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REGISTRY includes numerically searchable data for experimental and

predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

FILE CAPLUS

FILE COVERS 1907 - 10 Sep 2013 VOL 159 ISS 12
FILE LAST UPDATED: 9 Sep 2013 (20130909/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: July 2013
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: July 2013

CAplus includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2013.

CAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MARPAT

FILE CONTENT: 1961-PRESENT VOL 159 ISS 12 (20130906/ED)

MOST MARPAT RECORDS FOR 1961-1987 ARE DERIVED FROM INPI DATA.
In addition, we are continuing to expand MARPAT's backfile with additional unique data! MARPAT now contains English-, French- and German-language patents from 1985-1987, and Japanese-language patents from 1987.

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES (COVERAGE TO THESE DATES IS NOT COMPLETE):

US 20130197097 01 AUG 2013
DE 102013200123 18 JUL 2013
EP   2617718 24 JUL 2013
JP   2013145877 25 JUL 2013
WO   2013110741 01 AUG 2013
GB   2498146 03 JUL 2013
FR   2984737 28 JUN 2013
RU   2488583 27 JUL 2013
CA   2762717 22 JUN 2013

The new MARPAT User Guide is now available at:
http://www.cas.org/File%20Library/Training/STN/User%20Docs/marpatug.pdf

Assembled MARPAT displays are now available by default for QHIT and FQHIT formats. Two new display formats, QHITEXG and FQHITEXG, have also been implemented.

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 10 Sep 2013 (20130910/PD)

FILE LAST UPDATED: 10 Sep 2013 (20130910/ED)

HIGHEST GRANTED PATENT NUMBER: US8533861

HIGHEST APPLICATION PUBLICATION NUMBER: US20130232651

CA INDEXING IS CURRENT THROUGH 9 Sep 2013 (20130909/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 10 Sep 2013 (20130910/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: July 2013

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: July 2013

USPATFULL includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2013.

USPATFULL now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

To ensure comprehensive retrieval of US patent information, including US patent application information, search USPATFULL in combination with USPAT2.

SELECT PN, PNK, PATS, AP, APPS, PRN and PRAI now bears a charge in this file. Please see HELP COST for pricing.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20306 7590 09/27/2013
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Sandra B. Weiss	(Depositor's name)
/Sandra B. Weiss/	(Signature)
December 16, 2013	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	07/18/2007	Domenico Fanara	06-796	9142

TITLE OF INVENTION: Pharmaceutical Composition Of Piperazine Derivatives

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	12/27/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
RODRIGUEZ, RAYNA B	1628	514-252120

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 McDonnell Boehnen Hulbert & Berghoff LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: UCB Pharma, S.A.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Brussels, Belgium

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 13-2490 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Sandra B. Weiss/ Date December 16, 2013

Typed or printed name Sandra B. Weiss Registration No. 30,814

Electronic Patent Application Fee Transmittal

Application Number:	10599451
Filing Date:	18-Jul-2007
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Filer:	Sandra B. Weiss
Attorney Docket Number:	06-796

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	17665211
Application Number:	10599451
International Application Number:	
Confirmation Number:	9142
Title of Invention:	Pharmaceutical Composition Of Piperazine Derivatives
First Named Inventor/Applicant Name:	Domenico Fanara
Customer Number:	20306
Filer:	Sandra B. Weiss
Filer Authorized By:	
Attorney Docket Number:	06-796
Receipt Date:	16-DEC-2013
Filing Date:	18-JUL-2007
Time Stamp:	16:10:37
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2080
RAM confirmation Number	3646
Deposit Account	132490
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	06-796_Issue_Fee.pdf	534618 72c8a609e556832de50692d49a42c18933bfad0c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32043 5daf7e9184e3ef021dd503dc95f60043967f98e2	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	566661	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Change(s) applied to document,

/S.X.S./
10/28/2013

Application Number	10599451
Filing Date	2007-07-18
First Named Inventor	Domenico Fanara
Art Unit	1628
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5891913	A	1999-04-06	Sallmann, et al. ~~Novartis Finance Corporation~~	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0605203	EP	A2	1994-07-06	Senju Pharmaceutical Co., Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /TPT/

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10599451
Filing Date	2006-08-28
First Named Inventor	Domenico Fanara
Art Unit	1614
Examiner Name	Timothy P. Thomas
Attorney Docket Number	06-796

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4705683		1987-11-10	Dettmar	
Change(s) applied to document, /M.A./ 11/8/2013	2	6004968		~~1999-11-24~~ December 21, 1999	Casey et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090137645	A1	2009-05-28	Zhang et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,451	01/21/2014	8633194	06-796	9142

20306 7590 12/31/2013

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 832 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Domenico Fanara, Wanze, BELGIUM;
Jean Scouvart, Brussels, BELGIUM;
Claire Poulain, Brussels, BELGIUM;
Michel Deleers, Linkebeek, BELGIUM;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of New York on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
18-CV-03404-VM	4/18/2018	Southern District of New York

PLAINTIFF	DEFENDANT
UCB, Inc. and UCB Biopharma SPRL	Apotex Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,633,194	1/21/2014	UCB Biopharma SPRL
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1---Upon initiation of action, mail this copy to Director Copy 3---Upon termination of action, mail this copy to Director
Copy 2---Upon filing document adding patent(s), mail this copy to Director Copy 4---Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of Florida on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
18-cv-60846-MGC	4/17/2018	Southern District of Florida

PLAINTIFF	DEFENDANT
UCB, Inc.	UCB Biopharma SPRL

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 ~~See Complaint~~		
2 8633199		
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Steven M. Larimore	Ledys M. Rodriguez	4/17/2018

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**