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

04016519.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Pharmaceutical composition of piperazine derivatives

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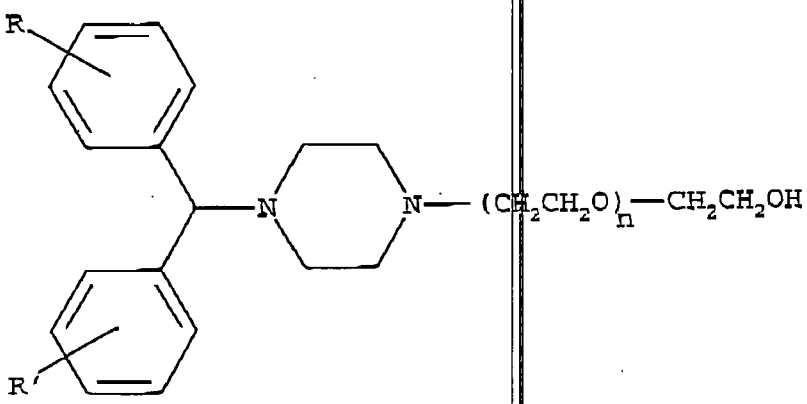
Pharmaceutical composition of piperazine derivatives

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

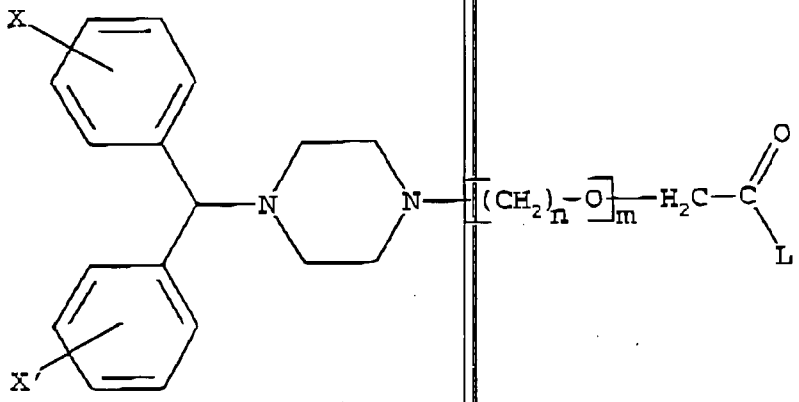


in which R and R^1 independently of one another represent a hydrogen or halogen atom, an alkyl or alkoxy group, it being possible for R and R^1 to be in the ortho, meta or para position, and n stands for the number 1 or 2, as well as their pharmaceutically acceptable salts.

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

2



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	1.0×10^8
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

10

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	3.7×10^5	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.

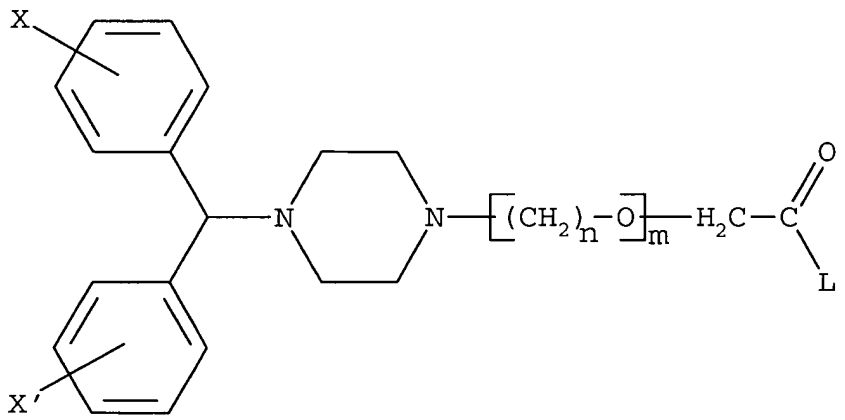
5

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.

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.

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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.

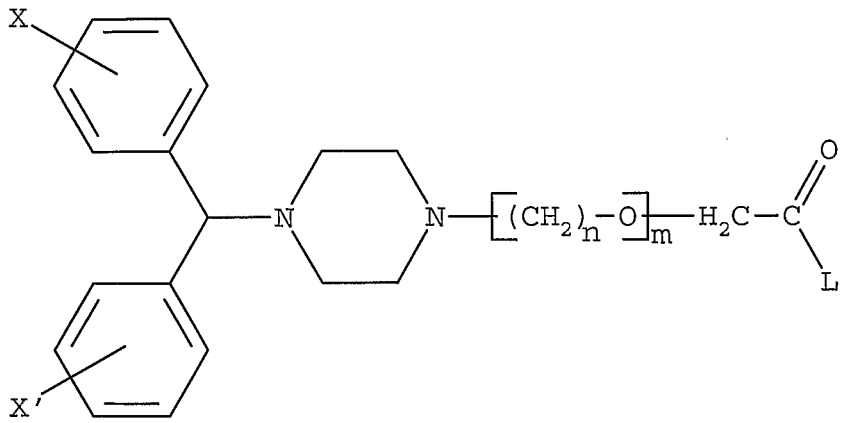
17.80.WO

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	1.6×10^5
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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(71) Applicant *(for all designated States except US)*: **UCB FARCHIM SA** [CH/CH]; Z.I. Planchy, Chemin de Croix Blanche 10, C.P. 411, CH-1630 Bulle (CH).

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(75) Inventors/Applicants *(for US only)*: **FANARA, Domenico** [IT/BE]; Rue Pont de Soleil, 2A, B-4520 Wanze (BE). **SCOUVART, Jean** [BE/BE]; Tir aux Pigeons, 72, B-1150 Brussels (BE). **POULAIN, Claire** [FR/BE]; 23 rue de Jonker, B-1060 Brussels (BE). **DEELERS, Michel** [BE/BE]; Square des braves, 12, B-1630 Linkebeek (BE).

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(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.

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INTERNATIONAL SEARCH REPORT

International application No
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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)
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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

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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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
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LECHIEN, Monique
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Date
24.11.06

Reference	Application No./Patent No.
	05758582.0 - 2101 PCT/EP2005007340
Applicant/Proprietor	
UCB FARCHIM S.A.	

Entry into the European phase before the European Patent Office

These notes describe the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read them carefully: failure to take the necessary action in time can lead to your application being deemed withdrawn.

1. The above-mentioned international patent application has been given European application No. **05758582.0**.

2. Applicants **without** a residence or their principal place of business in an EPC contracting state may themselves initiate European processing of their international applications, provided they do so before expiry of the 31st month from the priority date (see also point 6 below).

   During the European phase before the EPO as designated or elected Office, however, such applicants must be represented by a professional representative (Arts. 133(2) and 134(1), (7) EPC).

   Procedural acts performed after expiry of the 31st month by a professional representative who acted during the international phase but is not authorised to act before the EPO have no legal effect and therefore lead to loss of rights.

   Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise, the EPO has to send all communications direct to the applicant.

3. Applicants **with** a residence or their principal place of business in an EPC contracting state are not obliged to appoint, for the European phase before the EPO as designated or elected Office, a professional representative authorised to act before the EPO.
   However, in view of the complexity of the procedure it is recommended that they do so.

4. Applicants and professional representatives are also strongly advised to initiate the European phase using EPO Form 1200 (available free of charge from the EPO). This however is not compulsory.

5. **To enter the European phase before the EPO**, the following acts must be performed.
(N.B.: Failure validly to do so will entail loss of rights or other adverse legal consequences.)

5.1 If the EPO is acting as **designated** or **elected** Office (Arts. 22(1)(3) and 39(1) PCT respectively), applicants must, within 31 months from the date of filing or (where applicable) the earliest priority date:

a) Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such a language (Art. 22(1) PCT and R. 107(1)(a) EPC).
If the translation is not filed in time, the international application is deemed withdrawn before the EPO (R. 108(1) EPC).
This loss of rights is deemed not to have occurred if the translation is then filed within a two-month grace period as from notification of an EPO communication, provided a surcharge is paid at the same time (R. 108(3) EPC).

b) Pay the national basic fee (EUR 170,00) and, where a supplementary European search report has to be drawn up, the search fee (EUR 720,00 ; R. 107(1)(c) and (e) EPC).

c) If the time limit under Article 79(2) EPC expires before the 31-month time limit, pay the designation fee (EUR 80,00) for each contracting state designated (R. 107(1)(d) EPC).

d) If the time limit under Article 94(2) EPC expires before the 31-month time limit, file the written request for examination **and** pay the examination fee (EUR 1335,00 ; R. 107(1)(f) EPC).

e) Pay the third-year renewal fee (EUR 400,00) if it falls due before expiry of the 31-month time limit (R. 107(1)(g) EPC).

If the fees under (b) to (d) above are not paid in time, or the written request for examination is not filed in time, the international application is deemed withdrawn before the EPO, or the contracting-state designation(s) in question is (are) deemed withdrawn (R. 108(1) and (2) EPC). However, the fees may still be validly paid within a two-month grace period as from notification of an EPO communication, provided the necessary surcharges are paid at the same time (R. 108(3) EPC). For the renewal fee under (e) above, the grace period is **six** months from the fee's due date (Art. 86(2) EPC).

For an overview of search and examination fees, see OJ EPO 11/2005, 577 and 03/2006.

5.2 If the application documents on which the European grant procedure is to be based comprise more then ten claims, a claims fee is payable within the 31-month time limit under Rule 107(1) EPC for the eleventh and each subsequent claim (R. 110(1) EPC). The fee can however still be paid within a one-month grace period as from notification of an EPO communication pointing out the failure to pay (R. 110(2) EPC).

6. If the applicant had a representative during the application's international phase, the present notes will be sent to the representative, asking him to inform the applicant accordingly.

All subsequent communications will be sent to the applicant, or - if the EPO is informed of his appointment in time - to the applicant's European representative.

7. For more details about time limits and procedural acts before the EPO as designated and elected Office, see the EPO brochure

   How to get a European patent
   Guide for applicants - Part 2
   PCT procedure before the EPO - "Euro-PCT"

   This brochure, the list of professional representatives before the EPO, Form 1200 and details of the latest fees are now all available on the Internet under

   http://www.european-patent-office.org

Receiving section

P.B.5818 - Patentlaan 2
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Europäisches Patentamt	European Patent Office	Office européen des brevets
Generaldirektion 1	Directorate General 1	Direction générale 1

UCB FARCHIM S.A.
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Chemin de Croix Blanche, 10
C.P. 411
CH-1630 Bulle
SUISSE

EPO Customer Services

Tel.: +31 (0)70 340 45 00

Date
12.12.06

Reference	Application No./Patent No.
	05758582.0 - 2101
Applicant/Proprietor	
UCB FARCHIM S.A.	

The international search report, or the declaration under Article 17(2)(a) PCT, has been published under Article 21(3) and Rule 48 PCT on 07.12.06. That publication takes the place of the mention of publication of the European search report (Art. 157(1) EPC).

The request for examination must be filed within **six months** from the above date (Art. 94(2) in conjunction with Art. 157(1) EPC). It is not deemed to have been filed until the examination fee has been paid. However, under Article 22 or 39 PCT in conjunction with Article150(2) and Rule 107(1) EPC, the time limit for filing it does not expire before the end of the 31st month from the filing date (or earliest priority date). Payment of the designation fees must also be made within the above-mentioned period (R. 107(1) EPC). The same applies also for the extension fees.

If the request for examination is not filed in due time, and at least one designation fee is not paid, the European patent application is deemed to be withdrawn (Art. 94(3), 79(3) and R. 108(1) EPC).

For more details see the Guide for applicants Part 2: PCT proceedings before the EPO-"Euro-PCT".

Receiving Section

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An das Europäische Patentamt
To the European Patent Office
A l'Office européen des brevets

Eintritt in die europäische Phase (EPA als Bestimmungsamt oder ausgewähltes Amt)

Entry into the European phase (EPO as designated or elected Office)

Entrée dans la phase européenne (l'OEB agissant en qualité d'office désigné ou élu)

Europäische Anmeldenummer oder, falls nicht bekannt, PCT-Aktenzeichen oder PCT-Veröffentlichungsnummer

European application number, or, if not known, PCT application or publication number

Numéro de la demande de brevet européen ou, à défaut, numéro de dépôt PCT ou de publication PCT

PCT/EP2005/007340

Zeichen des Anmelders oder Vertreters (max. 15 Positionen)

Applicant's or representative's reference (max. 15 characters including spaces)

Référence du demandeur ou du mandataire (15 caractères ou espaces au maximum)

17.80.EP (WO)

1. Anmelder

☒ Die Angaben über den (die) Anmelder sind in der internationalen Veröffentlichung enthalten oder vom Internationalen Büro nach der internationalen Veröffentlichung vermerkt worden.

☐ Änderungen, die das Internationale Büro noch nicht vermerkt hat, sind auf einem Zusatzblatt angegeben.

☐ Fehlende Angaben über den oder die Anmelder sind auf einem Zusatzblatt angegeben.

1. Applicant

Indications concerning the applicant(s) are contained in the international publication or recorded by the International Bureau after the international publication.

Changes which have not yet been recorded by the International Bureau are set out on an additional sheet.

Indications missing for the applicant(s) are given on an additional sheet.

1. Demandeur

Les indications concernant le(s) demandeur(s) figurent dans la publication internationale ou ont été enregistrées par le Bureau international après la publication internationale.

Les changements qui n'ont pas encore été enregistrés par le Bureau international sont indiqués sur une feuille additionnelle.

Les indications manquantes concernant un ou plusieurs demandeurs sont mentionnées sur une feuille additionnelle.

Zustellanschrift
(siehe Merkblatt II, 1)

Address for correspondence
(see Notes II, 1)

Adresse pour la correspondance
(voir notice II, 1)

UCB S.A. - IPD Department
60, Allée de la Recherche
B-1070 Brussels (Belgium)

2. Vertreter

Name und **Geschäftsanschrift** (**Nur einen** Vertreter angeben, der in das europäische Patentregister eingetragen und an den zugestellt wird)

2. Representative

Name and **address of place of business** (Name **only one** representative who will be listed in the Register of European Patents and to whom notification will be made)

2. Mandataire

Nom et **adresse professionnelle** (N'indiquer **qu'un seul** mandataire, qui sera inscrit au Registre européen des brevets et auquel signification sera faite)

Monique LECHIEN
UCB S.A. - IPD Dpt
60, Allée de la Recherche
B-1070 Brussels (Belgium)

Telefon/Telephone/Téléphone +32 2 559 9374 **Telefax/Fax/Téléfax** +32 2 559 9409

☐ Weitere(r) Vertreter auf Zusatzblatt / Additional representative(s) on additional sheet / Autre(s) mandataire(s) sur une feuille additionnelle

3. Vollmacht

3. Authorisation

3. Pouvoir

☒ Vollmacht ist beigefügt. / Authorisation is attached. / Un pouvoir est joint.

☐ Allgemeine Vollmacht ist registriert unter Nummer: / General authorisation is registered under No.: / Un pouvoir général est enregistré sous le n° :

40375

☐ Allgemeine Vollmacht ist eingereicht, aber noch nicht registriert. / A general authorisation has been filed, but not yet registered. / Un pouvoir général a été déposé, mais n'est pas encore enregistré.

☐ Die beim EPA als PCT-Anmeldeamt eingereichte Vollmacht schließt ausdrücklich die europäische Phase ein. / The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase. / Le pouvoir déposé à l'OEB agissant en qualité d'office récepteur au titre du PCT inclut expressément la phase européenne.

4. Prüfungsantrag

4. Request for examination

4. Requête en examen

☒ 4.1 Hiermit wird die Prüfung der Anmeldung gemäß Art. 94 EPÜ beantragt. Die Prüfungsgebühr wird (wurde) entrichtet. / 4.1 Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid. / 4.1 Il est demandé par la présente que soit examinée la demande de brevet conformément à l'art. 94 CBE. Il est (a été, sera) procédé au paiement de la taxe d'examen.

Prüfungsantrag in einer zugelassenen Nichtamtssprache *(siehe Merkblatt III, 19.2)*: / Request for examination in an admissible non-EPO language *(see Notes III, 19.2)*: / Requête en examen dans une langue non officielle autorisée *(voir notice III, 19.2)* :

"Si richiede di esaminare la domanda ai sensi dell'art.94"

☐ 4.2 Auf die Aufforderung nach Art. 96 (1) EPÜ, zu erklären, ob die Anmeldung aufrechterhalten wird, wird verzichtet. / 4.2 The applicant waives his right to an invitation under Art. 96(1) EPC to indicate whether he wishes to proceed further with the application. / 4.2 Le demandeur renonce à être invité, conformément à l'art. 96 (1) CBE, à déclarer s'il maintient sa demande.

5. Abschriften

5. Copies

5. Copies

☐ Zusätzliche Abschrift(en) der im ergänzenden europäischen Recherchenbericht angeführten Schriftstücke wird (werden) beantragt. / Additional copy (copies) of the documents cited in the supplementary European search report is (are) requested. / Prière de fournir une ou plusieurs copies supplémentaires des documents cités dans le rapport complémentaire de recherche européenne.

Anzahl der **zusätzlichen** Sätze von Abschriften / Number of **additional** sets of copies / Nombre de jeux **supplémentaires** de copies

6. Für das Verfahren vor dem EPA bestimmte Unterlagen

6.1 Dem Verfahren vor dem EPA als **Bestimmungsamt** (PCT I) sind folgende Unterlagen zu Grunde zu legen:

☒ die vom Internationalen Büro **veröffentlichten Anmeldungsunterlagen** (mit **allen** Ansprüchen, Beschreibung und Zeichnungen), gegebenenfalls mit den geänderten Ansprüchen nach Art. 19 PCT

☐ soweit sie nicht ersetzt werden durch die beigefügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen.

6.2 Dem Verfahren vor dem EPA als **ausgewähltem Amt** (PCT II) sind folgende Unterlagen zu Grunde zu legen:

☒ die dem **internationalen vorläufigen Prüfungsbericht zu Grunde gelegten Unterlagen,** einschließlich seiner eventuellen **Anlagen**

☐ soweit sie nicht ersetzt werden durch die beigefügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen.

☒ Sind dem EPA als mit der internationalen vorläufigen Prüfung beauftragten Behörde **Versuchsberichte** zugegangen, dürfen diese dem Verfahren vor dem EPA zu Grunde gelegt werden.

7. Übersetzungen

Beigefügt sind die nachfolgend angekreuzten Übersetzungen in einer der Amtssprachen des EPA (Deutsch, Englisch, Französisch):

*a) Im Verfahren vor dem EPA als **Bestimmungsamt oder ausgewähltem Amt** (PCT I + II):*

☐ 7.1 Übersetzung der **internationalen Anmeldung in der ursprünglich eingereichten Fassung** (Beschreibung, Ansprüche, etwaige Textbestandteile in den Zeichnungen), der veröffentlichten Zusammenfassung und etwaiger Angaben über biologisches Material nach Regel 13*bis*.3 und 13*bis*.4 PCT

☐ 7.2 Übersetzung der **prioritätsbegründenden Anmeldung(en)**

☐ 7.3 Es wird hiermit erklärt, dass die internationale Anmeldung in ihrer ursprünglich eingereichten Fassung eine vollständige Übersetzung der früheren Anmeldung ist (Regel 38 (5) EPÜ).

6. Documents intended for proceedings before the EPO

6.1 Proceedings before the EPO as **designated Office** (PCT I) are to be based on the following documents:

the **application documents published** by the International Bureau (with **all** claims, description and drawings), where applicable with amended claims under Art. 19 PCT

unless replaced by the **amendments** enclosed.

For further details see additional sheet.

6.2 Proceedings before the EPO as **elected Office** (PCT II) are to be based on the following documents:

the **documents on which the international preliminary examination report is based,** including any **annexes**

unless replaced by the **amendments** enclosed.

For further details see additional sheet.

If the EPO as International Preliminary Examining Authority has received **test reports,** these may be used as the basis of proceedings before the EPO.

7. Translations

Translations in one of the official languages of the EPO (English, French, German) are enclosed as crossed below:

*(a) In proceedings before the EPO as **designated or elected Office** (PCT I + II):*

7.1 Translation of the **international application** (description, claims, any text in the drawings) **as originally filed,** of the abstract as published and of any indication under Rule 13*bis*.3 and 13*bis*.4 PCT regarding biological material

7.2 Translation of **the priority application(s)**

7.3 It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 38(5) EPC).

6. Pièces destinées à la procédure devant l'OEB

6.1 La procédure devant l'OEB agissant en qualité **d'office désigné** (PCT I) doit se fonder sur les pièces suivantes :

les **pièces de la demande publiées** par le Bureau international (avec **toutes** les revendications, la description et les dessins), éventuellement avec les revendications modifiées conformément à l'art. 19 PCT

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle.

6.2 La procédure devant l'OEB **agissant en qualité d'office élu** (PCT II) doit se fonder sur les pièces suivantes :

les **pièces sur lesquelles se fonde le rapport d'examen préliminaire international,** y compris ses **annexes** éventuelles

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle.

Si l'OEB, agissant en qualité d'administration chargée de l'examen préliminaire international, a reçu des **rapports d'essais,** ceux-ci peuvent constituer la base de la procédure devant l'OEB.

7. Traductions

Vous trouverez, ci-joint, les traductions cochées ci-après dans l'une des langues officielles de l'OEB (allemand, anglais, français) :

*a) Dans la procédure devant l'OEB agissant en qualité d'**office désigné ou élu** (PCT I + II) :*

7.1 Traduction de la **demande internationale telle que déposée initialement** (description, revendications, textes figurant éventuellement dans les dessins), de l'abrégé publié, et de toutes indications visées aux règles 13*bis*.3 et 13*bis*.4 PCT concernant le matériel biologique

7.2 Traduction de la (des) **demande(s) dont la priorité est revendiquée**

7.3 Il est déclaré par la présente que la demande internationale telle que déposée initialement est une traduction intégrale de la demande antérieure (règle 38(5) CBE).

b) ***Zusätzlich*** *im Verfahren vor dem EPA als* ***Bestimmungsamt*** *(PCT I):*

☐ 7.4 Übersetzung der nach Art. 19 PCT **geänderten Ansprüche** nebst Erklärung, falls diese dem Verfahren vor dem EPA zu Grunde gelegt werden sollen (siehe Feld 6)

c) ***Zusätzlich*** *im Verfahren vor dem EPA als* ***ausgewähltem Amt*** *(PCT II):*

☐ 7.5 Übersetzung der **Anlagen zum internationalen vorläufigen Prüfungsbericht**

8. Biologisches Material

☐ Die Erfindung bezieht sich auf bzw. verwendet biologisches Material, das nach Regel 28 EPÜ hinterlegt worden ist.

☐ Die **Angaben nach Regel 28(1) c) EPÜ** (falls noch nicht bekannt, die Hinterlegungsstelle und das (die) Bezugszeichen [Nummer, Symbole usw.] des Hinterlegers) sind in der internationalen Veröffentlichung oder in der gemäß Feld 7 eingereichten Übersetzung enthalten auf Seite(n) / Zeile(n):

Die **Empfangsbescheinigung(en)** der Hinterlegungsstelle

☐ ist (sind) beigefügt

☐ wird (werden) nachgereicht

☐ Verzicht auf die Verpflichtung des Antragstellers nach Regel 28 (3) EPÜ auf gesondertem Schriftstück

9. Nucleotid- und Aminosäuresequenzen

☐ 9.1 Die nach den Regeln 5.2 und 13*ter* PCT sowie den Regeln 27a und 111 (3) EPÜ erforderlichen Unterlagen liegen dem EPA bereits vor.

☐ 9.2 Das schriftliche Sequenzprotokoll wird anliegend nachgereicht.

☐ Das Sequenzprotokoll geht nicht über den Inhalt der Anmeldung in der ursprünglich eingereichten Fassung hinaus.

☐ 9.3 Der vorgeschriebene Datenträger ist beigefügt.

☐ Die auf dem Datenträger gespeicherte Information stimmt mit dem schriftlichen Sequenzprotokoll überein.

(b) ***In addition****, in proceedings before the EPO as* ***designated Office*** *(PCT I):*

7.4 Translation of **amended claims** and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6)

(c) ***In addition****, in proceedings before the EPO as* ***elected Office*** *(PCT II):*

7.5 Translation of any **annexes to the international preliminary examination report**

8. Biological material

The invention relates to and/or uses biological material deposited under Rule 28 EPC.

The **particulars referred to in Rule 28(1)(c) EPC** (if not yet known, the depository institution and the identification reference(s) [number, symbols, etc.] of the depositor) are given in the international publication or in the translation submitted under Section 7 on page(s) / line(s):

The **receipt(s) of deposit** issued by the depositary institution

is (are) enclosed

will be filed at a later date

Waiver of the right to an undertaking from the requester pursuant to Rule 28(3) EPC attached

9. Nucleotide and amino acid sequences

9.1 The items pursuant to Rules 5.2 and 13*ter* PCT, Rules 27a and 111(3) EPC are already with the EPO.

9.2 The written sequence listing is furnished herewith.

The sequence listing does not include matter which goes beyond the content of the application as filed.

9.3 The prescribed data carrier is enclosed.

The information recorded on the data carrier is identical to the written sequence listing.

b) ***De plus****, dans la procédure devant l'OEB agissant en qualité d'* ***office désigné*** *(PCT I) :*

7.4 Traduction des **revendications modifiées** et de la déclaration faite conformément à l'art. 19 PCT, si la procédure devant l'OEB doit être fondée sur les revendications modifiées (voir la rubrique 6)

c) ***De plus****, dans la procédure devant l'OEB agissant en qualité d'* ***office élu*** *(PCT II) :*

7.5 Traduction des **annexes du rapport d'examen préliminaire international**

8. Matière biologique

L'invention concerne et/ou utilise de la matière biologique, déposée conformément à la règle 28 CBE.

Les **indications visées à la règle 28(1)c) CBE** (si non encore connues, l'autorité de dépôt et la (les) référence(s) d'identification [numéro ou symboles etc.] du déposant) figurent dans la publication internationale ou dans une traduction produite conformément à la rubrique 7 à la / aux page(s) / ligne(s) :

Le(s) **récépissé(s) de dépôt** délivré(s) par l'autorité de dépôt

est (sont) joint(s)

sera (seront) produit(s) ultérieurement

Renonciation, sur document distinct, à l'engagement du requérant au titre de la règle 28(3) CBE

9. Séquences de nucléotides et d'acides aminés

9.1 Les pièces requises conformément aux règles 5.2 et 13*ter* PCT et aux règles 27*bis* et 111(3) CBE ont déjà été déposées auprès de l'OEB.

9.2 La liste de séquences écrite est produite ci-joint.

La liste de séquences ne contient pas d'éléments s'étendant au-delà du contenu de la demande telle qu'elle a été déposée.

9.3 Le support de données prescrit est joint.

L'information figurant sur le support de données est identique à celle que contient la liste de séquences écrite.

10. Benennungsgebühren

☒ 10.1 Es ist derzeit beabsichtigt, den **siebenfachen** Betrag einer Benennungsgebühr zu entrichten. Damit gelten die Benennungsgebühren für **alle Vertragsstaaten des EPÜ**[1] als entrichtet (Art. 2 Nr. 3 GebO), soweit sie **in der internationalen Anmeldung** bestimmt sind[2].

10.2 Abweichend von der Erklärung in Nr. 10.1 ist derzeit beabsichtigt, **weniger als sieben** Benennungsgebühren für folgende **in der internationalen Anmeldung bestimmte Vertragsstaaten des EPÜ**[2] zu entrichten:

(1) ☐ _____
(2) ☐ _____
(3) ☐ _____

☐ Soweit unter Nr. 10.2 Vertragsstaaten aufgeführt sind, wird beantragt, für die dort nicht aufgeführten Vertragsstaaten von der Zustellung einer Mitteilung nach Regel 108 (3) EPÜ abzusehen.

☒ 10.3 Wird ein **automatischer Abbuchungsauftrag** erteilt (Feld 12), so wird das EPA beauftragt, bei Ablauf der Grundfrist nach Regel 107 (1) d) EPÜ den siebenfachen Betrag der Benennungsgebühr abzubuchen. Sind unter Nr. 10.2 Staaten angegeben, so sollen die Benennungsgebühren nur für die dort angegebenen Vertragsstaaten abgebucht werden, sofern dem EPA nicht vor Ablauf der Grundfrist ein anderslautender Auftrag zugeht.

10. Designation fees

10.1 It is currently intended to pay **seven times** the amount of the designation fee. The designation fees for **all the EPC contracting states**[1] **designated in the international application**[2] are thereby deemed to have been paid (Art. 2 No. 3 RFees).

10.2 The declaration in No. 10.1 does not apply. Instead, it is currently intended to pay **fewer than seven** designation fees for the following **EPC contracting states**[2] **designated in the international application**:

(4) ☐ _____
(5) ☐ _____
(6) ☐ _____

If contracting states are indicated under No. 10.2, it is requested that no communication under Rule 108(3) EPC be issued for contracting states not thus indicated.

10.3 If an **automatic debit order** has been issued (Section 12), the EPO is authorised, on expiry of the basic period under Rule 107(1)(d) EPC, to debit seven times the amount of the designation fee. If states are indicated under No. 10.2, the EPO is authorised to debit designation fees only for those states, unless instructed otherwise before expiry of the basic period.

10. Taxes de désignation

10.1 Il est actuellement envisagé de payer un montant correspondant à **sept fois** la taxe de désignation. Les taxes de désignation sont ainsi réputées payées pour **tous les Etats contractants de la CBE**[1] **désignés dans la demande internationale**[2] (art. 2, point 3 RRT).

10.2 Contrairement à ce qui est indiqué au nº 10.1, il est actuellement envisagé de payer **moins de sept** taxes de désignation pour les **Etats contractants de la CBE**[2] suivants **désignés dans la demande internationale** :

(4) ☐ _____
(5) ☐ _____
(6) ☐ _____

Si des Etats contractants sont mentionnés au nº 10.2, prière de ne pas procéder à la signification d'une notification prévue par la règle 108(3) CBE pour les Etats contractants n'y étant pas mentionnés.

10.3 Si un **ordre de prélèvement automatique** est donné (rubrique 12), il est demandé à l'OEB de prélever, à l'expiration du délai normal visé à la règle 107(1)d) CBE, un montant correspondant à sept fois la taxe de désignation. Si des Etats sont mentionnés au nº 10.2, les taxes de désignation ne sont à prélever que pour les Etats contractants qui y sont indiqués, sauf instruction contraire reçue par l'OEB avant l'expiration du délai normal.

11. Erstreckung des europäischen Patents

Diese Anmeldung gilt auch als Erstreckungsantrag für die in der internationalen Anmeldung bestimmten "Erstreckungsstaaten"[3]. Er gilt jedoch als zurückgenommen, wenn die Erstreckungsgebühr nicht fristgerecht entrichtet wird.
Es ist beabsichtigt, diese Gebühr(en) für folgende Staaten zu entrichten:

☒	AL	Albanien
☒	MK	Ehemalige jugoslawische Republik Mazedonien
☒	HR	Kroatien
☒	YU	Serbien und Montenegro
☒	BA	Bosnien und Herzegowina
☒	LT	Litauen
☒	LV	Lettland

☐ _____

11. Extension of the European patent

This application is also deemed to be a request for extension to all the "extension states"[3] designated in the international application. However, the request is deemed withdrawn if the extension fee is not paid within the prescribed time limit.
It is intended to pay the fee(s) for the following states:

Albania
Former Yugoslav Republic of Macedonia
Croatia
Serbia and Montenegro
Bosnia and Herzegovina
Lithuania
Latvia

11. Extension des effets du brevet européen

La présente demande est également réputée être une requête en extension à tous les "Etats autorisant l'extension"[3] désignés dans la demande internationale. Toutefois, si la taxe d'extension n'est pas acquittée en temps utile, cette requête est réputée retirée.
Il est envisagé de payer la taxe (les taxes) d'extension pour les Etats suivants :

Albanie
Ancienne République yougoslave de Macédoine
Croatie
Serbie-et-Monténégro
Bosnie-Herzégovine
Lituanie
Lettonie

12. Automatischer Abbuchungsauftrag *(Nur möglich für Inhaber von beim EPA geführten laufenden Konten)*

☒ Das EPA wird beauftragt, nach Maßgabe der Vorschriften über das automatische Abbuchungsverfahren fällige Gebühren und Auslagen vom untenstehenden laufenden Konto abzubuchen. In Bezug auf die **Benennungsgebühren** wird auf Feld 10.3 verwiesen. Das EPA wird ferner beauftragt, die **Erstreckungsgebühren** für jeden in Feld 11 angekreuzten "Erstreckungsstaat" bei Ablauf der Grundfrist für ihre Zahlung abzubuchen, sofern ihm nicht bis dahin ein anderslautender Auftrag zugeht.

12. Automatic debit order *(for EPO deposit account holders only)*

The EPO is hereby authorised, under the Arrangements for the automatic debiting procedure, to debit from the deposit account below any fees and costs falling due. For **designation fees**, see Section 10.3. The EPO is also authorised, on expiry of the basic period for paying the **extension fees**, to debit those fees for each of the "extension states" marked with a cross in Section 11, unless instructed otherwise before the said period expires.

12. Ordre de prélèvement automatique *(uniquement possible pour les titulaires de comptes courants ouverts auprès de l'OEB)*

Par la présente, il est demandé à l'OEB de prélever du compte courant ci-dessous les taxes et frais venant à échéance, conformément à la réglementation relative à la procédure de prélèvement automatique. Pour les **taxes de désignation**, se reporter à la rubrique 10.3. Il est en outre demandé à l'OEB de prélever, à l'expiration du délai normal prévu pour leur paiement, les **taxes d'extension** pour chaque "Etat autorisant l'extension" coché à la rubrique 11, sauf instruction contraire reçue avant l'expiration de ce délai.

Nummer und Kontoinhaber / Number and account holder / Numéro et titulaire du compte

2802 0032 - UCB S.A. - IPD Dpt

☒ **13. Eventuelle Rückzahlungen auf das beim EPA geführte laufende Konto**

13. Any reimbursement to EPO deposit account

13. Remboursements éventuels à effectuer sur le compte courant ouvert auprès de l'OEB

Nummer und Kontoinhaber / Number and account holder / Numéro et titulaire du compte

2802 0032 - UCB S.A. - IPD Dpt

14. Unterschrift(en) des (der) Anmelders) oder Vertreters

14. Signature(s) of applicant(s) or representative

14. Signature(s) du (des) demandeur(s) ou du mandataire

Brussels, December 18, 2006
Ort / Datum / **Place / Date**

Monique LECHIEN
Lieu / Date

Name(n) des (der) Unterzeichneten bitte in Druckschrift wiederholen. Bei juristischen Personen bitte auch die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft in Druckschrift angeben.

Please print name(s) under signature(s). In the case of legal persons, the position of the signatory(ies) within the company should also be printed.

Le ou les noms du ou des signataires doivent être indiqués en caractères d'imprimerie. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires doit également être indiquée en caractères d'imprimerie.

Für Angestellte (Art. 133 (3) EPÜ) mit allgemeiner Vollmacht Nr.:

For employees (Art. 133(3) EPC) with general authorisation No.:

Pour les employés (art. 133(3) CBE) disposant d'un pouvoir général n° :

1 Stand bei Drucklegung: 31 Vertragsstaaten, und zwar: / Status when this form was printed: 31 contracting states, namely / Situation à la date d'impression : 31 Etats contractants, à savoir : **AT** Österreich / Austria / Autriche, **BE** Belgien / Belgium / Belgique, **BG** Bulgarien / Bulgaria / Bulgarie, **CH / LI** Schweiz und Liechtenstein / Switzerland and Liechtenstein / Suisse et Liechtenstein, **CY** Zypern / Cyprus / Chypre, **CZ** Tschechische Republik / Czech Republic / République tchèque, **DE** Deutschland / Germany / Allemagne, **DK** Dänemark / Denmark / Danemark, **EE** Estland / Estonia / Estonie, **ES** Spanien / Spain / Espagne, **FI** Finnland / Finland / Finlande, **FR** Frankreich / France / France, **GB** Vereinigtes Königreich / United Kingdom / Royaume-Uni, **GR** Griechenland / Greece / Grèce, **HU** Ungarn / Hungary / Hongrie, **IE** Irland / Ireland / Irlande, **IS** Island / Iceland / Islande, **IT** Italien / Italy / Italie, **LT** Litauen / Lithuania / Lituanie, **LU** Luxemburg / Luxembourg / Luxembourg, **LV** Lettland / Latvia / Lettonie, **MC** Monaco / Monaco / Monaco, **NL** Niederlande / Netherlands / Pays-Bas, **PL** Polen / Poland / Pologne, **PT** Portugal / Portugal / Portugal, **RO** Rumänien / Romania / Roumanie, **SE** Schweden / Sweden / Suède, **SI** Slowenien / Slovenia / Slovénie, **SK** Slowakische Republik / Slovak Republic / République slovaque, **TR** Türkei / Turkey / Turquie

2 Für folgende Staaten nur möglich, falls in der internationalen Anmeldung am oder nach dem folgenden Tag bestimmt: Polen 1. März 2004, Island 1. November 2004, Litauen 1. Dezember 2004, Lettland 1. Juli 2005. / Possible for the following states only if they are designated in the international application on or after the date specified: Poland 1 March 2004, Iceland 1 November 2004, Lithuania 1 December 2004, Latvia 1 July 2005. / Possible pour les Etats suivants uniquement s'ils ont été désignés dans la demande internationale à partir des dates suivantes : 1er mars 2004 pour la Pologne, 1er novembre 2004 pour l'Islande, 1er décembre 2004 pour la Lituanie et 1er juillet 2005 pour la Lettonie.

3 Nur möglich, falls der Staat in der internationalen Anmeldung bestimmt wurde und die internationale Anmeldung eingereicht wurde, während das Erstreckungsabkommen mit dem betreffenden Staat in Kraft war, d. h. für Albanien ab 1. Februar 1996, für die ehemalige jugoslawische Republik Mazedonien ab 1. November 1997, für Kroatien ab 1. April 2004, für Serbien und Montenegro ab 1. November 2004, für Bosnien und Herzegowina ab 1. Dezember 2004, für Litauen vom 5. Juli 1994 bis 30. November 2004 und für Lettland vom 1. Mai 1995 bis 30. Juni 2005. / Possible only if the state was designated in an international application filed while the extension agreement with the state concerned was in force: Albania from 1 February 1996, the former Yugoslav Republic of Macedonia from 1 November 1997, Croatia from 1 April 2004, Serbia and Montenegro from 1 November 2004, Bosnia and Herzegovina from 1 December 2004, Lithuania from 5 July 1994 to 30 November 2004, and Latvia from 1 May 1995 to 30 June 2005. / Possible uniquement si l'Etat a été désigné dans la demande internationale et que la demande internationale ait été déposée pendant la période où l'accord d'extension était en vigueur avec l'Etat concerné, c'est-à-dire à partir du 1er février 1996 pour l'Albanie, à partir du 1er novembre 1997 pour l'ancienne République yougoslave de Macédoine, à partir du 1er avril 2004 pour la Croatie, à partir du 1er novembre 2004 pour la Serbie-et-Monténégro, à partir du 1er décembre 2004 pour la Bosnie-Herzégovine, du 5 juillet 1994 au 30 novembre 2004 pour la Lituanie et du 1er mai 1995 au 30 juin 2005 pour la Lettonie.

4 Platz für Staaten, mit denen Erstreckungsabkommen nach Drucklegung dieses Formblatts in Kraft treten und die in der internationalen Anmeldung bestimmt waren / Space for States with which extension agreements enter into force after this form has been printed and which were designated in the international application. / Prévu pour des Etats à l'égard desquels des accords d'extension entreront en vigueur après l'impression du présent formulaire et qui ont été désignés dans la demande internationale.

17.80.EP (WO)

JH/MC

UCB S.A./N.V. - Département Propriété Intellectuelle - Allée de la Recherche 60, B-1070 Bruxelles
Intellectuele Eigendom Departement - Researchdreef 60, B-1070 Brussel
Intellectual Property Department - Allée de la Recherche 60, B-1070 Brussels

FACSIMILE & REGISTERED MAIL

EUROPEAN PATENT OFFICE
D-80898 MÜNCHEN (Germany)

Our ref.: Case 17.80.EP (WO)
IPD/0612-050

→ *Please quote in all correspondence*

Brussels, December 18, 2006

Your ref.:

Re: Patent Application No PCT/EP2005/007340
Entry into the European phase

Dear Sirs,

Please find herewith enclosed the following documents:

- Form 1200 "Entry into the European phase" (6 pages), duly completed and signed;
- The first page of the International Patent Application published with the Publication No. WO 2006/005507 (Priority date: 14 July 2004 (1 page);
- General Authorization 40375.

Best regards,

Monique LECHIEN
European Patent Attorney

Enclosures

Kopie für den Bevollmächtigten
To be returned to authorisee
Copie destinée au mandataire

1 **ALLGEMEINE VOLLMACHT**
GENERAL AUTHORISATION
POUVOIR GENERAL

AV Nr. (bitte bei jeder Korrespondenz angeben)
GA No. (please quote in all correspondence)
PG n° (prière de mentionner dans toute correspondance)

40375

2 Ich (Wir) /I (We) /Je (Nous)

UCB FARCHIM, S.A.,
Z.I. de Planchy
Ch. de Croix Blanche, 10
C.P. 411
CH-1630 BULLE (Suisse)

3 bevollmächtige(n) hiermit /do hereby authorise /autorise (autorisons) par la présente

Monique LECHIEN
UCB, S.A.
Allée de la Recherche 60
B-1070 BRUXELLES, Belgique

4 mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (uns) vorzunehmen und Zahlungen für mich (uns) in Empfang zu nehmen.
to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions and to receive payments on my (our) behalf.
à me (nous) représenter pour ce qui concerne toutes mes (nos) affaires de brevet dans toute procédure instituée par la Convention sur le brevet européen et, à ce titre, à agir en mon (notre) nom et à recevoir des paiements pour mon (notre) compte.

☒ Die Vollmacht gilt auch für Verfahren nach dem Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Petentwesens.
This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.
Ce pouvoir s'applique également à toute procédure instituée par le Traité de coopération en matière de brevets.

☐ Weitere Vertreter sind auf einem gesonderten Blatt angegeben. / Additional representatives indicated on supplementary sheet.
Les autres mandataires sont mentionnés sur une feuille supplémentaire.

5 ☐ Untervollmacht kann erteilt werden. / Sub-authorisation may be given. / Le pouvoir pourra être délégué.

6 ☒ Bitte die gelbe Kopie, ergänzt um die Nr. der allgemeinen Vollmacht, an den Vollmachtgeber zurücksenden.
Please return the yellow copy, supplemented by the General Authorisation No., to the authorisor.
Prière de renvoyer la copie jaune au mandant, munie du n° du pouvoir général.

Ort/Place/Lieu Bruxelles
Datum / Date le 16 avril 1999

Unterschrift(en) / Signature(s)

Gilles CAPART, proxy and legal Representative / fondé de pouvoir.

7 Das Formblatt muß vom (von den) Vollmachtgeber(n) (bei juristischen Personen vom Unterschriftsberechtigten) eigenhändig unterzeichnet sein. Nach der Unterschrift bitte den (die) Namen des (der) Unterzeichneten mit Schreibmaschine wiederholen (bei juristischen Personen die Stellung des Unterschriftsberechtigten innerhalb der Gesellschaft angeben).
The form must bear the personal signature(s) of the authorisor(s). (In the case of legal persons, that of the officer empowered to sign). After the signature, please type the name(s) of the signatory(ies) adding, in the case of legal persons, his (their) position within the company.
Le formulaire doit être signé de la propre main du (des) mandant(s) (dans le cas de personnes morales, de la personne ayant qualité pour signer). Veuillez ajouter à la machine après la signature, le (les) nom(s) du (des) signataire(s) en mentionnant, dans le cas de personnes morales, ses (leurs) fonctions au sein de la société.

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

(19) World Intellectual Property Organization
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(25) Filing Language: English

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(30) Priority Data:
04016519.3 14 July 2004 (14.07.2004) EP

(71) Applicant *(for all designated States except US)*: **UCB FARCHIM SA** [CH/CH]; Z.I. Planchy, Chemin de Croix Blanche 10, C.P. 411, CH-1630 Bulle (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FANARA, Domenico** [IT/BE]; Rue Pont de Soleil, 2A, B-4520 Wanze (BE). **SCOUVART, Jean** [BE/BE]; Tir aux Pigeons, 72, B-1150 Brussels (BE). **POULAIN, Claire** [FR/BE]; 23 rue de Jonker, B-1060 Brussels (BE). **DEELERS, Michel** [BE/BE]; Square des braves, 12, B-1630 Linkebeek (BE).

(74) Agent: **LECHIEN, Monique**; UCB, S.A., Allée de la Recherche 60, B-1070 Bruxelles (BE).

(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.

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

Published:
— *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.

WO 2006/005507 A2

(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.

Search result: 1 of 1

(WO/2006/005507) PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Publication Number: WO/2006/005507 **International Application No.:** PCT/EP2005/007340
Publication Date: 19.01.2006 **International Filing Date:** 07.07.2005

Int. Class.: *A61K 31/495* (2006.01), *A61K 9/08* (2006.01)

Applicants: **UCB FARCHIM SA** [CH/CH]; Z.I. Planchy, Chemin de Croix Blanche 10, C.P. 411, CH-1630 Bulle (CH) *(All Except US)*.
FANARA, Domenico [IT/BE]; Rue Pont de Soleil, 2A, B-4520 Wanze (BE) *(US Only)*.
SCOUVART, Jean [BE/BE]; Tir aux Pigeons, 72, B-1150 Brussels (BE) *(US Only)*.
POULAIN, Claire [FR/BE]; 23 rue de Jonker, B-1060 Brussels (BE) *(US Only)*.
DELEERS, Michel [BE/BE]; Square des braves, 12, B-1630 Linkebeek (BE) *(US Only)*.

Inventors: **FANARA, Domenico** [IT/BE]; Rue Pont de Soleil, 2A, B-4520 Wanze (BE).
SCOUVART, Jean [BE/BE]; Tir aux Pigeons, 72, B-1150 Brussels (BE).
POULAIN, Claire [FR/BE]; 23 rue de Jonker, B-1060 Brussels (BE).
DELEERS, Michel [BE/BE]; Square des braves, 12, B-1630 Linkebeek (BE).

Agent: **LECHIEN, Monique**; UCB, S.A., Allée de la Recherche 60, B-1070 Bruxelles (BE).

Priority Data: 04016519.3 14.07.2004 EP

Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

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.

Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DI 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, P 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.
African Regional Intellectual Property Org. (ARIPO) (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: English (EN)

Filing Language: English (EN)

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Tag des Eingangs/Day of receipt/ Date de réception

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59

21. Dez. 2006

Nur für amtlichen Gebrauch/For official use only/ Cadre réservé à l'administration

An das Europäische Patentamt
To the European Patent Office
A l'Office européen des brevets

Eintritt in die europäische Phase (EPA als Bestimmungsamt oder ausgewähltes Amt)

Entry into the European phase (EPO as designated or elected Office)

Entrée dans la phase européenne (l'OEB agissant en qualité d'office désigné ou élu)

Europäische Anmeldenummer oder, falls nicht bekannt, PCT-Aktenzeichen oder PCT-Veröffentlichungsnummer

European application number, or, if not known, PCT application or publication number

Numéro de la demande de brevet européen ou, à défaut, numéro de dépôt PCT ou de publication PCT

PCT/EP2005/007340

Zeichen des Anmelders oder Vertreters (max. 15 Positionen)

Applicant's or representative's reference (max. 15 characters including spaces)

Référence du demandeur ou du mandataire (15 caractères ou espaces au maximum)

17.80.EP (WO)

1. Anmelder

☒ Die Angaben über den (die) Anmelder sind in der internationalen Veröffentlichung enthalten oder vom Internationalen Büro nach der internationalen Veröffentlichung vermerkt worden.

☐ Änderungen, die das Internationale Büro noch nicht vermerkt hat, sind auf einem Zusatzblatt angegeben.

☐ Fehlende Angaben über den oder die Anmelder sind auf einem Zusatzblatt angegeben.

1. Applicant

Indications concerning the applicant(s) are contained in the international publication or recorded by the International Bureau after the international publication.

Changes which have not yet been recorded by the International Bureau are set out on an additional sheet.

Indications missing for the applicant(s) are given on an additional sheet.

1. Demandeur

Les indications concernant le(s) demandeur(s) figurent dans la publication internationale ou ont été enregistrées par le Bureau international après la publication internationale.

Les changements qui n'ont pas encore été enregistrés par le Bureau international sont indiqués sur une feuille additionnelle.

Les indications manquantes concernant un ou plusieurs demandeurs sont mentionnées sur une feuille additionnelle.

Zustellanschrift
(siehe Merkblatt II, 1)

Address for correspondence
(see Notes II, 1)

Adresse pour la correspondance
(voir notice II, 1)

UCB S.A. - IPD Department
60, Allée de la Recherche
B-1070 Brussels (Belgium)

2. Vertreter / **2. Representative** / **2. Mandataire**

Name und **Geschäftsanschrift** (**Nur einen** Vertreter angeben, der in das europäische Patentregister eingetragen und an den zugestellt wird) / **Name** and **address of place of business** (Name **only one** representative who will be listed in the Register of European Patents and to whom notification will be made) / **Nom** et **adresse professionnelle** (N'indiquer **qu'un seul** mandataire, qui sera inscrit au Registre européen des brevets et auquel signification sera faite)

Monique LECHIEN
UCB S.A. - IPD Dpt
60, Allée de la Recherche
B-1070 Brussels (Belgium)

Telefon/Telephone/Téléphone +32 2 559 9374 **Telefax/Fax/Téléfax** +32 2 559 9409

☐ Weitere(r) Vertreter auf Zusatzblatt / Additional representative(s) on additional sheet / Autre(s) mandataire(s) sur une feuille additionnelle

3. Vollmacht / **3. Authorisation** / **3. Pouvoir**

☒ Vollmacht ist beigefügt. / Authorisation is attached. / Un pouvoir est joint.

☐ Allgemeine Vollmacht ist registriert unter Nummer: / General authorisation is registered under No.: / Un pouvoir général est enregistré sous le n° :

40375

☐ Allgemeine Vollmacht ist eingereicht, aber noch nicht registriert. / A general authorisation has been filed, but not yet registered. / Un pouvoir général a été déposé, mais n'est pas encore enregistré.

☐ Die beim EPA als PCT-Anmeldeamt eingereichte Vollmacht schließt ausdrücklich die europäische Phase ein. / The authorisation filed with the EPO as PCT receiving Office expressly includes the European phase. / Le pouvoir déposé à l'OEB agissant en qualité d'office récepteur au titre du PCT inclut expressément la phase européenne.

4. Prüfungsantrag / **4. Request for examination** / **4. Requête en examen**

☒ 4.1 Hiermit wird die Prüfung der Anmeldung gemäß Art. 94 EPÜ beantragt. Die Prüfungsgebühr wird (wurde) entrichtet. / 4.1 Examination of the application under Art. 94 EPC is hereby requested. The examination fee is being (has been, will be) paid. / 4.1 Il est demandé par la présente que soit examinée la demande de brevet conformément à l'art. 94 CBE. Il est (a été, sera) procédé au paiement de la taxe d'examen.

Prüfungsantrag in einer zugelassenen Nichtamtssprache *(siehe Merkblatt III, 19.2)*: / Request for examination in an admissible non-EPO language *(see Notes III, 19.2)*: / Requête en examen dans une langue non officielle autorisée *(voir notice III, 19.2)* :

"Si richiede di esaminare la domanda ai sensi dell'art.94"

☐ 4.2 Auf die Aufforderung nach Art. 96 (1) EPÜ, zu erklären, ob die Anmeldung aufrechterhalten wird, wird verzichtet. / 4.2 The applicant waives his right to an invitation under Art. 96(1) EPC to indicate whether he wishes to proceed further with the application. / 4.2 Le demandeur renonce à être invité, conformément à l'art. 96 (1) CBE, à déclarer s'il maintient sa demande.

5. Abschriften / **5. Copies** / **5. Copies**

☐ Zusätzliche Abschrift(en) der im ergänzenden europäischen Recherchenbericht angeführten Schriftstücke wird (werden) beantragt. / Additional copy (copies) of the documents cited in the supplementary European search report is (are) requested. / Prière de fournir une ou plusieurs copies supplémentaires des documents cités dans le rapport complémentaire de recherche européenne.

Anzahl der **zusätzlichen** Sätze von Abschriften / Number of **additional** sets of copies / Nombre de jeux **supplémentaires** de copies

6. Für das Verfahren vor dem EPA bestimmte Unterlagen

6.1 Dem Verfahren vor dem EPA als **Bestimmungsamt** (PCT I) sind folgende Unterlagen zu Grunde zu legen:

☒ die vom Internationalen Büro **veröffentlichten Anmeldungsunterlagen** (mit **allen** Ansprüchen, Beschreibung und Zeichnungen), gegebenenfalls mit den geänderten Ansprüchen nach Art. 19 PCT

☐ soweit sie nicht ersetzt werden durch die beigefügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen.

6.2 Dem Verfahren vor dem EPA als **ausgewähltem Amt** (PCT II) sind folgende Unterlagen zu Grunde zu legen:

☒ die dem **internationalen vorläufigen Prüfungsbericht zu Grunde gelegten Unterlagen,** einschließlich seiner eventuellen **Anlagen**

☐ soweit sie nicht ersetzt werden durch die beigefügten **Änderungen.**

Falls nötig, sind Klarstellungen auf einem Zusatzblatt einzureichen.

☒ Sind dem EPA als mit der internationalen vorläufigen Prüfung beauftragten Behörde **Versuchsberichte** zugegangen, dürfen diese dem Verfahren vor dem EPA zu Grunde gelegt werden.

7. Übersetzungen

Beigefügt sind die nachfolgend angekreuzten Übersetzungen in einer der Amtssprachen des EPA (Deutsch, Englisch, Französisch):

*a) Im Verfahren vor dem EPA als **Bestimmungsamt oder ausgewähltem Amt** (PCT I + II):*

☐ 7.1 Übersetzung der **internationalen Anmeldung in der ursprünglich eingereichten Fassung** (Beschreibung, Ansprüche, etwaige Textbestandteile in den Zeichnungen), der veröffentlichten Zusammenfassung und etwaiger Angaben über biologisches Material nach Regel 13*bis*.3 und 13*bis*.4 PCT

☐ 7.2 Übersetzung der **prioritätsbegründenden Anmeldung(en)**

☐ 7.3 Es wird hiermit erklärt, dass die internationale Anmeldung in ihrer ursprünglich eingereichten Fassung eine vollständige Übersetzung der früheren Anmeldung ist (Regel 38 (5) EPÜ).

6. Documents intended for proceedings before the EPO

6.1 Proceedings before the EPO as **designated Office** (PCT I) are to be based on the following documents:

the **application documents published** by the International Bureau (with **all** claims, description and drawings), where applicable with amended claims under Art. 19 PCT

unless replaced by the **amendments** enclosed.

For further details see additional sheet.

6.2 Proceedings before the EPO as **elected Office** (PCT II) are to be based on the following documents:

the **documents on which the international preliminary examination report is based**, including any **annexes**

unless replaced by the **amendments** enclosed.

For further details see additional sheet.

If the EPO as International Preliminary Examining Authority has received **test reports**, these may be used as the basis of proceedings before the EPO.

7. Translations

Translations in one of the official languages of the EPO (English, French, German) are enclosed as crossed below:

*(a) In proceedings before the EPO as **designated or elected Office** (PCT I + II):*

7.1 Translation of the **international application** (description, claims, any text in the drawings) **as originally filed**, of the abstract as published and of any indication under Rule 13*bis*.3 and 13*bis*.4 PCT regarding biological material

7.2 Translation of **the priority application(s)**

7.3 It is hereby declared that the international application as originally filed is a complete translation of the previous application (Rule 38(5) EPC).

6. Pièces destinées à la procédure devant l'OEB

6.1 La procédure devant l'OEB agissant en qualité **d'office désigné** (PCT I) doit se fonder sur les pièces suivantes :

les **pièces de la demande publiées** par le Bureau international (avec **toutes** les revendications, la description et les dessins), éventuellement avec les revendications modifiées conformément à l'art. 19 PCT

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle.

6.2 La procédure devant l'OEB **agissant en qualité d'office élu** (PCT II) doit se fonder sur les pièces suivantes :

les **pièces sur lesquelles se fonde le rapport d'examen préliminaire international**, y compris ses **annexes** éventuelles

dans la mesure où elles ne sont pas remplacées par les **modifications** jointes.

Le cas échéant, des explications doivent être jointes sur une feuille additionnelle.

Si l'OEB, agissant en qualité d'administration chargée de l'examen préliminaire international, a reçu des **rapports d'essais**, ceux-ci peuvent constituer la base de la procédure devant l'OEB.

7. Traductions

Vous trouverez, ci-joint, les traductions cochées ci-après dans l'une des langues officielles de l'OEB (allemand, anglais, français) :

*a) Dans la procédure devant l'OEB agissant en qualité d'**office désigné ou élu** (PCT I + II) :*

7.1 Traduction de la **demande internationale telle que déposée initialement** (description, revendications, textes figurant éventuellement dans les dessins), de l'abrégé publié, et de toutes indications visées aux règles 13*bis*.3 et 13*bis*.4 PCT concernant le matériel biologique

7.2 Traduction de la (des) **demande(s) dont la priorité est revendiquée**

7.3 Il est déclaré par la présente que la demande internationale telle que déposée initialement est une traduction intégrale de la demande antérieure (règle 38(5) CBE).

b) ***Zusätzlich*** *im Verfahren vor dem EPA als* ***Bestimmungsamt*** *(PCT I):*

☐ 7.4 Übersetzung der nach Art. 19 PCT **geänderten Ansprüche** nebst Erklärung, falls diese dem Verfahren vor dem EPA zu Grunde gelegt werden sollen (siehe Feld 6)

c) ***Zusätzlich*** *im Verfahren vor dem EPA als* ***ausgewähltem Amt*** *(PCT II):*

☐ 7.5 Übersetzung der **Anlagen zum internationalen vorläufigen Prüfungsbericht**

8. Biologisches Material

☐ Die Erfindung bezieht sich auf bzw. verwendet biologisches Material, das nach Regel 28 EPÜ hinterlegt worden ist.

☐ Die **Angaben nach Regel 28(1) c) EPÜ** (falls noch nicht bekannt, die Hinterlegungsstelle und das (die) Bezugszeichen [Nummer, Symbole usw.] des Hinterlegers) sind in der internationalen Veröffentlichung oder in der gemäß Feld 7 eingereichten Übersetzung enthalten auf Seite(n) / Zeile(n):

Die **Empfangsbescheinigung(en)** der Hinterlegungsstelle

☐ ist (sind) beigefügt

☐ wird (werden) nachgereicht

☐ Verzicht auf die Verpflichtung des Antragstellers nach Regel 28 (3) EPÜ auf gesondertem Schriftstück

9. Nucleotid- und Aminosäuresequenzen

☐ 9.1 Die nach den Regeln 5.2 und 13*ter* PCT sowie den Regeln 27a und 111 (3) EPÜ erforderlichen Unterlagen liegen dem EPA bereits vor.

☐ 9.2 Das schriftliche Sequenzprotokoll wird anliegend nachgereicht.

☐ Das Sequenzprotokoll geht nicht über den Inhalt der Anmeldung in der ursprünglich eingereichten Fassung hinaus.

☐ 9.3 Der vorgeschriebene Datenträger ist beigefügt.

☐ Die auf dem Datenträger gespeicherte Information stimmt mit dem schriftlichen Sequenzprotokoll überein.

(b) ***In addition****, in proceedings before the EPO as* ***designated Office*** *(PCT I):*

7.4 Translation of **amended claims** and any statement under Art. 19 PCT, if the claims as amended are to form the basis for the proceedings before the EPO (see Section 6)

(c) ***In addition****, in proceedings before the EPO as* ***elected Office*** *(PCT II):*

7.5 Translation of any **annexes to the international preliminary examination report**

8. Biological material

The invention relates to and/or uses biological material deposited under Rule 28 EPC.

The **particulars referred to in Rule 28(1)(c) EPC** (if not yet known, the depository institution and the identification reference(s) [number, symbols, etc.] of the depositor) are given in the international publication or in the translation submitted under Section 7 on page(s) / line(s):

The **receipt(s) of deposit** issued by the depositary institution

is (are) enclosed

will be filed at a later date

Waiver of the right to an undertaking from the requester pursuant to Rule 28(3) EPC attached

9. Nucleotide and amino acid sequences

9.1 The items pursuant to Rules 5.2 and 13*ter* PCT, Rules 27a and 111(3) EPC are already with the EPO.

9.2 The written sequence listing is furnished herewith.

The sequence listing does not include matter which goes beyond the content of the application as filed.

9.3 The prescribed data carrier is enclosed.

The information recorded on the data carrier is identical to the written sequence listing.

b) ***De plus****, dans la procédure devant l'OEB agissant en qualité d'* ***office désigné*** *(PCT I) :*

7.4 Traduction des **revendications modifiées** et de la déclaration faite conformément à l'art. 19 PCT, si la procédure devant l'OEB doit être fondée sur les revendications modifiées (voir la rubrique 6)

c) ***De plus****, dans la procédure devant l'OEB agissant en qualité d'* ***office élu*** *(PCT II) :*

7.5 Traduction des **annexes du rapport d'examen préliminaire international**

8. Matière biologique

L'invention concerne et/ou utilise de la matière biologique, déposée conformément à la règle 28 CBE.

Les **indications visées à la règle 28(1)c) CBE** (si non encore connues, l'autorité de dépôt et la (les) référence(s) d'identification [numéro ou symboles etc.] du déposant) figurent dans la publication internationale ou dans une traduction produite conformément à la rubrique 7 à la / aux page(s) / ligne(s) :

Le(s) **récépissé(s) de dépôt** délivré(s) par l'autorité de dépôt

est (sont) joint(s)

sera (seront) produit(s) ultérieurement

Renonciation, sur document distinct, à l'engagement du requérant au titre de la règle 28(3) CBE

9. Séquences de nucléotides et d'acides aminés

9.1 Les pièces requises conformément aux règles 5.2 et 13*ter* PCT et aux règles 27*bis* et 111(3) CBE ont déjà été déposées auprès de l'OEB.

9.2 La liste de séquences écrite est produite ci-joint.

La liste de séquences ne contient pas d'éléments s'étendant au-delà du contenu de la demande telle qu'elle a été déposée.

9.3 Le support de données prescrit est joint.

L'information figurant sur le support de données est identique à celle que contient la liste de séquences écrite.

10. Benennungsgebühren

☒ 10.1 Es ist derzeit beabsichtigt, den **siebenfachen** Betrag einer Benennungsgebühr zu entrichten. Damit gelten die Benennungsgebühren für **alle Vertragsstaaten des EPÜ**[1] als entrichtet (Art. 2 Nr. 3 GebO), soweit sie **in der internationalen Anmeldung** bestimmt sind[2].

10.2 Abweichend von der Erklärung in Nr. 10.1 ist derzeit beabsichtigt, **weniger als sieben** Benennungsgebühren für folgende **in der internationalen Anmeldung bestimmte Vertragsstaaten des EPÜ**[2] zu entrichten:

(1) ☐ _____ (4) ☐ _____
(2) ☐ _____ (5) ☐ _____
(3) ☐ _____ (6) ☐ _____

☐ Soweit unter Nr. 10.2 Vertragsstaaten aufgeführt sind, wird beantragt, für die dort nicht aufgeführten Vertragsstaaten von der Zustellung einer Mitteilung nach Regel 108 (3) EPÜ abzusehen.

☒ 10.3 Wird ein **automatischer Abbuchungsauftrag** erteilt (Feld 12), so wird das EPA beauftragt, bei Ablauf der Grundfrist nach Regel 107 (1) d) EPÜ den siebenfachen Betrag der Benennungsgebühr abzubuchen. Sind unter Nr. 10.2 Staaten angegeben, so sollen die Benennungsgebühren nur für die dort angegebenen Vertragsstaaten abgebucht werden, sofern dem EPA nicht vor Ablauf der Grundfrist ein anderslautender Auftrag zugeht.

10. Designation fees

10.1 It is currently intended to pay **seven times** the amount of the designation fee. The designation fees for **all the EPC contracting states**[1] **designated in the international application**[2] are thereby deemed to have been paid (Art. 2 No. 3 RFees).

10.2 The declaration in No. 10.1 does not apply. Instead, it is currently intended to pay **fewer than seven** designation fees for the following **EPC contracting states**[2] **designated in the international application**:

(1) ☐ _____ (4) ☐ _____
(2) ☐ _____ (5) ☐ _____
(3) ☐ _____ (6) ☐ _____

☐ If contracting states are indicated under No. 10.2, it is requested that no communication under Rule 108(3) EPC be issued for contracting states not thus indicated.

10.3 If an **automatic debit order** has been issued (Section 12), the EPO is authorised, on expiry of the basic period under Rule 107(1)(d) EPC, to debit seven times the amount of the designation fee. If states are indicated under No. 10.2, the EPO is authorised to debit designation fees only for those states, unless instructed otherwise before expiry of the basic period.

10. Taxes de désignation

10.1 Il est actuellement envisagé de payer un montant correspondant à **sept fois** la taxe de désignation. Les taxes de désignation sont ainsi réputées payées pour **tous les Etats contractants de la CBE**[1] **désignés dans la demande internationale**[2] (art. 2, point 3 RRT).

10.2 Contrairement à ce qui est indiqué au n° 10.1, il est actuellement envisagé de payer **moins de sept** taxes de désignation pour les **Etats contractants de la CBE**[2] suivants **désignés dans la demande internationale** :

(1) ☐ _____ (4) ☐ _____
(2) ☐ _____ (5) ☐ _____
(3) ☐ _____ (6) ☐ _____

☐ Si des Etats contractants sont mentionnés au n° 10.2, prière de ne pas procéder à la signification d'une notification prévue par la règle 108(3) CBE pour les Etats contractants n'y étant pas mentionnés.

10.3 Si un **ordre de prélèvement automatique** est donné (rubrique 12), il est demandé à l'OEB de prélever, à l'expiration du délai normal visé à la règle 107(1)d) CBE, un montant correspondant à sept fois la taxe de désignation. Si des Etats sont mentionnés au n° 10.2, les taxes de désignation ne sont à prélever que pour les Etats contractants qui y sont indiqués, sauf instruction contraire reçue par l'OEB avant l'expiration du délai normal.

11. Erstreckung des europäischen Patents

Diese Anmeldung gilt auch als Erstreckungsantrag für die in der internationalen Anmeldung bestimmten "Erstreckungsstaaten"[3]. Er gilt jedoch als zurückgenommen, wenn die Erstreckungsgebühr nicht fristgerecht entrichtet wird.
Es ist beabsichtigt, diese Gebühr(en) für folgende Staaten zu entrichten:

11. Extension of the European patent

This application is also deemed to be a request for extension to all the "extension states"[3] designated in the international application. However, the request is deemed withdrawn if the extension fee is not paid within the prescribed time limit.
It is intended to pay the fee(s) for the following states:

11. Extension des effets du brevet européen

La présente demande est également réputée être une requête en extension à tous les "Etats autorisant l'extension"[3] désignés dans la demande internationale. Toutefois, si la taxe d'extension n'est pas acquittée en temps utile, cette requête est reputée retirée.
Il est envisagé de payer la taxe (les taxes) d'extension pour les Etats suivants :

☒	AL	Albanien	Albania	Albanie
☒	MK	Ehemalige jugoslawische Republik Mazedonien	Former Yugoslav Republic of Macedonia	Ancienne République yougoslave de Macédoine
☒	HR	Kroatien	Croatia	Croatie
☒	YU	Serbien und Montenegro	Serbia and Montenegro	Serbie-et-Monténégro
☒	BA	Bosnien und Herzegowina	Bosnia and Herzegovina	Bosnie-Herzégovine
☒	LT	Litauen	Lithuania	Lituanie
☒	LV	Lettland	Latvia	Lettonie

☐ _____

12. Automatischer Abbuchungsauftrag *(Nur möglich für Inhaber von beim EPA geführten laufenden Konten)*

[X] Das EPA wird beauftragt, nach Maßgabe der Vorschriften über das automatische Abbuchungsverfahren fällige Gebühren und Auslagen vom untenstehenden laufenden Konto abzubuchen. In Bezug auf die **Benennungsgebühren** wird auf Feld 10.3 verwiesen. Das EPA wird ferner beauftragt, die **Erstreckungsgebühren** für jeden in Feld 11 angekreuzten "Erstreckungsstaat" bei Ablauf der Grundfrist für ihre Zahlung abzubuchen, sofern ihm nicht bis dahin ein anderslautender Auftrag zugeht.

12. Automatic debit order *(for EPO deposit account holders only)*

The EPO is hereby authorised, under the Arrangements for the automatic debiting procedure, to debit from the deposit account below any fees and costs falling due. For **designation fees**, see Section 10.3. The EPO is also authorised, on expiry of the basic period for paying the **extension fees**, to debit those fees for each of the "extension states" marked with a cross in Section 11, unless instructed otherwise before the said period expires.

12. Ordre de prélèvement automatique *(uniquement possible pour les titulaires de comptes courants ouverts auprès de l'OEB)*

Par la présente, il est demandé à l'OEB de prélever du compte courant ci-dessous les taxes et frais venant à échéance, conformément à la réglementation relative à la procédure de prélèvement automatique. Pour les **taxes de désignation**, se reporter à la rubrique 10.3. Il est en outre demandé à l'OEB de prélever, à l'expiration du délai normal prévu pour leur paiement, les **taxes d'extension** pour chaque "Etat autorisant l'extension" coché à la rubrique 11, sauf instruction contraire reçue avant l'expiration de ce délai.

Nummer und Kontoinhaber	Number and account holder	Numéro et titulaire du compte
2802 0032 - UCB S.A. - IPD Dpt		

[X] **13. Eventuelle Rückzahlungen auf das beim EPA geführte laufende Konto**

13. Any reimbursement to EPO deposit account

13. Remboursements éventuels à effectuer sur le compte courant ouvert auprès de l'OEB

Nummer und Kontoinhaber	Number and account holder	Numéro et titulaire du compte
2802 0032 - UCB S.A. - IPD Dpt		

14. Unterschrift(en) des (der) Anmelder(s) oder Vertreters

14. Signature(s) of applicant(s) or representative

14. Signature(s) du (des) demandeur(s) ou du mandataire

Ort / Datum	Place / Date	Lieu / Date
Brussels, December 18, 2006		Monique LECHIEN

Name(n) des (der) Unterzeichneten bitte in Druckschrift wiederholen. Bei juristischen Personen bitte auch die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft in Druckschrift angeben.

Please print name(s) under signature(s). In the case of legal persons, the position of the signatory(ies) within the company should also be printed.

Le ou les noms du ou des signataires doivent être indiqués en caractères d'imprimerie. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires doit également être indiquée en caractères d'imprimerie.

Für Angestellte (Art. 133 (3) EPÜ) mit allgemeiner Vollmacht Nr.:	**For employees (Art. 133(3) EPC) with general authorisation No.:**	**Pour les employés (art. 133(3) CBE) disposant d'un pouvoir général n° :**

1 Stand bei Drucklegung: 31 Vertragsstaaten, und zwar: / Status when this form was printed: 31 contracting states, namely / Situation à la date d'impression : 31 Etats contractants, à savoir : **AT** Österreich / Austria / Autriche, **BE** Belgien / Belgium / Belgique, **BG** Bulgarien / Bulgaria / Bulgarie, **CH / LI** Schweiz und Liechtenstein / Switzerland and Liechtenstein / Suisse et Liechtenstein, **CY** Zypern / Cyprus / Chypre, **CZ** Tschechische Republik / Czech Republic / République tchèque, **DE** Deutschland / Germany / Allemagne, **DK** Dänemark / Denmark / Danemark, **EE** Estland / Estonia / Estonie, **ES** Spanien / Spain / Espagne, **FI** Finnland / Finland / Finlande, **FR** Frankreich / France / France, **GB** Vereinigtes Königreich / United Kingdom / Royaume-Uni, **GR** Griechenland / Greece / Grèce, **HU** Ungarn / Hungary / Hongrie, **IE** Irland / Ireland / Irlande, **IS** Island / Iceland / Islande, **IT** Italien / Italy / Italie, **LT** Litauen / Lithuania / Lituanie, **LU** Luxemburg / Luxembourg / Luxembourg, **LV** Lettland / Latvia / Lettonie, **MC** Monaco / Monaco / Monaco, **NL** Niederlande / Netherlands / Pays-Bas, **PL** Polen / Poland / Pologne, **PT** Portugal / Portugal / Portugal, **RO** Rumänien / Romania / Roumanie, **SE** Schweden / Sweden / Suède, **SI** Slowenien / Slovenia / Slovénie, **SK** Slowakische Republik / Slovak Republic / République slovaque, **TR** Türkei / Turkey / Turquie

2 Für folgende Staaten nur möglich, falls in der internationalen Anmeldung am oder nach dem folgenden Tag bestimmt: Polen 1. März 2004, Island 1. November 2004, Litauen 1. Dezember 2004, Lettland 1. Juli 2005. / Possible for the following states only if they are designated in the international application on or after the date specified: Poland 1 March 2004, Iceland 1 November 2004, Lithuania 1 December 2004, Latvia 1 July 2005. / Possible pour les Etats suivants uniquement s'ils ont été désignés dans la demande internationale à partir des dates suivantes : 1er mars 2004 pour la Pologne, 1er novembre 2004 pour l'Islande, 1er décembre 2004 pour la Lituanie et 1er juillet 2005 pour la Lettonie.

3 Nur möglich, falls der Staat in der internationalen Anmeldung bestimmt wurde und die internationale Anmeldung eingereicht wurde, während das Erstreckungsabkommen mit dem betreffenden Staat in Kraft war, d. h. für Albanien ab 1. Februar 1996, für die ehemalige jugoslawische Republik Mazedonien ab 1. November 1997, für Kroatien ab 1. April 2004, für Serbien und Montenegro ab 1. November 2004, für Bosnien und Herzegowina ab 1. Dezember 2004, für Litauen vom 5. Juli 1994 bis 30. November 2004 und für Lettland vom 1. Mai 1995 bis 30. Juni 2005. / Possible only if the state was designated in an international application filed while the extension agreement with the state concerned was in force: Albania from 1 February 1996, the former Yugoslav Republic of Macedonia from 1 November 1997, Croatia from 1 April 2004, Serbia and Montenegro from 1 November 2004, Bosnia and Herzegovina from 1 December 2004, Lithuania from 5 July 1994 to 30 November 2004, and Latvia from 1 May 1995 to 30 June 2005. / Possible uniquement si l'Etat a été désigné dans la demande internationale et que la demande internationale ait été déposée pendant la période où l'accord d'extension était en vigueur avec l'Etat concerné, c'est-à-dire à partir du 1er février 1996 pour l'Albanie, à partir du 1er novembre 1997 pour l'ancienne République yougoslave de Macédoine, à partir du 1er avril 2004 pour la Croatie, à partir du 1er novembre 2004 pour la Serbie-et-Monténégro, à partir du 1er décembre 2004 pour la Bosnie-Herzégovine, du 5 juillet 1994 au 30 novembre 2004 pour la Lituanie et du 1er mai 1995 au 30 juin 2005 pour la Lettonie.

4 Platz für Staaten, mit denen Erstreckungsabkommen nach Drucklegung dieses Formblatts in Kraft treten und die in der internationalen Anmeldung bestimmt waren. / Space for States with which extension agreements enter into force after this form has been printed and which were designated in the international application. / Prévu pour des Etats à l'égard desquels des accords d'extension entreront en vigueur après l'impression du présent formulaire et qui ont été désignés dans la demande internationale.

JH/MC

UCB S.A./N.V. - Département Propriété Intellectuelle - Allée de la Recherche 60, B-1070 Bruxelles
Intellectuele Eigendom Departement - Researchdreef 60, B-1070 Brussel
Intellectual Property Department - Allée de la Recherche 60, B-1070 Brussels

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to (fax No.) +49.89.2399.4465

EUROPEAN PATENT OFFICE
D-80898 MÜNCHEN (Germany)

Our ref.: Case 17.80.EP (WO)
IPD/0612-050

→ *Please quote in all correspondence*

Brussels, December 18, 2006

Your ref.:

Re: Patent Application No PCT/EP2005/007340
Entry into the European phase

Dear Sirs,

Please find herewith enclosed the following documents:

- Form 1200 "Entry into the European phase" (6 pages), duly completed and signed;
- The first page of the International Patent Application published with the Publication No. WO 2006/005507 (Priority date: 14 July 2004 (1 page);
- General Authorization 40375.

Best regards,

Monique LECHIEN
European Patent Attorney

Enclosures

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

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International Bureau

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(74) Agent: **LECHIEN, Monique**; UCB, S.A., Allée de la Recherche 60, B-1070 Bruxelles (BE).

(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.

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

Published:
— *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.

WO 2006/005507 A2

(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.

Search result: 1 of 1

(WO/2006/005507) PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Publication Number: WO/2006/005507 **International Application No.:** PCT/EP2005/007340
Publication Date: 19.01.2006 **International Filing Date:** 07.07.2005

Int. Class.: ***A61K 31/495*** (2006.01), ***A61K 9/08*** (2006.01)

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Agent: **LECHIEN, Monique**; UCB, S.A., Allée de la Recherche 60, B-1070 Bruxelles (BE).

Priority Data: 04016519.3 14.07.2004 EP

Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

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.

Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DI 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, P 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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Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: English (EN)

Filing Language: English (EN)

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1 **ALLGEMEINE VOLLMACHT**
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POUVOIR GENERAL

AV Nr. (bitte bei jeder Korrespondenz angeben)
GA No. (please quote in all correspondence)
PG n° (prière de mentionner dans toute correspondance)

40375

2 Ich (Wir) /I (We) /Je (Nous)

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Z.I. de Planchy
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3 bevollmächtige(n) hiermit /do hereby authorise /autorise (autorisons) par la présente

Monique LECHIEN
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4 mich (uns) in den durch das Europäische Patentübereinkommen geschaffenen Verfahren in allen meinen (unseren) Patentangelegenheiten zu vertreten, alle Handlungen für mich (uns) vorzunehmen und Zahlungen für mich (uns) in Empfang zu nehmen.
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Ort/Place/Lieu Bruxelles

Datum / Date le 16 avril 1999

Unterschrift(en) / Signature(s)

Gilles CAPART, proxy and legal Representative / fondé de pouvoir.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 17.80.WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2005/007340	International filing date *(day/month/year)* 07 July 2005 (07.07.2005)	Priority date *(day/month/year)* 14 July 2004 (14.07.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UCB FARCHIM SA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 16 January 2007 (16.01.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnes Wittmann-Regis e-mail: pt06@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/007340	07.07.2005	14.07.2004

International Patent Classification (IPC) or both national classification and IPC
A61K9/08, A61K31/495

Applicant
UCB FARCHIM SA

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

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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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

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

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

Name and mailing address of the ISA:

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Authorized Officer

Villa Riva, A

Telephone No. +49 89 2399-8404

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/007340

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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

1. Statement

Novelty (N)	Yes:	Claims	3-7,11
	No:	Claims	1,2,8-10,12
Inventive step (IS)	Yes:	Claims	3-5
	No:	Claims	1,2,8-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents :
D1: WO 2004/004705 A , diclosing ready to drink compositions comprising an active substance and sodium benzoate as a preservative. The active substance may be cetirizine (selection from a list of 5 active substances).
D2: US 5 504 113 A , disclosing cetirizine preparations comprising benzalkonium chloride as a preservative;
D3: US 6 319 927 B1, disclosing cetirizine hydrochloride nasal sprays with benzalkonium chloride / benzyl alcohol as preservatives
D4: US 6 432 961 B1, wherein a passage mentions a syrup containing cetirizine Hcl, methyl- and propylparaben, saccharinum, and water in undefined quantities.
D5: EP 0 605 203 A, wherein ex 5 discloses an ophthalmic composition comprising 3 mg/ml cetirizine, 2 mg/ml methylparaben and 1 mg/ml propylparaben.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

D1-D3 all disclose cetirizine solutions with different preservatives in amounts which fall within the claimed ranges (where clear, see point VIII below). Hence, the subject-matter of claims 1,2,8-10,12 cannot be considered novel under Art. 33(1) and (2) PCT.

Claims 3-7, 11 appear to be novel. For claims 3-5 the closest prior art is D5; the difference is the specific (lower) amounts and ratios of the preservatives; some effect appears to be shown in the application, and the reduction of the paraben amount while maintaining antimicrobial activity is certainly advantageous. Claims 3-5 appear to be inventive over D5 (Art. 33(1) and (3) PCT).
For claims 6,7 and 11 any of D1-D3 can be chosen as closest prior art; the difference is the choice of the preservative (6,7) and the optical isomer of the active principle (11); in this case the presence of an inventive step is doubtful; the preservatives choosen are well known ones among those available to the skilled person whishing to provide a liquid pharmaceutical formulation; the effect of preservatives is the same on both optical isomers

of cetirizine.

Re Item VIII
Certain observations on the international application

The amount of preservative in the case of other preservatives (than parahydroxy-benzoate esters) as defined in claim 1, namely which "corresponds to the bacterial effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1,5 mg/ml." does not enable the skilled person to determine which technical features are necessary to perform the stated function.
Moreover, claim 1 attempts to define the subject-matter in terms of the result to be achieved (preservative efficacy), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.
Therefore claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined.

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Tel.: +31 (0)70 340 45 00

Date
05-03-2007

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2108 PCT/EP2005007340
Applicant/Proprietor: UCB FARCHIM S.A.	

Communication pursuant to Rules 109 and 110 EPC

(1) Amendment of application documents, especially the claims (R. 109 EPC)

The above mentioned international (Euro-PCT) application has entered the European phase, or can do so, once the necessary conditions are fulfilled.

Under Articles 28, 41 PCT, Rules 52, 78 PCT and Rule 86(2) to (4) EPC, the applicant may amend the application documents after receiving the international search report.

Whether or not he has already done so, he now has a further opportunity to file amended claims or other application documents within a non-extendable time limit of one month after notification of the present communication (R. 109 EPC).

The claims applicable on expiry of the above time limit, i.e. those filed on entry into the European phase or in response to the present communication, will form the basis for the calculation of any claims fee to be paid (see page 2) and for any supplementary search to be carried out under Article 157(2) EPC (R. 109 EPC).

--2/

(2) Claims fees under Rule 110 EPC

If the application documents on which the European grant procedure is to be based comprise more than ten claims, a claims fee shall be payable for the eleventh and each subsequent claim within the period provided for in Rule 107(1) EPC.

☐ Based on the application documents currently on file, all necessary claims fees have already been paid (or the documents do not comprise more than 10 claims).

☑ All necessary fees will be/have been debited automatically according to the automatic debit order.

☐ The claims fees due for the claims ..... to ..... were not paid within the above-mentioned period.

Any non-paid claims fee, either based on the current set of claims or on any amended claims to be filed pursuant to Rule 109 EPC (see page 1), may still be validly paid within a non-extendable period of grace of **one month** after notification of this communication.

If a payment is made for only some of the claims, it must be indicated for which claims it is intended. If a claims fee is not paid in due time, the claim concerned is deemed to be abandoned (R. 110(4) EPC).

If claims fees have already been paid, but on expiry of the above-mentioned time limit there is a new set of claims containing fewer fee-incurring claims than previously, the claims fees in excess of those due under Rule 110(2), 2nd sentence, EPC will be refunded (R. 110(3) EPC).

You are reminded that any supplementary search under Article 157(2) EPC will relate only to the last set of claims applicable on expiry of the above time limit AND will be confined to those fee-incurring claims for which fees have been paid in due time.

The fee for the eleventh and each subsequent claim is EUR 45,00.

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Date
07.03.07

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2108 PCT/EP2005007340
Applicant/Proprietor: UCB FARCHIM S.A.	

Notification of European publication number and information on the application of Article 67(3) EPC

The provisional protection under Article 67(1) and (2) EPC in the individual contracting states becomes effective only when the conditions referred to in Article 67(3) EPC have been fulfilled (for further details, see information brochure of the European Patent Office "National Law relating to the EPC" and additional information in the Official Journal of the European Patent Office).

A request has been made for extension of the patent to: AL BA HR MK YU
See Official Journal 1-2/1994 for further information on provisional protection.

Pursuant to Article 158(1) EPC the publication under Article 21 PCT of an international application for which the European Patent Office is a designated Office takes the place of the publication of a European patent application.

The bibliographic data of the above-mentioned Euro-PCT application will be published on 04.04.07 in Section I.1 of the European Patent Bulletin. The European publication number is 1768649.

In all future communications to the European Patent Office, please quote the application number plus Directorate number.

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Date
04.04.07

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0-2108-EP2005007340
Applicant/Proprietor: UCB FARCHIM S.A.	

Refund of fees

The following fee was paid in respect of the application 05758582.0:

Fee	Code	Voucher No	Date	Currency	Amount
Search fee	002	00177054	14.02.07	EUR	1 000,00

According to the present state of the file the refund will be made by:

CREDITING THE DEPOSIT ACCOUNT 28020032.

Amount refundable:	Code	Currency	Amount	Voucher No
	002	EUR	1.000,00	00258774

Reason for refund: Undue payment.

The Authorising Officer
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(49)(89)23992668

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Application No.	Ref.	Date
05 758 582.0 - 2112	17.80.EP (WO)	25.02.2008
Applicant: UCB FARCHIM S.A.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

VILLA RIVA, A
Primary Examiner
for the Examining Division

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Enclosure(s): 2 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**:

The examination is being carried out on the **following application documents**:

Description, Pages

1-16 as published

Claims, Numbers

1-12 as published

Reference is made to the following documents :

D1: WO 2004/004705 A , diclosing ready to drink compositions comprising an active substance and sodium benzoate as a preservative. The active substance may be cetirizine (selection from a list of 5 active substances).
D2: US 5 504 113 A , disclosing cetirizine preparations comprising benzalkonium chloride as a preservative;
D3: US 6 319 927 B1, disclosing cetirizine hydrochloride nasal sprays with benzalkonium chloride / benzyl alcohol as preservatives
D4: US 6 432 961 B1, wherein a passage mentions a syrup containing cetirizine Hcl, methyl- and propylparaben, saccharinum, and water in undefined quantities.
D5: EP 0 605 203 A, wherein ex 5 discloses an ophthalmic composition comprising 3 mg/ml cetirizine, 2 mg/ml methylparaben and 1 mg/ml propylparaben.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

D1-D3 all disclose cetirizine solutions with different preservatives in amounts which fall within the claimed ranges (where clear, see point VIII below). Hence, the subject-matter of claims 1,2,8-10,12 cannot be considered novel under Art. 54(1) and (2) EPC.

Claims 3-7, 11 appear to be novel. For claims 3-5 the closest prior art is D5; the difference is the specific (lower) amounts and ratios of the preservatives; some effect appears to be shown in the application, and the reduction of the paraben amount while maintaining antimicrobial activity is certainly advantageous. Claims 3-5 appear to be inventive over D5 (Art. 56 EPC).

For claims 6,7 and 11 any of D1-D3 can be chosen as closest prior art; the difference is the choice of the preservative (6,7) and the optical isomer of the active principle (11); in this case the presence of an inventive step is not acknowledged ; the preservatives choosen are well known ones among those available to the skilled person wishing to provide a liquid pharmaceutical formulation; the effect of preservatives is the same on both optical isomers of cetirizine.

The amount of preservative in the case of preservatives other than parahydroxy-benzoate esters as defined in claim 1, namely which “corresponds to the bacterial effect of a parahydroxybenzoate esters concentration of more than 0 and less than 1,5 mg/ml.” does not enable the skilled person to determine which technical features are necessary to perform the stated function and to reproduce it (Art. 83 EPC).

Moreover, claim 1 attempts to define the subject-matter in terms of the result to be achieved (preservative efficacy), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Therefore claim 1 does not meet the requirements of Article 84 EPC in that the matter for which protection is sought is not clearly defined.

The applicant is invited to file new claims which take account of the above comments. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments made, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed on which these amendments are based (see Guidelines E-II, 1).

17.80.EP (WO)

ML/MC **UCB Pharma** SA - Département Propriété Intellectuelle - Allée de la Recherche 60 - B-1070 Bruxelles
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EUROPEAN PATENT OFFICE
D-80298 MÜNCHEN (Germany)

Our ref.: Case 17.80.EP (WO)
IPD/0803-001

→ *Please quote in all correspondence*

Brussels, March 3, 2008

Your ref.:

Re: European application No 05 758 582.0 – 2112 - UCB Farchim SA - Reply to communication pursuant to Article 94 (3) EPC, dated February 25, 2008

Dear Sirs,

This is a response to the communication pursuant to Art. 94 (3) EPC dated February 25, 2008.

Please find attached a set of amended claims with tracked changes and a clean copy of the amended set of claims.

Amended claims do not contain any subject matter extending beyond the content of the application as filed and thus fulfill Article 123(2) EPC as detailed hereafter:

- Pending claims 6-9 have been cancelled. The claims have been renumbered accordingly.
- Amended claim 1: the content of claim 3 has been introduced in claim 1. The second part of claim 1 has been deleted.

Applicants believe that they have dealt with all outstanding objections and request that the application proceed to grant.

Yours faithfully,

Monique LECHIEN
European Patent Attorney

Enclosures: - *Set of amended claims with tracked changes*
- *Set of amended claims (clean copy)*
- *Form 1037 (acknowledge of receipt)*

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, the preservative being 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.
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 preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.
4. A liquid pharmaceutical composition according to claim 1 or 2, 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.
5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.
6. A liquid pharmaceutical composition according to any of the claims 1 to 4, characterized in that the active substance is levocetirizine.
7. 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.

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.~~ the preservative being 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.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

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4.3. A liquid pharmaceutical composition according to claim 1 or ~~2~~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.~~4. A liquid pharmaceutical composition according to claim 1 or 2, 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.~~

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

6. A liquid pharmaceutical composition according to any of the claims 1 to ~~4~~12, characterized in that the active substance is levocetirizine.

~~12.~~

7. 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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0 8. März 2008

EUROPEAN PATENT OFFICE
D-80898 MÜNCHEN (Germany)

Our ref.: Case 17.80.EP (WO)
IPD/0803-001

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5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.
6. A liquid pharmaceutical composition according to any of the claims 1 to 4, characterized in that the active substance is levocetirizine.
7. 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.

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.~~ the preservative being 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.

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~~4.~~3. A liquid pharmaceutical composition according to claim 1 or 2~~3~~, characterized in that the preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

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~~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.~~

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~~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.~~

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

6. A liquid pharmaceutical composition according to any of the claims 1 to 4~~12~~, characterized in that the active substance is levocetirizine.

~~12.~~

7. 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.

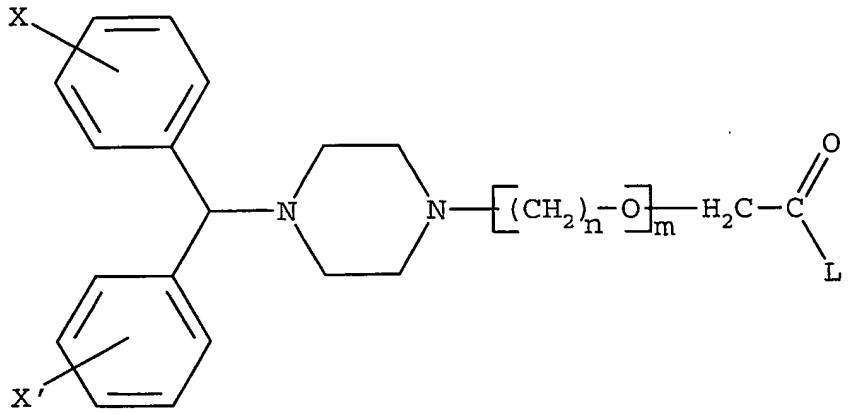
~~(17.80.WO(~~

~~(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

* Ophthalmic compositions with cetirizine as an active principle and parabens as preservatives are disclosed in EP 0 615 2019-00400), Ex. 1016, p. 118

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.

Reference

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.

/ (reference)

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, the preservative being 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.
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 preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.
4. A liquid pharmaceutical composition according to claim 1 or 2, 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.
5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.
6. A liquid pharmaceutical composition according to any of the claims 1 to 4, characterized in that the active substance is levocetirizine.
7. 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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Application No.: 05 758 582.0

IV.2. Patent classification

The classification indicated on the published patent application remains unchanged. It is as follows:

INV. A61K9/08 A61K31/495

IV.3. Title of the invention

The title indicated on the published patent application remains unchanged. It reads as follows:

PHARMAZEUTISCHE ZUSAMMENSETZUNG VON PIPERAZINDERIVATEN

PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

COMPOSITION PHARMACEUTIQUE DE DÉRIVÉS DE PIPÉRAZINE

IV.4. Documentation

08.12.08
Date

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Application No.	Ref.	Date
05 758 582.0 - 2112	17.80.EP (WO)	27.04.2009
Applicant: UCB FARCHIM S.A.		

Communication under Rule 71(3) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

Description, Pages

1-16 as published

Claims, Numbers

1-7 filed with telefax on 03.03.2008

With the following amendments to the above-mentioned documents by the examining division

Description, Pages 3*, 4,5,15,16**

Comments

* R42(1)(b) reference to closest prior art added
** adaptation of the description to the claims

A copy of the relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within a non-extendable period of **four months** of notification of this communication

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

		EUR
2a.	to pay the fee for grant including the fee for printing up to and including 35 pages; Reference 007	790.00
2b.	to pay the printing fee for the 36th and each subsequent page; number of pages: 0 Reference 008	0.00
3.	to pay the additional claim fee(s) (R. 71(6) EPC); number of claims fees payable: Reference 016	0.00
	Total amount	790.00

The mention of the grant of the patent shall be published in the European Patent Bulletin as soon as possible after the requirements concerning the translation of the claims and the payment of the fees for grant and printing, claims fees, designation fees and renewal fees as laid down in Rule 71(3), (4), (6) and (8) and (9) EPC are fulfilled.

Any divisional applications relating to this European patent application must be filed directly at the European Patent Office in Munich, The Hague or Berlin in accordance with Article 76(1) and Rule 36 EPC **before** the date on which the European Patent Bulletin mentions the grant of the patent (see Guidelines for Examination in the EPO, A-IV, 1.1.1).

If you do not approve the text intended for grant but wish to request amendments or corrections, the procedure described in Rule 71(4) EPC is to be followed.

If this communication is based upon an auxiliary request, and you reply within the time limit set that you maintain the main or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the enclosed claims contain amendments proposed by the Examining Division, and you reply within the time limit set that you cannot accept these amendments, refusal of the application under Article 97(2) EPC will result if agreement cannot be reached on the text for grant.

In all cases except those of the previous two paragraphs, if the fees for grant and printing or claims fees are not paid, or the translations are not filed, in due time, the European patent application will be deemed to be withdrawn (R. 71(7) EPC).

For all payments you are requested to use EPO Form 1010 or EPO Form 1010E or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://publications.european-patent-office.org or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent **together with one copy** of the patent specification provided that the request is filed within the time limit of Rule 71(3) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 71(3) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 71(3) EPC time limit, the certificate will be delivered without a copy of the patent specification (R.74 EPC, Decision of the President of the EPO, Special edition No.3, OJ EPO 2007, D.2).

Note on payment of renewal fees

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71(9) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office
www.epo.org ➞Patents ➞Law ➞Legal texts ➞National law relating to the EPC
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In case of a valid extension

As regards translation requirements prescribed by the Extension States, please consult the website of the European Patent Office
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Failure to supply a prescribed translation in a Contracting State or an Extension State may result in the patent being deemed to be void *ab initio* in the State concerned (Article 65(3) EPC).

Important note to users of the automatic debiting procedure

The fees for grant and printing and also any additional claims fees due under Rule 71(6) EPC will be debited automatically on the date of filing of the translation of the (relevant) claims, or on the last day of the period of this communication. However, if the designation fees become due as set out in Rule 71(8) EPC and/or a renewal fee becomes due as set out in Rule 71(9) EPC, these should be paid separately by another permitted means of payment in order not to delay the publication of the mention of grant. The same applies in these circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying Information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplement to OJ EPO 3/2009).

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Enclosure(s): Form 2056
17 Copies of the relevant documents

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Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 05 758 582.0

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:
- PHARMAZEUTISCHE ZUSAMMENSETZUNG VON PIPERAZINDERIVATEN
- PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES
- COMPOSITION PHARMACEUTIQUE DE DÉRIVÉS DE PIPÉRAZINE

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*)	If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, **all Contracting States/Extension States** are currently still deemed to be designated. See also Rule 71(8) EPC and, if applicable, the above Note to users of the automatic debiting procedure.
**)	If two or more applicants have designated different Contracting States, this is indicated here.

05 758 582.0
UCB PHARCHIM S.A.

PATENTANSPRÜCHE

1. Flüssige pharmazeutische Zusammensetzung, umfassend eine aktive Substanz, ausgewählt aus Cetirizin, Levocetirizin und Efletirizin, und mindestens ein Konservierungsmittel, wobei die Menge an Konservierungsmittel im Falle von Parahydroxybenzoatestern mehr als 0 und weniger als 1,5 mg/ml der Zusammensetzung beträgt, wobei das Konservierungsmittel aus der Gruppe von Methylparahydroxybenzoat, Ethylparahydroxybenzoat, Propylparahydroxybenzoat, einem Gemisch aus Methylparahydroxybenzoat und Ethylparahydroxybenzoat oder Propylparahydroxybenzoat und einem Gemisch aus Methylparahydroxybenzoat und Propylparahydroxybenzoat ausgewählt ist.

2. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, dass sie eine wässerige Zusammensetzung ist.

3. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass das Konservierungsmittel ein Gemisch aus Methylparahydroxybenzoat und Propylparahydroxybenzoat in einem Verhältnis von 9/1, ausgedrückt in Gewicht, ist.

4. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass die pharmazeutische Zusammensetzung eine Menge an p-Hydroxybenzoatestern (Methyl-p-hydroxybenzoat/Propyl-p-hydroxybenzoat in einem Verhältnis von 9/1, ausgedrückt in Gewicht) im Bereich von 0,0001 bis 1,4 mg/ml der Zusammensetzung enthält.

5. Flüssige pharmazeutische Zusammensetzung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, dass die aktive Substanz Cetirizin ist.

6. Flüssige pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass die aktive Substanz Levocetirizin ist.

7. Flüssige pharmazeutische Zusammensetzung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, dass die Zusammensetzung in Form oraler Lösungen, Nasentropfen, Augentropfen oder Ohrentropfen vorliegt.

R E V E N D I C A T I O N S

1. Composition pharmaceutique liquide comprenant une substance active choisie parmi la cétirizine, la lévocétirizine et l'éflétirizine et au moins un conservateur, dans laquelle la quantité du conservateur est, dans le cas de parahydroxybenzoate, supérieure à 0 et inférieure à 1,5 mg/ml de la composition, le conservateur étant choisi dans le groupe du parahydroxybenzoate de méthyle, du parahydroxybenzoate d'éthyle, du parahydroxybenzoate de propyle, d'un mélange de parahydroxybenzoate de méthyle et de parahydroxybenzoate d'éthyle ou de parahydroxybenzoate de propyle et d'un mélange de parahydroxybenzoate de méthyle et de parahydroxybenzoate de propyle.

2. Composition pharmaceutique liquide suivant la revendication 1, caractérisée en ce que c'est une composition aqueuse.

3. Composition pharmaceutique liquide suivant la revendication 1 ou 2, caractérisée en ce que les conservateurs sont un mélange de parahydroxybenzoate de méthyle et de parahydroxybenzoate de propyle dans un rapport de 9/1 exprimé en poids.

4. Composition pharmaceutique liquide suivant la revendication 1 ou 2, caractérisée en ce que la composition pharmaceutique contient une quantité de p-hydroxybenzoate (p-hydroxybenzoate de méthyle/p-hydroxybenzoate de propyle en un rapport de 9/1 exprimé en poids) choisie dans la plage comprise entre 0,0001 et 1,4mg/ml de la composition.

5. Composition pharmaceutique liquide suivant l'une quelconque des revendications précédentes, caractérisée en ce que la substance active est la cétirizine.

6. Composition pharmaceutique liquide suivant l'une quelconque des revendications 1 à 4, caractérisée en ce que la substance

active est la lévocétirizine.

7. Composition pharmaceutique liquide suivant l'une quelconque des revendications précédentes, caractérisée en ce que la composition est sous la forme de solutions orales, de gouttes nasales, de collyres ou de gouttes auriculaires.

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ML/MC

VIA REGISTERED MAIL

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EPO - Munich
20
23. Juni 2009

Our ref.: Case 17.80_EP (WO)
IPD/0906-060

→ *Please quote in all correspondence*

Brussels, June 19, 2009

Your ref.:

Reference: European Patent Application No.05 758 582.0-2112
In the Name of UCB Farchim SA.

Dear Sirs,

Reference is made to the Official Communication pursuant to R. 71(3) EPC dated April 27, 2009, issued in respect of the above-identified patent application.

In accordance with R. 71(3) EPC, you may find enclosed herewith the translation of the allowed claims of the present application in the two other official languages, i.e. in German and French language.

The grant fee is to be paid by debiting our current account No 28020128 (see our automatic debit order).

Yours faithfully

Monique LECHIEN
European Patent Attorney

Enclosures: Translation of the claims in German language (2 pages)
Translation of the claims in French language (2 pages);
Acknowledgement of receipt Form 1037

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27.08.09

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
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Decision to grant a European patent pursuant to Article 97(1) EPC

Following examination of European patent application No. 05758582.0 a European patent with the title and the supporting documents indicated in the communication pursuant to Rule 71(3) EPC dated 27.04.09 is hereby granted in respect of the designated Contracting States.

Patent No. : 1768649
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This decision will take effect on the date on which the European Patent Bulletin mentions the grant (Art. 97(3) EPC).

The mention of the grant will be published in European Patent Bulletin 09/39 of 23.09.09.

Examining Division

Villa Riva A Sproll S Kardas-Llorens E

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ANMERKUNG ZUR ENTSCHEIDUNG ÜBER DIE ERTEILUNG
EINES EUROPÄISCHEN PATENTS (EPA Form 2006)

1. **EPA Informationsbroschüre "Nationales Recht zum EPÜ"**
Diese Broschüre enthält nützliche Informationen zu den formalen Erfordernissen und den Handlungen, die vor den Patentbehörden der Vertragsstaaten vorzunehmen sind, um Rechte in diesen Staaten zu erlangen. Da diese Handlungen einem ständigen Wandel unterworfen sind, sollte immer nur die neueste Ausgabe der Broschüre benutzt werden. Nachträgliche Informationen werden im Amtsblatt veröffentlicht.

2. **Übersetzung der europäischen Patentschrift nach Artikel 65 (1) des Europäischen Patentübereinkommens**
Sie werden erneut darauf hingewiesen, dass bestimmte Vertragsstaaten nach Artikel 65 (1) EPÜ eine Übersetzung der europäischen Patentschrift verlangen; hierauf wird in der Mitteilung gemäß Regel 71 (5) EPÜ verwiesen. Die Nichteinreichung dieser Übersetzung kann zur Folge haben, dass das Patent in dem betreffenden Staat/in den betreffenden Staaten als von Anfang an nicht eingetreten gilt. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.

3. **Zahlung von Jahresgebühren für europäische Patente**
Nach Artikel 141 EPÜ können "nationale" Jahresgebühren für das europäische Patent für die Jahre erhoben werden, die an das Jahr anschließen, in dem der Hinweis auf die Erteilung des europäischen Patents im "Europäischen Patentblatt" bekanntgemacht wird. Weitere Einzelheiten entnehmen Sie bitte der oben genannten Broschüre.

NOTE RELATING TO THE DECISION TO GRANT A
EUROPEAN PATENT (EPO Form 2006)

1. **EPO Information Brochure "National law relating to the EPC"**
This brochure provides useful information regarding formal requirements and the steps to be taken before the patent authorities of the Contracting States in order to acquire rights in those states. Since the necessary steps are subject to change the latest edition of the brochure should always be used. Subsequent information is published In the Official Journal.

2. **Translation of the European patent application under Article 65(1) of the European Patent Convention**
Your attention is again drawn to the requirements regarding translation of the European patent specification laid down by a number of Contracting States under Article 65(1) EPC, to which reference is made in the communication under Rule 71(5) EPC. Failure to supply such translation(s) may result in the patent being deemed to be void "ab initio" in the State(s) in question. For further details you are recommended to consult the above-mentioned brochure.

3. **Payment of renewal fees for European patents**
Under Article 141 EPC "national" renewal fees in respect of a European patent may be imposed for the years which follow that in which the mention of the grant of the European patent is published in the "European Patent Bulletin". For further details you are recommended to consult the above-mentioned brochure.

REMARQUE RELATIVE A LA DECISION DE DELIVRANCE
D'UN BREVET EUROPEEN (OEB Form 2006)

1. **Brochure d'information de l'OEB "Droit national relatif à la CBE"**
Cette brochure fournit d'utiles renseignements sur les conditions de forme requises et sur les actes à accomplir auprès des offices de brevet des Etats contractants aux fins d'obtenir des droits dans les Etats contractants. Etant donné que les actes indispensables sont susceptibles de modifications, il serait bon de toujours consulter la dernière édition de la brochure. Toute information ultérieure est publiée au Journal Officiel.

2. **Traduction du fascicule du brevet européen en vertu de l'article 65(1) de la Convention sur le brevet européen**
Votre attention est de nouveau attirée sur l'obligation faite par certains Etats contractants, en vertu de l'article 65(1) CBE, da fournir une traduction du fascicule du brevet européen, à laquelle il est fait référence dans la notification établie conformément à la règle 71(5) CBE. Si la(les) traduction(s) n'est(ne sont) pas fournie(s), le brevet européen peut, dès l'origine, être réputé sans effet dans cet(ces) Etat(s). Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.

3. **Paiement des taxes annuelles pour le brevet européen**
Conformément à l'article 141 CBE des taxes annuelles "nationales" dues au titre du brevet européen peuvent être perçues pour les années suivant celle au cours de laquelle la mention de la délivrance du brevet européen est publiée au "Bulletin européen des brevets. Pour plus de détails, nous vous renvoyons à la brochure susmentionnée.

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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.

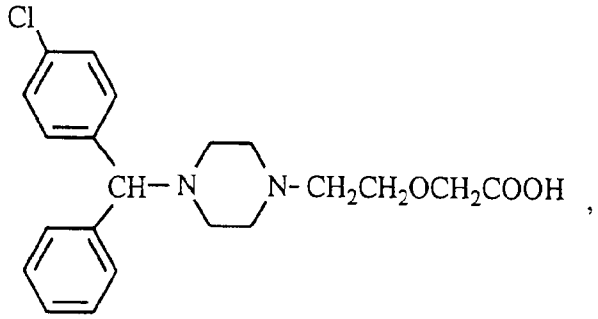
EP 0 605 203 A2

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 macro scopic 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

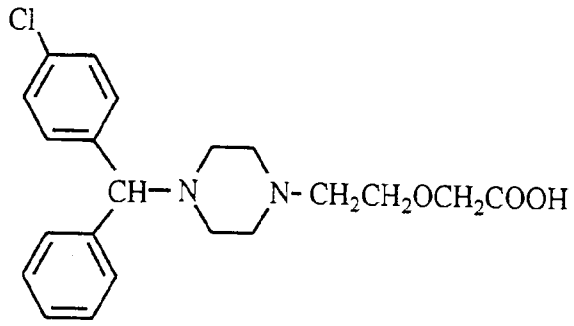
A nasal composition was prepared in solution form according to the following formulation:

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.

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United States Patent [19]

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[54] **OPHTHALMIC AND AURAL COMPOSITIONS CONTAINING DICLOFENAC POTASSIUM**

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[52] **U.S. Cl.** **514/567**; 514/912; 514/913

[58] **Field of Search** 514/567, 912, 514/913

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[57] **ABSTRACT**

The present invention describes an ophthalmic composition diclofenac potassium, the use of said composition as a medicament for treating inflammatory conditions of the eye, for treating glaucoma or for treating ear inflammatory conditions and/or painful conditions (otitis)-l as well as the use of diclofenac potassium in the preparation of a pharmaceutical composition for the treatment of any inflammatory condition of the eye, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

6 Claims, No Drawings

OPHTHALMIC AND AURAL COMPOSITIONS CONTAINING DICLOFENAC POTASSIUM

This application claims priority to European Patent Application No. 95/03844, filed on Sep. 28, 1995.

The present invention describes an ophthalmic composition comprising diclofenac potassium, the use of said composition as a medicament for treating inflammatory conditions of the eye, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis); as well as the use of diclofenac potassium in the preparation of a pharmaceutical composition for treating any inflammatory condition of the eye, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

Hitherto, predominantly corticosteroids have been used for the treatment of relatively severe acute or chronically recurrent inflammatory symptoms in the eye. The immunosuppressant action of these substances, however, conceals the risk of a deterioration in the clinical picture as a result of a bacterial or viral infection. Therefore, considerable efforts are still made, to develop potent non-steroidal anti-inflammatory agents and to introduce them into ophthalmological therapy.

EP 242 328 describes for example a medicament for the treatment of inflammations of the eye, which medicament comprises sodium 2-[(2,6-dichlorophenyl)amino]-phenyl acetate, known as diclofenac sodium.

Diclofenac-potassium, is chemically described as potassium 2-[(2,6-dichlorophenyl)amino]-phenyl acetate. It is known as a non-steroidal anti-inflammatory drug (NSAID). A Norwegian publication, Cephalalgia 13, 117–123(1993), describes for example the use of diclofenac potassium in the acute treatment of migraine.

A stabilized aqueous solution of pharmaceutically acceptable salts of 2-[(2,6-dichlorophenyl)amino]-phenyl acetic acid for ophthalmic use is disclosed in U.S. Pat. No. 4,960,799. Diclofenac potassium is not specifically disclosed in said application. Accordingly, all claims and working examples of said application disclose either diclofenac sodium or its free acid as a pharmaceutically active ingredient. Hence, said application is clearly directed towards the provision of a stable aqueous solution of a pharmaceutically acceptable salt of 2-[(2,6-dichlorophenyl) amino]-phenyl acetic acid containing an effective amount of a pharmaceutically acceptable salt of ethylenediamine tetraacetic acid.

Surprisingly it was found, that the potassium salt of 2-[(2,6-dichlorophenyl)amino]-phenyl acetic acid, diclofenac potassium, is especially suitable to treat inflammatory ocular processes in general. It has been demonstrated that for example the ocular penetration of diclofenac potassium is much superior in comparison to the corresponding diclofenac sodium. In addition to said advantage, pharmacological studies show a much better topical tolerance, e.g. ocular tolerance, and efficacy of diclofenac potassium in comparison to diclofenac sodium and also a surprisingly short onset of action as well a long lasting duration of action e.g. in the eye.

Therefore the present invention relates to an ophthalmic composition for treating inflammatory ocular conditions, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis), which composition comprises a therapeutically effective amount of diclofenac potassium and a carrier.

The present invention relates also to an ophthalmic composition for treating inflammatory conditions of the eye,

which composition comprises a therapeutically effective amount of diclofenac potassium and a carrier.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier and a stabilizer.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier and a solubilizer.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a stabilizer and a solubilizer.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclotenac potassium, a carrier, a solubilizer, a stabilizer and a complexing agent.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a solubilizer, a stabilizer, a complexing agent and a tonicity enhancing agent.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a solubilizer, a stabilizer, a complexing agent, a tonicity enhancing agent and a buffer.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a solubilizer, a stabilizer, a complexing agent, a tonicity enhancing agent, a buffer and a preservative.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium and a carrier, and is further comprising one or more of the excipients selected from the group consisting of buffers, complexing agents, tonicity enhancing agents, preservatives and fillers.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier and a stabilizer, and is further comprising one or more of the excipients selected from the group consisting of buffers, complexing agents, tonicity enhancing agents, preservatives and fillers.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier and a solubilizer, and is further comprising one or more of the excipients selected from the group consisting of buffers, complexing agents, tonicity enhancing agents, preservatives and fillers.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a solubilizer and a stabilizer, and is further comprising one or more of the excipients selected from the group consisting of buffers, complexing agents, tonicity enhancing agents, preservatives and fillers.

Another aspect of the present invention is the use of diclofenac potassium and a carrier in the preparation of a pharmaceutical composition for treating inflammatory ocular conditions, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

The present invention relates also to the use of diclofenac potassium and a carrier in the preparation of a pharmaceutical composition for treating inflammatory ocular processes.

The present invention relates also to the use of diclofenac potassium, a carrier and a stabilizer in the preparation of a

pharmaceutical composition for treating inflammatory ocular conditions, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

The present invention relates also to the use of diclofenac potassium, a carrier, a stabilizer and a solubilizer in the preparation of a pharmaceutical composition for treating inflammatory ocular conditions, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

Still another aspect of the present invention is a method of treating inflammatory ocular conditions, which method comprises administering topically to the eye of a patient requiring such treatment a therapeutically effective amount of an ophthalmic composition comprising diclofenac potassium and a carrier.

The present invention relates also to a method of treating inflammatory ocular conditions, which method comprises administering topically to the eye of a patient requiring such treatment a therapeutically effective amount of an ophthalmic composition comprising diclofenac potassium, a carrier and a stabilizer.

The present invention relates also to a method of treating inflammatory ocular conditions, which method comprises administering topically to the eye of a patient requiring such treatment a therapeutically effective amount of an ophthalmic composition comprising diclofenac potassium, a carrier, a stabilizer and a solubilizer.

In the present invention, treating inflammatory ocular conditions means, treating all ophthalmological diseases involving inflammatory processes, whatever the causes are.

Examples for such causes are e.g. allergic or non-allergic inflammation, immune and non-immune processes, acute or chronic disease. Examples for such treatments of ocular inflammations are the inhibition of miosis during ocular surgery, prevention or treatment of ocular pain during these processes or consequent upon surgery, inhibition of photophobia, treatment of uveitis or ocular inflammation of any cause and the like. Post operative inflammations are for example, of the type associated with cataract removal or photorefractive surgery or incisional refractive surgery, trabeculectomy and combined procedures thereof, painful eye-conditions (including photophobia and post-operative pain), pain associated with trauma or foreign bodies, prevention and treatment of macular edema (idiopathic or associated with surgical interventions or diabetes) and inhibition of miosis.

According to the present invention an ophthalmic composition may also be used for treating glaucoma in connection with non-inflammatory induced elevated intraocular pressure associated with administered or endogenous glucocorticoids.

According to the present invention an ophthalmic composition may also be used for treating ear inflammatory and/or painful conditions (otitis).

According to the present invention an ophthalmic composition may preferably be used for treating inflammatory ocular conditions.

According to the invention an ophthalmic composition is advantageously applied topically to the eye, especially in the form of a solution, a suspension, an ointment, a gel or a solid insert. Such compositions comprise the active ingredient, for example, in a range of from approximately 0.000001 to approximately 5.0% by weight, preferably from approximately 0.001 to approximately 1.0% by weight, or more preferably in the range of from approximately 0.01 to approximately 0.5% by weight and most preferably in the range of from 0.025 to 0.1% by weight. The dose of the active ingredient may depend on various factors, such as mode of administration, requirement, age and/or individual condition. Analogously an above ophthalmic composition may be also topically applied to an ear.

There are used for a corresponding ophthalmic composition customary pharmaceutically acceptable excipients and additives known to the person skilled in the art, for example those of the type mentioned below, especially carriers, stabilizers, solubilizers, tonicity enhancing agents, buffer substances, preservatives, thickeners, complexing agents and other excipients. Examples of such additives and excipients can be found in U.S. Pat. Nos. 5,134,124 and 4,906,613. Such compositions are prepared in a manner known per se, for example by mixing the active ingredient with the corresponding excipients and/or additives to form corresponding ophthalmic compositions. The active ingredient is preferably administered in the form of eye drops, the active ingredient being conventionally dissolved, for example, in a carrier. The solution is, where appropriate, adjusted and/or buffered to the desired pH and, where appropriate, a stabilizer, a solubilizer or a tonicity enhancing agent is added. Where appropriate, preservatives and/or other excipients are added to an ophthalmic composition.

Carriers used in accordance to the present invention are typically suitable for topical or general administration, and are for example water, mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethylcellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone and other non-toxic water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar and acacia, starch-derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid, such as neutral Carbopol, or mixtures of those polymers. Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, neutral Carbopol, or mixtures thereof. The concentration of the carrier is, for example, from 1 to 100 000 times the concentration of the active ingredient.

The solubilizers used for an ophthalmic composition of the present invention are, for example, tyloxapol, fatty acid glycerol poly-lower alkylene glycol esters, fatty acid poly-lower alkylene glycol esters, polyethylene glycols, glycerol ethers vitamin E and vitamin E derivatives, such as Vitamin E Tocopherol Polyethylene Glycol 1000 Succinate (TPGS) or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL® or Cremophor RH 40®. Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is tyloxapol. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For

example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.

According to the present invention lower alkylene means linear or branched alkylene with up to and including 7 C-atoms. Examples are methylene, ethylene, 1,3-propylene, 1,2-propylene, 1,5-pentylene, 2,5-hexylene or 1,7-heptylene.

Lower alkylene is preferably linear or branched alkylene with up to and including 4 C-atoms.

Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate/carbonate, citrate, gluconate, lactate, phosphate, propionate and TRIS (tromethamine) buffers. Tromethamine and borate buffer are preferred buffers. The amount of buffer substance added is, for example, that necessary to ensure and maintain a physiologically tolerable pH range. The pH range is typically in the range of from 5 to 9, preferably from 6 to 8.2 and more preferably from 6.8 to 8.1.

Tonicity enhancing agents are, for example, ionic compounds, such as alkali metal or alkaline earth metal halides, such as, for example, $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, or boric acid. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose. For example, sufficient tonicity enhancing agent is added to impart to the ready-for-use ophthalmic composition an osmolality of approximately from 50 to 1000 mOsmol, preferred from 100 to 400 mOsmol, more preferred from 200 to 400 mOsmol and even more preferred from 280 to 350 mOsmol.

Examples of preservatives are quaternary ammonium salts, such as cetrimide, benzalkonium chloride or benzoxonium chloride, alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate, parabens, such as, for example, methylparaben or propylparaben, alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide, or sorbic acid. Preferred preservatives are cetrimide, benzalkonium chloride, benzoxonium chloride and parabens. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi.

The ophthalmic compositions may comprise further non-toxic excipients, such as, for example, emulsifiers, wetting agents or fillers, such as, for example, the polyethylene glycols designated 200, 300, 400 and 600, or Carbowax designated 1000, 1500, 4000, 6000 and 10 000. Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. They are especially complexing agents, such as disodium-EDTA or EDTA, antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butyl-hydroxyanisole, butyl-hydroxytoluene or α-tocopherol acetate; stabilizers, such as a cyclodextrin, thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol vitamin E and vitamin E derivatives, such as Vitamin E Tocopherol Polyethylene Glycol 1000 Succinate (TPGS); or other excipients, such as, for example, lauric acid sorbitol ester, triethanol amine oleate or palmitic acid ester. Preferred excipients are complexing agents, such as disodium-EDTA and stabilizers, such as a cyclodextrin. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from approximately 0.0001 to approximately 90% by weight.

A cyclodextrin as is referred to within the present invention is either an α-, β- or γ- cyclodextrin itself, a derivative thereof, e.g. a partially etherified derivative as e.g. a hydroxyalkyl ether or a mixture thereof. Examples of cyclodextrin derivatives are alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated α-, β- or γ-cyclodextrins. Other typical examples are carbohydrate derivatives of cyclodextrins such as mono- or diglycosyl-α-, β- or γ- cyclodextrin, mono- or dimaltosyl-α-, β- or γ-cyclodextrin or panosylcyclodextrin. Another parameter which describes the substitution pattern of a cyclodextrin derivative is the degree of substitution (d.s.). A cyclodextrin is composed of several glucose units which have three free hydroxy groups per glucose. Accordingly the d.s. may vary from 0.125 up to 3. In the latter case all free (γ-cyclodextrin has 24) hydroxy groups may be substituted, while in the former case only 1 may be substituted. Preferably the d.s. may vary from 0.125 to 1.5 and more preferably from 0.125 to 0.5.

Preferred cyclodextrins are β- and γ- ciclodextrin, derivatives and mixtures thereof.

Strongly preferred cyclodextrins are hydroxypropyl-β-ciclodextrin, hydroxypropyl-γcyclodextrin, dimethyl-β-cyclodextrin and dimethyl-γ- ciclodextrin.

The amount of a cyclodextrin used in accordance with the present invention may preferably range from 0.01–20% by weight, more preferably from 0.1–15 % by weight and even more preferably from 1–10% by weight.

The present invention relates also to an ophthalmic composition, which comprises a therapeutically effective amount of diclofenac potassium, a carrier, a solubilizer and another therapeutically effective pharmaceutical agent which may be, for example, an antibiotic, an antiallergic, an anesthetic, another antiphlogistic, a corticosteroide, an agent suitable for lowering intra-ocular pressure, or another drug.

Several animal models are used for the demonstration of the claimed therapeutic efficacy of the ophthalmic compositions comprising diclofenac potassium. In each animal model several ophthalmic reference drugs are administered for comparison.

In a first animal model, the ocular distribution and lens penetration of diclofenac potassium and diclofenac sodium is determined after multiple topical ocular administration of a corresponding eye drop composition. Hence 14C labelled eye drop material is topically administered to the eyes of chinchilla pigmented rabbits (5 instillations, 50 μl each, within 20 minutes). At regular intervals post-instillation (0.5, 1.5, 2.0 hours), the animals are sacrificed and both eyes are removed. Said eyes are microdissected and the ocular distribution of the radioactivity is measured by a standard scintillation beta counting method. The highest concentrations are found in the cornea, and in descending order in the aqueous humor, in the iris ciliary body and in the vitreous. According to this experimental setup, the diclofenac potassium treated animals clearly displayed higher levels of radioactivity in the aforementioned areas than the diclofenac sodium treated animals.

Another animal model is used for the comparison of the ocular anti-inflammatory efficacy of diclofenac potassium in comparison to diclofenac sodium, which model is the arachidonic acid induced uveitis in pigmented rabbits. Repeated instillations of arachidonic acid into the eye of rabbits induce an ocular inflammation, which inflammation significantly increases the flare level in the anterior chamber of rabbits. A laser cell flare meter (LCFM) is used for the quantification of said flare levels. This method is described by e.g. M. Kuchle et al., Ophthalmologe 91, 219(1994), and

is a non-invasive method. It has been demonstrated, that the flare determination by LCFM reflects the amounts of proteins comprised in the aqueous humor. These proteins are commonly used as markers in assessing the degree of an inflammation. For the non-invasive evaluation of the efficacy of an anti-inflammatory drug, said drugs are administered by using two instillations one hour and 45 minutes before the induction of an arachidonic acid induced inflammation as described above. A control group of animals is treated with a single instillation of non-preserved saline (Unilarm®). The inflammation process is monitored during 6 hours post-inflammation by the above described LCFM measurements.

In a further animal model the ocular anti-inflammatory efficacy of diclofenac potassium is determined with a traumatic uveitis model. Uveitis is induced in said model by an argon laser iris photocoagulation in pigmented rabbits. Said iris photocoagulation is induced by 500 μm argon laser burns (power 750 mW, duration 0.1 sec). The inflammatory processes resulting therefrom are measured every 30 minutes after the laser induced photo-coagulation, by using the laser cell flare meter (LCFM) technique. For the evaluation of the efficacy of an anti-inflammatory drug, said drugs are again administered by two instillations, one hour and 45 minutes prior to the induction of an inflammation as described above. A control group of animals is treated with instillations of non-preserved saline (Unilarm®). Again the inflammation process is monitored during 6 hours.

In addition to the non invasive LCFM evaluation of the above mentioned animal model, an invasive evaluation is carried out. Therefore the rabbits are sacrificed one hour and in regular intervals after which said eyes have been subjected to the traumatic uveitis by photocoagulation, and the aqueous humor of said rabbit eyes is sampled. The aqueous protein levels, cell counts and prostaglandins (PGE2, PGD2, 6-keto PGF1α) which represent the degree of an inflammation are biochemically investigated and quantified.

Another animal model is used for the induction of a traumatic uveitis. It is the induction of a uveitis by the paracentesis of the anterior chamber of the rabbit eye. In analogy to the previously described laser induced uveitis model, drugs to be tested, are again administred prior to the paracentesis challenge. In this animal model, the animals are again sacrificed at regular intervals, and the inflammatory process is investigated by sampling the aqueous humor of the challenged rabbit eyes. The aqueous protein levels are again analyzed, quantified and then correlated with the degree of an inflammation.

In all the aforementioned animal models, there is clear evidence that animals which are treated with diclofenac potassium benefit from a better efficacy compared to the animals treated with diclofenac sodium.

Typical experimental procedures which illustrate the present invention, but are not intended to limit it in any way, are described below.

EXAMPLE 1

Formulation of diclofenac potassium eye drops (0.1%)

diclofenac potassium	1.00 mg/ml
thiomersal	0.04 mg/ml
boric acid	19.0 mg/ml
cremophor EL ® (polyoxyl 35 castor oil)	50.0 mg/ml
tromethamine	6.0 mg/ml
deion. water ad.	1.0 ml

EXAMPLE 2

Formulation of diclofenac potassium eye drops (0.05%)

diclofenac potassium	0.50 mg/ml
benzalkonium chloride	0.05 mg/ml
disodium edetate	1.0 mg/ml
tyloxapol	1.0 mg/ml
γ-cyclodextrin	20.0 mg/ml
tromethamine	1.0 mg/ml
hydrochloric acid 10%	1.3 mg/ml
sorbitol	46.0 mg/ml
deion. water ad.	1.00 ml

EXAMPLE 3

Formulation of non-preserved uni-dose diclofenac potassium eye drops (0.1%)

diclofenac potassium	1.00 mg/ml
disodium edetate	1.0 mg/ml
tyloxapol	0.1 mg/ml
dimethyl-β-cyclodextrin	40.0 mg/ml
tromethamine	1.0 mg/ml
hydrochloric acid 10%	1.3 mg/ml
sorbitol	41.0 mg/ml
deion. water ad.	1.00 ml

EXAMPLE 4

Formulation of oily eye drops

diclofenac potassium	0.50 mg/ml
benzalkonium chloride	0.1 mg/ml
cremophor RH 40 ®, (polyoxyl 40 hydrogenated castor oil)	20.0 mg/ml
castor oil ad.	1.00 ml

EXAMPLE 5

Formulation of an eye gel

diclofenac potassium	0.50 mg/g
thiomersal	0.04 mg/g
boric acid	1.8 mg/g
cremophor EL ® (polyoxyl 35 castor oil)	4.0 mg/g
tromethamine	13.0 mg/g
carbomer 980	4.0 mg/g
deion. water ad.	1.00 g

EXAMPLE 6

Formulation of an eye gel

diclofenac potassium	1.00 mg/g
benzalkonium chloride	0.1 mg/g
tyloxapol	1.0 mg/g
mannitol	30.0 mg/g
hydrochloric acid 10%	1.0 mg/g
disodium edetate	0.5 mg/g
chitosan	10.0 mg/g
deion. water ad.	1.00 g

EXAMPLE 7

Formulation of an eye ointment

diclofenac potassium	1.00 mg/g
phenylethyl alcohol	5.0 mg/g
tyloxapol	1.0 mg/g
disodium edetate	0.5 mg/g
γ-cyclodextrin	20.0 mg/g
deion. water	140 mg/g
cetylstearyl alcohol	22.0 mg/g
liquid paraffin	207 mg/g
white petrolatum	462 mg/g
wool fat	141.5 mg/g

EXAMPLE 8

Formulation of diclofenac potassium eye drops (0.05%)

diclofenac potassium	0.5 mg/ml
cremophor RH ® (polyoxyl 40 hydrogenated castor oil)	0.6 mg/ml
tromethamine	1.0 mg/ml
disodium edetate	0.5 mg/ml
sorbitol	49.0 mg/ml
benzalkonium chloride	0.15 mg/ml
hydrochloric acid 1N	5.1 mg/ml
water for injections ad	1.0 ml
pH	7.53
osmolality (mOsmol):	317

EXAMPLE 9

Formulation of diclofenac sodium eye drops (0.1%)

diclofenac sodium	1.0 mg/ml
cremophor RH ® (polyoxyl 40 hydrogenated castor oil)	0.6 mg/ml
tromethamine	1.0 mg/ml
disodium edetate	0.5 mg/ml
sorbitol	49.0 mg/l
benzalkonium chloride	0.15 mg/ml
hydrochloric acid 1N	5.52 mg/ml
water for injections ad	1.0 ml
pH	7.49
osmolality (mOsmol):	308

EXAMPLE 10

Formulation of an eye drop vehicle

cremophor RH ® (polyoxyl 40 hydrogenated castor oil)	0.6 mg/ml
tromethamine	1.0 mg/ml
disodium edetate	0.5 mg/ml
sorbitol	49.0 mg/ml
benzalkonium chloride	0.15 mg/ml
hydrochloric acid 1N	5.0 mg/ml
water for injections ad	1.0 ml
pH:	7.53
osmolality (mOsmol):	301

EXAMPLE 11

Formulation of diclofenac potassium eye drops (0.1%)

diclofenac potassium	1.0 mg/ml
cremophor RH ® (polyoxyl 40 hydrogenated castor oil)	0.6 mg/ml
tromethamine	1.0 mg/ml
disodium edetate	0.5 mg/ml
sorbitol	49.0 mg/ml
benzalkonium chloride	0.15 mg/ml
hydrochloric acid 1N	5.7 mg/ml
water for injections ad	1.0 ml
pH:	7.35
osmolality (mOsmol):	314

EXAMPLE 12

Changes in aqueous flares (expressed as the area under the kinetic curves (AUC)) for the arachidonic acid induced uveitis model, carried out in pigmented rabbits.

The drugs listed infra (including placebo) are applied topically (30 μl each) to the left eye of pigmented rabbits (chinchilla pigmented female rabbits) one hour before arachidonic acid instillations. Each opposite eye is instilled for control with 30 μl of the vehicle formulation of example 10. Before the instillation of arachidonic acid, the animals are anesthetized with intramuscular injections of 35 mg/kg ketamine (Imalgene 1000®, Rhone Merieux) and 15 mg/kg xylazine (Rompun-Bayer). Arachidonic acid (0.5% aqueous solution, freshly prepared before use) is then instilled into both eyes of the rabbits with a Hamilton syringe (twice 50 μl). A time interval of 5 minutes is kept between each instillation. The flares are then measured hourly, using an LCFM over a total period of 6 hrs after the arachidonic acid challenge. Before each measurement, the animals are freshly anesthetized with intramuscular injections of 35 mg/kg ketamine (Imalgene 1000®, Rhone Mérieux) and 15 mg/kg xylazine (Rompun-Bayer), in order to completely immobilize the eyes. The LCFM method is similar to a slit lamp microscopy examination. The laser beam of a Kowa FC-1000 LCFM is scanning vertically within a distance of 0.6 mm towards the center of the anterior chamber. Each measurement lasts about 0.5 seconds. Such a measurement is repeated five times for each eye and the average of the photon counts is then calculated and plotted versus the observation time, which lasts in total 6 hours calculated from the induction of the inflammation. The results are summarized below, which show the integrated photon counts of the treated and of the control eyes (AUC(treated) and AUC (control)), representing the overall degree of said induced inflammation over said 6 hours. Accordingly a high AUC number represents a strong inflammation, whereas a low AUC number represents a low degree of inflammation.

The ratio, AUC(treated) divided by AUC(control), is calculated as well. A low ratio value represents a strong anti-inflammatory efficacy, whereas a ratio value of about 1 reflects the substantial absence of an anti-inflammatory effect.

Drug	AUC(t)reated Mean ± SEM	AUC(c)ontrol Mean ± SEM	Ratio AUC(t)/AUC(c) Mean ± SEM
placebo group (Unilarm ®)	1616 ± 130	1793 ± 171	0.93 ± 0.09
diclofenac potassium Example 8	99 ± 20	1043 ± 186	0.1 ± 0.02
diclofenac sodium Example 9	558 ± 141	1462 ± 270	0.46 ± 0.12

The AUC(treated) values show the superior efficacy of diclofenac potassium (example 8) in comparison to the efficacy of diclofenac sodium (example 9). The inflamma-

tion in the animal group receiving diclofenac potassium is almost totally suppressed. Taking into account the fact that the drug concentration of diclofenac sodium (example 9) is twice the concentration of diclofenac potassium (0.1% versus 0.05%), diclofenac potassium is considered to have more than five fold efficacy of diclofenac sodium.

EXAMPLE 13

Lens penetration and ocular distribution of diclofenac potassium and diclofenac sodium were determined after multiple topical ocular administration of corresponding 14-C labelled eye drop composition into the conjunctival sac of the right eye of pigmented rabbits.

At 0.5, 1.5, 2 hours post-instillation, 5 animals for each time-point and each treatment group were sacrificed and the radioactivity content (in ng-Eq/g of structure) in the cornea, aqueous humor, iris-ciliary body, vitreous, whole blood and plasma was measured. At 2 hours post-instillation, the left eyes were removed and the ocular distribution was measured by a standard scintillation beta counting method. The right lenses were used for autoradiography.

The areas under the curve (AUC: ng-Eq/g of structure versus time) were calculated and statistically compared.

The results indicated that the ocular penetration of diclofenac potassium is much superior in comparison to diclofenac sodium:

	Sampling time (hour)	AUC: (ng-Eq/g) Mean = 5	SEM
Example 8	0.5	58978	19724
14-C-diclofenac	1.5	34385	3669
potassium	2.0	23114	4093
Example 9	0.5	30342	5721
14-C-diclofenac sodium	1.5	20201	5061
	2.0	13840	3497

Example 8

14-C-diclofenac potassium

AUC: (ng-Eq/g) * hour Mean = 5	SEM
61056	9131

Example 9

14-C-diclofenac sodium

AUC: (ng-Eq/g) * hour Mean = 5	SEM
33782	3826

The highest concentration were found for both studied drugs in the comea and in descending order in aqueous humor, iris-ciliary body and vitreous.

EXAMPLE 14

Eye drop formulations

diclofenac potassium	1.00 mg	0.5 mg
tromethamine	1.00 mg	1.00 mg
propylene glycol	20.5 mg	20.5 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg
benzalkonium chloride	0.06 mg	0.06 mg
hydrochloric acid 1N	qs	qs
water for injections ad	1.00 ml	1.00 ml
pH	7.90	7.90
osmolality (mOsmol)	296	296
preservative efficacy (Ph. Eur.)	A	A

The European Pharmacopoeia (Ph. Eur.) describes an efficacy test for antimicrobial preservation. Accordingly a preserved solution is inoculated with micro-organisms, characterized in that 10^5 to 10^6 micro-organisms are contained in one milliliter of the challenged preparation. The inoculum used does not exceed 1% of the total volume of said preparation. Five micro-organisms are used for the challenge, each separately namely, pseudomonas aeruginosa, staphylococcus aureus, candida albicans and aspergillus niger. The challenged solutions are kept at room temperature and protected from light. At regular time intervals samples are removed and the number of viable micro-organisms is determined either by plate count or by membrane filtration. For ophthalmic preparations the European Pharmacopoeia recommends criteria "A", which require e.g. that the bacterial micro-organisms are reduced by a factor of 1000, 24 hours after the challenge. Criteria "B" are still acceptable according to the recommendations of the European Pharmacopoeia, and require e.g. that the bacterial micro-organisms are reduced by a factor of 10, 24 hours after the challenge (for details refer to the European Pharmacopoeia, 1994). Accordingly, whenever the preservative efficacy recommendations of the European Pharmacopoeia are referred to herein, this relates to the 1994 version.

EXAMPLE 15

Diclofenac potassium eye drop formulations

diclofenac potassium	1.00 mg	0.5 mg
tyloxapol USP	1.00 mg	1.00 mg
tromethamine	1.00 mg	1.00 mg
propylene glycol	19.0 mg	19.0 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg
benzalkonium chloride	0.05 mg	0.05 mg
hydrochloric acid 1N	qs	qs
water for injections ad	1.00 ml	1.00 ml
pH	7.96	7.98
osmolality (mOsmol)	305	303

EXAMPLE 16

Eye gel formulation comprising diclofenac potassium

diclofenac potassium	1.00 mg	1.00 mg
tyloxapol USP	1.00 mg	1.00 mg
tromethamine	6.50 mg	6.50 mg
propylene glycol		19.0 mg
sorbitol	40.0 mg	
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg

-continued

disodium edetate	1.00 mg	1.00 mg
benzalkonium chloride	0.05 mg	0.05 mg
carbopol 980	3.50 mg	3.50 mg
water for injections ad	1.00 ml	1.00 ml
pH	8.06	8.00
osmolality (mOsmol)	298	308
viscosity (mPa s)	450	380

EXAMPLE 17

Eye drops SDU (single dose units, non-preserved)

diclofenac potassium	1.00 mg	0.5 mg
tyloxapol USP	1.00 mg	1.00 mg
tromethamine	1.00 mg	1.00 mg
propylene glycol	19.0 mg	19.0 mg
hydroxypropyl-γ-cyclodextrin	20.0 mg	20.0 mg
disodium edetate	1.00 mg	1.00 mg
hydrochloric acid 1N	qs	qs
water for injections ad	1.00 ml	1.00 ml
pH	7.95	7.98
osmolality (mOsmol)	301	300

EXAMPLE 18

Preservative efficacy

diclofenac sodium	1.00 mg	1.00 mg	—
diclofenac potassium	—	—	1.00 mg
2-hydroxypropyl-β-cyclodextrin	15.0 mg	20.0 mg	15.0 mg
2-hydroxyethyl-β-cyclodextrin	15.0 mg	20.0 mg	15.0 mg
hydroxypropyl-γ-cyclodextrin	—	—	—
boric acid	13.0 mg	13.0 mg	13.0 mg
borax	8.6 mg	8.6 mg	8.6 mg
methylparabene	0.26 mg	0.26 mg	0.26 mg
propylparabene	0.14 mg	0.14 mg	0.14 mg
sodium hydroxide 0.1N	8.0 mg	6.0 mg	—
water for injections ad	1.0 ml	1.0 ml	1.0 ml
pH:	7.80	7.86	7.89
Osmolality (mOsmol)	332	325	308
preservative efficacy Ph. Eur.	r.n.m.	r.n.m.	r.n.m.

-continued

r.n.m.(recommendations not met), the preservative efficacy of the corresponding composition does not meet the recommendations of the European Pharmacopoeia.

EXAMPLE 19

Preservative efficacy

diclofenac sodium	—	—	1.00 mg
diclofenac potassium	1.00 mg	1.00 mg	—
2-hydroxypropyl-β-cyclodextrin	20.0 mg	—	—
2-hydroxyethyl-β-cyclodextrin	20.0 mg	—	—
hydroxypropyl-γ-cyclodextrin	—	20.0 mg	20.0 mg
boric acid	13.0 mg	13.0 mg	13.0 mg
borax	8.6 mg	8.6 mg	8.6 mg
methylparabene	0.26 mg	0.26 mg	0.26 mg
propylparabene	0.14 mg	0.14 mg	0.14 mg
sodium hydroxide 0.1N	2.0 mg	0.3 mg	0.4 mg
water for injections ad	1.0 ml	1.0 ml	1.0 ml
pH: (8 ± 0.3)	7.90	7.89	7.92
Osmolality (mOsmol), (300 ± 30)	323	288	285
preservative efficacy Ph. Eur.	r.n.m.	r.n.m.	r.n.m.

We claim:

1. A method of treating inflammatory ocular conditions, or glaucoma, which method comprises administering topically to the eye of a patient requiring such treatment a therapeutically effective amount of an ophthalmic composition comprising diclofenac potassium and a carrier.

2. The method of claim **1** wherein said ophthalmic composition further comprises a stabilizer.

3. The method of claim **1** wherein said ophthalmic composition further comprises a solubilizer.

4. The method of claim **1** wherein said ophthalmic composition further comprises a stabilizer and a solubilizer.

5. The method of claim **2** wherein said stabilizer is a cyclodextrin.

6. The method of claim **1** wherein said ophthalmic composition comprises from 0.000001 to 5% by weight of diclofenac potassium.

* * * * *

OPPOSITION AGAINST EP 1 768 649 B1

Facts and arguments

The opposed patent EP 1 768 649 B1, herein after referred to as B1, has been filed on 07.07.2005 and claims priority from a European patent application EP04016519 filed on 14.07.2004.

Cited documents

D1 EP 0 605 203 A2 (publ. 6 July 1994)

D2 US 5,891,913 A (publ. 6 April 1999)

D3 KIBBE A.H., "Handbook of Pharmaceutical Excipients", 3. edition 2000, American Pharmaceutical Association, pages 340, 450.

D4 WANG D.Y., "Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers", Allergy 56, (2001), pages 339-343

D5 Marketing authorization for ZODAC®GTT in Slovakia

D6 Marketing authorization for ZODAC®SIR in Slovakia

D7 Marketing authorization for ZODAC®GTT in the Czech Republic

D8 Marketing authorization for ZODAC®SIR in the Czech Republic

D9 Summary of product characteristics for ZODAC®GTT

D10 Summary of product characteristics for ZODAC®SIR

D11 Thomson Reuters Newport Premium: Launched Drug Forms Detail

Claim 1 – independent claim

Claim 1 discloses a liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, and at least one preservative being 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. The amount of preservative is said to be more than 0 and less than 1.5 mg/ml.

Levocetirizine is the levorotatory enantiomer of cetirizine, cetirizine being the racemate of [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid. Efletirizine is 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid. All these active substances are substituted benzhydryl piperazines. The preservatives are all parahydroxybenzoate esters, i.e. parabens.

As indicated in the description of B1 (paragraph [0014]) the processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in EP 0058146, GB 2225320, GB 2225321, US 5478941, EP 0601028, EP 0801064 and WO 97/37982. The preparation of levocetirizine is described in GB 2225321, US 4800162 and US 5057427 (B1, paragraph [0015]) and processes for preparing efletirizine and pharmaceutically acceptable salt thereof have been described in EP1034171, WO97/37982 and WO03/009849 (paragraph [0016]).

Lack of Novelty – Art. 54(1) and (2) EPC – Public prior use

Claim 1 lacks novelty based on public prior use of two products named ZODAC®GTT and ZODAC®SIR.

The marketing authorizations for these products were granted on 29 November 2000 in Slovakia (D5 and D6) and 18 April 2001 in the Czech Republic (D7 and D8) for the company Leciva. The company Leciva has later become the opponent Zentiva. When the marketing authorizations had been granted the information for the patient information leaflets, the summary of product characteristics (SmPC's) (D9 and D10) were published, i.e. well before the priority date of B1.

ZODAC®GTT and ZODAC®SIR were launched in the Czech Republic the launch took place on 31 October 2001 and in Slovakia on 30 September 2002, i.e. also before the priority date of B1. The launch dates can be found from the Thomson Reuters Newport Premium: Launched Drug Forms Detail –list (D11).

ZODAC®GTT is a cetirizine product in the form of drops. According to the SmPC (D9) the composition of ZODAC®GTT comprises 1.35 mg/ml of methylparaben and 0.15 mg/ml of propylparaben.

ZODAC®SIR is a cetirizine product in the form of syrup. According to the SmPC (D10) the composition of ZODAC®GTT comprises 1.35 mg/ml of methylparaben and 0.15 mg/ml of propylparaben.

Independently of whether the information on the amounts of parabens of ZODAC®GTT and ZODAC®SIR was published at the priority date of B1 or not, the compositions of the products were part of the state of the art after the launch of the products since the composition of the products could be analyzed without undue burden. This is confirmed by T406/86 and G1/92.

Further evidence of the public prior use and the products ZODAC®GTT and ZODAC®SIR being publicly on the market will be provided later if needed. Translations of the marketing authorizations will be filed in accordance with the Implementing Regulations.

The margin of experimental error of a numerical range

From D9 to D11 it is evident that both the ZODAC®GTT and ZODAC®SIR, publicly used before the priority date of B1, comprise a total amount of 1.5 mg/ml of methylparaben and propylparaben. Claim 1 of B1, comprises a range of "more than 0 and less than 1.5 mg/ml" of parahydroxybenzoates. Thus, the question is whether the claimed upper limit "lower than 1.5 mg/ml" is novel over the prior use value 1.5 mg/ml.

In T 594/01 the claimed subject matter was distinguished from a specific experimental value disclosed in the prior art only in the terms of an upper limit to be required to be "lower than" the specific value. In this decision the board stated that it is common general knowledge that experimental measurements cannot be dissociated from the margin of uncertainty attached to the measurement and therefore the claimed subject matter in this case was not distinguishable from the prior art within the margin of experimental error. Therefore the upper limit distinguished only by the terms "lower than" was not considered novel. Thus, since there is always a tolerance area around a certain value the upper end point of the claimed range "lower than 1.5 mg/ml" is not novel over the public prior use of 1.5 mg/ml.

Thus, all the features of claim 1 have been disclosed during the public prior use and therefore claim 1 lacks novelty.

Lack of Inventive Step – Art. 56 EPC – D1 and D3

D1 is considered to be the closest prior art, since D1 relates to a composition comprising cetirizine or a salt thereof as an active ingredient and parahydroxybenzoate esters as preservatives.

More in detail D1 discloses a liquid pharmaceutical composition comprising an active ingredient cetirizine and thereto as preservatives methylparaben (i.e. methyl parahydroxybenzoate) and propylparaben

(i.e. propyl parahydroxybenzoate) (Page 11, Example 5). D1 therefore discloses the preservative being methylparaben, propylparaben or a mixture of these and thereto D1 generally states that p-hydroxybenzoates are used as preservatives (page 3, l. 52).

D1 does not disclose;

i) the amount of the parahydroxybenzoate ester being more than 0 and less than 1.5 mg/ml but discloses the amount of the parabens (i.e. the parahydroxybenzoate esters) being 2 mg/ml of methyl paraben and 1 mg/ml of propyl parahydroxybenzoate (Page 11, Example 5). Thereto it is indicated in D1 (page 3, l. 56-57) that the amount of additive (for example the amount of preservative) to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic and nasal solutions.

ii) the alternatives where the active substance is levocetirizine or efletirizine

iii) the alternatives where the paraben is ethyl parahydroxybenzoate or a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate.

The effect of the first missing feature i) is achieving the recommended efficacy criteria of antimicrobial preservation for different uses of the composition. The problem to be solved is thus how to achieve a useful composition having this recommended efficacy of antimicrobial preservation.

In a Handbook of Pharmaceutical Excipients (D3) the person skilled in the art finds information regarding the concentrations of methylparabens and propylparabens that should be used for different uses.

D3 discloses using 0.15-2 mg/ml methylparabens and/or 0.05-0.1 mg/ml propylparabens in ophthalmic preparations, 0.15-2 mg/ml methylparabens and/or 0.1-0.2 mg/ml propylparabens in oral solutions and suspensions and 0.33 mg/ml methylparabens and/or 0.17 mg/ml propylparabens in nasal solutions.

According to D3 the amount of methylparabens should be 0.15-2 mg/ml and/or the amount of propylparabens 0.05-0.1 mg/ml in an ophthalmic composition, as the one disclosed in D1 (Page 11, Example 5). Three of the explicitly disclosed points (0.15, 0.05 and 0.1) of the overlapping prior art ranges falls in the claimed range "more than 0 and less than 1.5 mg/ml".

D1 indicates that the amount of preservatives to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic and nasal solutions. In a relevant handbook relating to excipients in pharmaceuticals (D3) the person skilled in the art finds different concentrations for different uses of parabens.

For the person skilled in the art preparing a liquid composition it is obvious to have the preservatives on the lowest possible level. Thereto a person working with pharmaceuticals and parabens before and at the time of the priority date of B1 was certainly aware of the controversial discussions going on about parabens. This controversial scientific discussion regarding the safety and toxicology of parabens used as preservatives especially in cosmetics, but also in pharmaceuticals, gave a further incentive for the person skilled in the art to consider the amount of preservatives to be used carefully, for example by consulting a handbook.

Thus, the skilled person had a reason to consider the amount of preservative carefully and would without an inventive step have arrived at an embodiment where the amount of paraben is chosen

within the claimed range. Since three of the explicitly disclosed points of D3 falls in the claimed range, claim 1 lacks inventive step based on D1 and D3 when the active compound is chosen to be cetirizine and the preservatives are methyl parahydroxybenzoate, propyl parahydroxybenzoate or a mixture thereof.

As defined above D1 does further not disclose (point ii)) the alternatives of the active substance being levocetirizine or efletirizine. However, according to the description of B1 all the mentioned active substances are substituted benzhydryl piperazines and the invention relates to the finding of an active substance belonging to the family of substituted benzhydryl piperazines giving the alleged effect of the invention (B1, [0009]). B1 does not mention any special technical effect of levocetirizine or efletirizine. See additional argumentation regarding levocetirizine for claim 6 below.

D1 does not either disclose (point iii)) the alternatives of the paraben being ethyl parahydroxybenzoate or a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate. Ethyl parahydroxybenzoate is however, a common paraben widely used as preservative. The description of B1 does further not mention any special technical effect of ethyl parahydroxybenzoate or the mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate. Thereto D1 (page 3, l. 52-53) generally mentions the use of parahydroxybenzoates and D11 mentions the use of methylparaben in combination with other parabens (page 340, point 7).

Thus the use of the levocetirizine or efletirizine as the active substance and ethyl parahydroxybenzoate or a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate as preservatives in the pharmaceutical composition of the invention are obvious alternatives to the use of cetirizine and methyl- and propylparabens of D1 and D3.

Claims 2, 3, 5, 7 – dependent from claim 1 to 4

Lack of Novelty – Art. 54(1) and (2) EPC – public prior use

The additional features disclosed in claims 2, 3, 5 and 7 (the oral solution) only lists further features of the ZODAC compositions of the public prior use according to D5 to D11.

As shown above claim 1 lacks novelty over the prior use and also the additional features disclosed in claims 2, 3, 5 (dependent on claim 1-3) and 7 (partially, dependent on claim 1-3 and 5) lack novelty over the public prior use.

Lack of Inventive Step – Art. 56 EPC – D1 and D3

The additional features disclosed in claims 2, 3, 5 and 7 only lists further features already disclosed in D1 and/or D3.

D1 is considered to be the closest prior art for these dependent claims since D1 already discloses the features mentioned for claim 1 above and thereto further discloses the liquid pharmaceutical composition being an aqueous composition and the active substance being cetirizine (D1, Page 11, Example 5). Further many of the different forms of compositions of claim 7 are also disclosed in D1. D1 mentions the whole field of ophthalmology and otorhinology and especially ophthalmic solutions and nasal solutions (page 4, l. 3-11).

D3 discloses using a mixture of 0.18 % methylparaben and 0.2 % propylparaben, i.e. in a ratio of 9/1. Thereto D3 discloses the use of methylparaben in nasal solutions, ophthalmic preparations, oral solutions and suspensions as well as in topical preparations.

According to D2 ophthalmic compositions comprising parabens and used for example for allergic inflammations may be used for treating ear inflammatory conditions or topically applied to an ear (paragraph

3, 51-52 and paragraph 4, l. 2-3). Thus, the composition of the invention in the form of ear drops is implicitly comprised in both D1 and D3 both relating to ophthalmic solutions or preparations. D3 thereto also discloses topical preparations.

It should be noted that Claim 7 only defines the form of the composition, but does not bring any other new features, and B1 contains no support that these more specific forms of the composition would involve an inventive step. On the contrary, according to the description of B1 ([0027]) these pharmaceutical forms are prepared by conventional pharmaceutical methods.

As shown above claim 1 lacks inventive step over D1 and D3 and based on the above also the additional features disclosed in claims 2, 3, 5 (dependent on claim 1-3) and 7 (dependent on claim 1-3 or 5) lack inventive step over D1 combined with D3.

Claim 4 dependent from claims 1 or 2 and claims 5 and 7 – dependent from claim 4

Lack of Inventive Step – Art. 56 – D1 and D3

D1 is considered to be the closest prior art for dependent claim 4 since D1 already discloses the features mentioned for claim 1 above and thereto the use of a mixture of methylparaben and propylparaben (Page 11, Example 5).

D1 does not disclose the ratio 9/1 of methylparaben/propylparaben expressed in weight nor the total amount of p-hydroxybenzoate esters in the range of 0.0001 and 1.4 mg/ml of the composition.

However, for the same reason as for claim 1 the person skilled in the art would find D3, i.e. a handbook disclosing explicit points (0.15, 0.05 and 0.1) of the overlapping prior art ranges falling in the claimed range and thereto an indication that methylparaben and

propylparaben have been used in the ratio 9/1 for parenteral formulations. Based on the teaching in D3 a person skilled in the art would use between 0.5 mg/ml and 1.0 mg/ml of the mixture of methylparaben and propylparaben in the ratio 9/1 for ophthalmic preparations. The total amount is 0.05+0.45=0.5 mg/ml of propylparaben/methylparaben when the lower end point 0.05 mg/ml of propylparaben in ophthalmic preparations (D3, page 450, point 7) is used and 0.1+0.9=1.0 mg/ml when the higher end point 0.1 mg/ml of propylparaben is used. Both 0.5 mg/ml and 1.0 mg/ml fall within the claimed range of 0.0001 to 1.4 mg/ml, therefore making claim 4 not inventive.

Thus, the additional features of claim 4 are obvious for a person skilled in the art based on the teaching of D1 and D3, and therefore claim 4 lacks inventive step. Further, based on the above also claims 5 and 7 dependent from claim 4 only comprises further features already comprised in D1 and/or D3 and thus lacks inventive step over D1 and D3.

Claim 6 – dependent from claims 1 to 4

Lack of Inventive Step – Art. 56 – D1 and D3

The additional feature of claim 6 is that the active substance is levocetirizine. Thus claim 6 comprises no additional features compared to claim 1 already comprising the active substance being levocetirizine.

As showed above claim 1 lacks inventive step based on D1 and D3 when the active compound is chosen to be cetirizine and the preservatives are methyl parahydroxybenzoate, propyl parahydroxybenzoate or a mixture thereof.

Since levocetirizine is the levorotatory enantiomer of cetirizine it is implicitly disclosed in cetirizine. Thereto based on D4 it is clear that

using levocetririze as an alternative to cetirizine is favorable because a smaller amount of the active substance is sufficient. D4 is a comparison of the effect of levocetirizine, dextrocetirizine and racemic cetirizine in a study of healthy volunteers. In the discussion (page 342, left column, last paragraph) it has been found that 5 mg levocetirizine is equivalent to 10 mg racemic cetirizine. No effect has been observed with the other enantiomer dextrocetirizine (page 342 right column first paragraph).

The use of a levocetirizine enantiomer instead of the racemic cetirizine for a pharmaceutical composition of the invention is therefore obvious based on D4.

Conclusion

It has been shown that claims 1, 2, 3 and 5 lack novelty and that all the claims 1 to 7 lack an inventive step. Therefore it is requested that the opposed patent is revoked entirely based on Art. 100(a) EPC.

If the Opposition division would for some reason decide not to revoke the opposed patent entirely, then oral proceeding are kindly requested.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP1768649
Application No.	EP05758582.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	23 September 2009
Title of the invention	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

II. Proprietor of the patent

first named in the patent specification	UCB FARCHIM S.A.
Opponent's or representative's reference	B0199PI-EP

III. Opponent

Name	Zentiva k.s.
Address:	U kabelovny 130 102 37 Prague Czech Republic
State of residence or of principal place of business	Czech Republic
Multiple opponents (see additional sheet)	☐

IV. Authorisation

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Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC) ☒

• it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒

• patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☐

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☐

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

IX. Evidence presented

D1	Patent document	EP0605203 (A2) , 06.07.1994 original file name: EP0605203A2.pdf attached as: Published-Evidence-1.pdf
D10	Other evidence	Summary of product characteristics for ZODAC®SIR original file name: SmPC Zodac sir 2010 ENG.pdf attached as: Other-evidence-7.pdf
D11	Other evidence	Thomson Reuters Newport Premium: Launched Drug Forms Detail original file name: cetirizinliquidlaunch.pdf attached as: Other-evidence-5.pdf
D2	Patent document	US5,891,913 (A) , 06.04.1999 original file name: US5891913A.pdf attached as: Published-Evidence-2.pdf
D3	Non-patent literature - book	Kibbe (ed.), A.H., "Handbook of Pharmaceutical Excipients" Washington D.C, USA: American Pharmnaceutical Association, 2000, Ed. 3rd ISBN: 0-917330-96-X original file name: D10 Hanbook parabenes.pdf attached as: Published-Evidence-3.pdf
D4	Non-patent literature - article	Wang, D.Y. et al., "Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers, p. 339-343" Allergy, Vol. 56, 2001 ISSN: 0105-4538 original file name: Wang DY 2001.pdf attached as: Published-Evidence-4.pdf
D5	Other evidence	Marketing autthorization for ZODAC®GTT in Slovakia original file name: Registrace Zodac 20001129 SK.pdf attached as: Other-evidence-1.pdf
D6	Other evidence	Marketing autthorization for ZODAC®SIR in Slovakia original file name: Registrace Zodac sir 20001129 SK.pdf attached as: Other-evidence-2.pdf
D7	Other evidence	Marketing autthorization for ZODAC®GTT in the Czech Republic original file name: Registrace Zodac gtt 20010418 CZ.pdf attached as: Other-evidence-3.pdf
D8	Other evidence	Marketing autthorization for ZODAC®SIR in the Czech Republic original file name: Registrace Zodac sir 20010418 CZ.pdf attached as: Other-evidence-4.pdf
D9	Other evidence	Summary of product characteristics for ZODAC®GTT original file name: SmPC Zodac gtt 2010 ENG.pdf attached as: Other-evidence-6.pdf

X. Payment

Mode of payment	Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:	EUR
Deposit account number:	28150010
Account holder:	BORENIUS & Co Oy Ab

Refunds

Any refunds should be made to EPO deposit account:	28150010
Account holder:	BORENIUS & co Oy Ab

Fees	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	705.00	705.00
Total:		EUR	705.00

	A Forms	Details:	System file name:
A-1	Form for notice of opposition		ep-oppo.pdf

	B Attached document files	Original file name:	System file name:
B-1	1. Facts and arguments	B0199PI-OPPOSITION AGAINST EP1768649B1-final.pdf	OPPO.pdf

	C Attached evidence files	Original file name:	System file name:
C-1	1. Patent document	EP0605203A2.pdf	Published-Evidence-1.pdf
C-2	2. Patent document	US5891913A.pdf	Published-Evidence-2.pdf
C-3	1. Non-patent literature - article	Wang DY 2001.pdf	Published-Evidence-4.pdf
C-4	2. Non-patent literature - book	D10 Hanbook parabenes.pdf	Published-Evidence-3.pdf
C-5	1. Other evidence	Registrace Zodac 20001129 SK.pdf	Other-evidence-1.pdf
C-6	2. Other evidence	Registrace Zodac sir 20001129 SK.pdf	Other-evidence-2.pdf
C-7	3. Other evidence	Registrace Zodac gtt 20010418 CZ.pdf	Other-evidence-3.pdf

C-8	4. Other evidence	Registrace Zodac sir 20010418 CZ.pdf	Other-evidence-4.pdf
C-9	5. Other evidence	cetirizinliquidlaunch.pdf	Other-evidence-5.pdf
C-10	6. Other evidence	SmPC Zodac gtt 2010 ENG.pdf	Other-evidence-6.pdf
C-11	7. Other evidence	SmPC Zodac sir 2010 ENG.pdf	Other-evidence-7.pdf

Signature of opponent or representative

Place **Helsinki**

Date: **23 June 2010**

Signed by: **///Pia Hjelt/**

Capacity: **(Representative 1)**

Place **Helsinki**

Date: **23 June 2010**

Signed by: **FI, Borenius & Co. Oy Ab, C. Westerholm 5880**

Capacity: **(Representative 3)**

HANDBOOK OF PHARMACEUTICAL EXCIPIENTS

THIRD EDITION

EDITED BY

ARTHUR H. KIBBE

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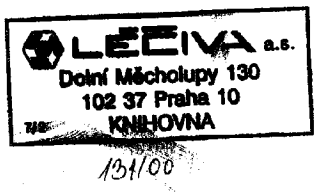


Methylparaben

1. Nonproprietary Names

BP: Methyl hydroxybenzoate
JP: Methyl parahydroxybenzoate
PhEur: Methylis parahydroxybenzoas
USP: Methylparaben

2. Synonyms

E218; 4-hydroxybenzoic acid methyl ester; *Methyl Chemosept*; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*.

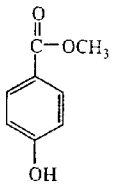
3. Chemical Name and CAS Registry Number

Methyl 4-hydroxybenzoate [99-76-3]

4. Empirical Formula / Molecular Weight

$C_8H_8O_3$ 152.15

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

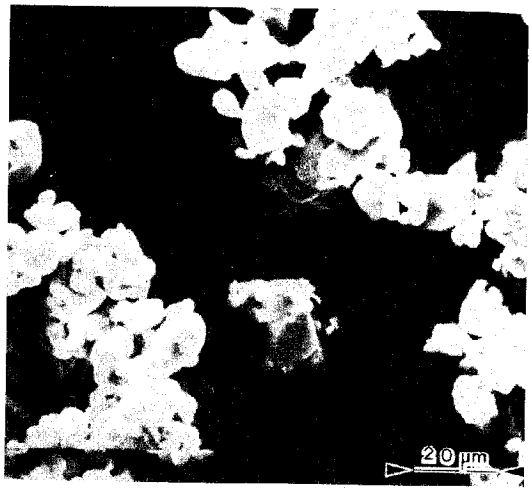
7. Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone, in combination with other parabens, or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative.[1]

The parabens are effective over a wide pH range 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; aqueous solubility however decreases. A mixture of parabens is thus frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of 2-5% propylene glycol, or by using parabens in combination with other antimicrobial agents such as imidurea, *see* Section 10.

Due to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. However, this raises the pH of poorly buffered formulations.

SEM: 1
Excipient: Methylparaben
Supplier: Bate Chemical Co Ltd
Magnification: 600×



Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations, *see* Section 14.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065-0.25
Inhalation solutions	0.025-0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015-0.2
Oral solutions and suspensions	0.015-0.2
Rectal preparations	0.1-0.18
Topical preparations	0.02-0.3
Vaginal preparations	0.1-0.18

[a] *See* Section 14.

8. Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Melting range	125-128°C	125-128°C	125-128°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.10%	—	≤ 0.05%
Sulfated ash	—	≤ 0.1%	—
Chloride	≤ 0.035%	—	—

Propylparaben

1. Nonproprietary Names

BP: Propyl hydroxybenzoate
JP: Propyl parahydroxybenzoate
PhEur: Propylis parahydroxybenzoas
USP: Propylparaben

2. Synonyms

Chemocide PK; E216; 4-hydroxybenzoic acid propyl ester; *Nipasol M*; propagin; *Propyl chemosept*; propyl *p*-hydroxybenzoate; *Propyl parasept*; *Solbrol P*; *Tegosept P*.

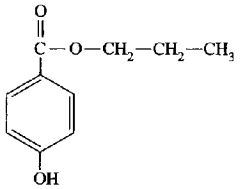
3. Chemical Name and CAS Registry Number

Propyl 4-hydroxybenzoate [94-13-3]

4. Empirical Formula Molecular Weight

$C_{10}H_{12}O_3$ 180.20

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

7. Applications in Pharmaceutical Formulation or Technology

Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used alone, in combination with other parahen esters, or with other antimicrobial agents. In cosmetics it is the second most frequently used preservative.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity although they are most effective against yeasts and molds, *see* Section 10.

Due to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

Propylparaben (0.02%) together with methylparaben (0.18%) has been used for the preservation of various parenteral pharmaceutical formulations, *see* Section 14.

See Methylparaben for further information.

Use	Concentration (%)
IM, IV, SC injections	0.005-0.2
Inhalation solutions	0.015
Intradermal injections	0.02-0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005-0.01
Oral solutions and suspensions	0.01-0.02
Rectal preparations	0.02-0.01
Topical preparations	0.01-0.6
Vaginal preparations	0.02-0.1

8. Description

Propylparaben occurs as a white, crystalline, odorless, and tasteless powder.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Melting range	96-99°C	96-99°C	95-98°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.1	—	≤ 0.05%
Sulfated ash	—	≤ 0.1%	—
Appearance of solution	—	+	—
Chloride	≤ 0.035%	—	—
Sulfate	≤ 0.024%	—	—
Heavy metals	≤ 20 ppm	—	—
Related substances	+	+	—
Readily carbonizable substances	+	—	—
Organic volatile impurities	—	—	+
Assay (dried basis)	≥ 99.0%	99.0-100.5%	99.0-100.5%

10. Typical Properties

Antimicrobial activity: propylparaben exhibits antimicrobial activity between pH 4-8. Preservative efficacy decreases with increasing pH due to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria. The activity of the parabens increases with increasing chain length of the alkyl moiety; solubility however decreases. Activity may be improved by using combinations of parabens since additive effects occur. Propylparaben has thus been used with methylparaben in parenteral preparations and is used with combinations of other parabens in topical and oral formulations. Activity has also been reported to be improved by the addition of other excipients, *see* Methylparaben for further information.

Reported minimum inhibitory concentrations (MICs) for propylparaben are shown in Table I:[2]

Boiling point: 295°C
Density (bulk): 0.426 g/cm$^{3(a)}$
Density (tapped): 0.706 g/cm$^{3(a)}$
Density(true): 1.288 g/cm$^{3(a)}$
Dissociation constant: pKa = 8.4 at 22°C

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Short communication

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

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Background: Cetirizine, an effective H_1-receptor antagonist, is a racemate mixture of two enantiomers: levocetirizine (*R* enantiomer) and dextrocetirizine (*S* enantiomer).
Methods: To investigate the pharmacologic activity of the two enantiomers of cetirizine, we conducted a randomized, double-blind, four-way, crossover study to assess the effect of treatment with 5 mg levocetirizine, 5 mg dextrocetirizine, and 10 mg cetirizine and matched placebo, on histamine-induced changes in the nasal airways of 24 healthy volunteers. Four hours after a single oral intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold were calculated together with the absolute number of sneezes after each challenge.
Results: Both levocetirizine and cetirizine significantly attenuated the histamine-induced increase in nasal airway resistance by nearly 50% (from a median resistance of 2.51 Pa per cm^3/s to 1.29 and 1.31 Pa per cm^3/s, respectively) at the maximal concentration, and they concomitantly increased the histamine threshold by fourfold (from 8 to 32 mg/ml), compared with placebo. Sneezing was also attenuated by both levocetirizine and cetirizine. However, these antihistaminic effects were not seen with dextrocetirizine.
Conclusions: This study shows a similar activity of levocetirizine and cetirizine on the inhibition of histamine-induced increase in nasal resistance, indicating that the antihistaminic properties of cetirizine are probably attributable to levocetirizine.

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

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

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

Material and methods

Subjects

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

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

Study design

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

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

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

Measurement of nasal resistance

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

Histamine nasal provocation test

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

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

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

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

[1]Global evaluation with Friedman test.
[2]When global evaluation was statistically significant ($P<0.05$), two-by-two comparison of treatment was done. Only comparisons with $P \leq 0.10$ are mentioned in tables:
+ $0.05 < P < 0.10$
* $0.025 < P < 0.05$
** $0.01 < P < 0.025$
*** $0.001 < P < 0.01$.

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

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

Results of comparisons
Statistics were done on difference between logarithms (in base 2) of threshold concentration between each pair of treatments. For these calculations, threshold of >32 was replaced by 64 mg/ml.
Friedman test
Global evaluation $P=0.001$
Two-by-two comparisons
Levocetirizine *vs* dextrocetirizine $0.025 < P \leq 0.05$
Levocetirizine *vs* cetirizine $P > 0.10$
Levocetirizine *vs* placebo $0.01 < P \leq 0.025$
Dextrocetirizine *vs* cetirizine $0.05 < P \leq 0.10$
Dextrocetirizine *vs* placebo $P > 0.10$
Cetirizine *vs* placebo $0.025 < P \leq 0.05$.

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

Statistical analysis

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

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

Results

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

Effect of treatment on nasal resistance

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

Effect of treatment on histamine threshold concentration

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

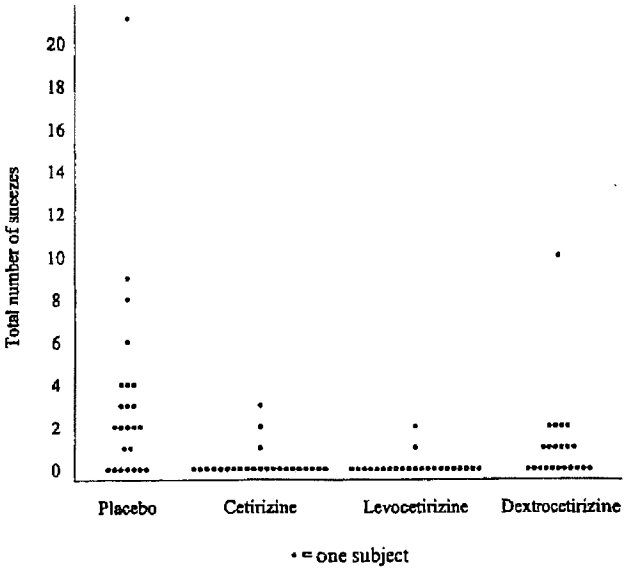

Figure 1. Effect of treatment for 4 h with placebo, 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine on histamine-induced sneezes.

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

Effect of treatment on sneezing

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

Evaluation of safety

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

Discussion

In this study, levocetirizine 5 mg and cetirizine 10 mg appeared to be comparable in their antihistaminic activity. They significantly attenuated histamine-induced increases in nasal airway resistance by almost 50% over placebo at the maximal concentration of 32 mg/ml. Concomitantly, the histamine threshold concentration was increased fourfold from 8 to 32 mg/ml. The number of sneezes induced by histamine nasal provocation was also significantly decreased by treatment with cetirizine or levocetirizine. In contrast, treatment with dextrocetirizine did not show a similar 'protective' effect as compared to placebo.

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

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

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

In conclusion, this study demonstrates that the antihistaminic properties noted for cetirizine in the management of seasonal and perennial allergic rhinitis are probably due to the levocetirizine enantiomer. Further studies are required to substantiate these findings in patients with ongoing seasonal and perennial allergic rhinitis.

Acknowledgments

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Č. J.	VYŘIZUJE/LINKA	DATUM
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ROZHODNUTÍ
o registraci léčivého přípravku

Státní ústav pro kontrolu léčiv se sídlem v Praze 10, Šrobárova 48 (dále jen „Ústav"), jako orgán příslušný k rozhodnutí podle § 9 odst. 1 písm.a) bod 1 zákona č. 79/1997 Sb., o léčivech a o změnách a doplnění některých souvisejících zákonů, ve znění pozdějších předpisů (dále jen „zákon"), rozhodl podle § 25 a 26 zákona po provedeném registračním řízení takto:

Léčivý přípravek :

ZODAC GTT lék. forma: **gtt.**

o jehož registraci byla podána žádost firmou:

Léčiva a.s., Praha, ČR

která byla doručena Ústavu dne **31.1.2000** se registruje a přiděluje se mu registrační číslo:

24/154/01-C

1. Výdej léčivého přípravku je vázán na lékařský předpis.
2. Léčivý přípravek neobsahuje omamnou látku nebo psychotropní látku uvedenou v přílohách zákona č. 167/1998 Sb., o návykových látkách a o změně některých dalších zákonů, ve znění pozdějších předpisů.
3. Zprávu o nežádoucích účincích registrovaného léčivého přípravku dle § 26 odst. 5 písm. d) bude držitel rozhodnutí o registraci písemně předkládat Ústavu po 5 letech (spolu s žádostí o prodloužení registrace).
4. Pokud byl při výrobě přípravku použit materiál z přežvýkavců, držitel rozhodnutí o registraci doloží do 30.11.2001 zabezpečení přípravku vzhledem k riziku přenosu BSE.
5. Přílohami tohoto rozhodnutí, které jsou jeho nedílnou součástí, je identifikační list přípravku (Příloha č. 1, která sestává z 1 strany), příbalová informace pro používání léčivého přípravku a zacházení s ním (Příloha č. 2, která sestává ze 3 stran) a schválený souhrn údajů o léčivém přípravku (Příloha č. 3, která sestává ze 4 stran).

O d ů v o d n ě n í

Dne **31.1.2000** byla Ústavu doručena žádost firmy:

Léčiva a.s., Praha, ČR

o registraci léčivého přípravku:

ZODAC GTT lék. forma: **gtt.**

V rámci registračního řízení Ústav posuzoval, zda léčivý přípravek splňuje požadavky na registraci stanovené právními předpisy. Po provedení tohoto posouzení Ústav konstatuje, že nebyly shledány důvody pro zamítnutí žádosti a jsou splněny požadavky na registraci léčivého přípravku. Na základě zjištění těchto skutečností rozhodl Ústav o registraci způsobem, který je uveden ve výroku tohoto rozhodnutí.

Č. J.
3316/00

DATUM
18.4.2001

Poučení o odvolání

Proti tomuto rozhodnutí je možno podat podle ustanovení § 53 a násl. zákona č.71/1967 Sb., o správním řízení (správní řád) u Ústavu odvolání, a to ve lhůtě 15 dnů ode dne jeho doručení. O odvolání rozhoduje Ministerstvo zdravotnictví.

Státní ústav pro kontrolu léčiv v Praze

MUDr. Milan Šmíd, CSc.
ředitel ústavu

Příloha č.1 k rozhodnutí o registraci č.j. 3316/00

Identifikační list

Registrační číslo přípravku: 24/154/01-C

Název léčivého přípravku	Doplněk názvu	Kód SÚKL	ZEM	VYR	STAV
ZODAC GTT	GTT 1X20ML/0.2GM	58834	CZ	LEX	R

Ve sloupci označeném STAV je pod zkratkou B uveden registrovaný přípravek před provedením změny, pod zkratkou R přípravek po provedení změny. Pod zkratkami ZEM a VYR je uvedeno místo/a výroby, kde dochází k propouštění přípravku a příslušný subjekt:

LEX CZ: LÉČIVA A.S., PRAHA, Česká republika

STÁTNÍ ÚSTAV
PRO KONTROLU LÉČIV
SCHVÁLENO
18. 4. 2001

Příloha č. 3 k rozhodnutí o registraci č.j. 3316/00

SOUHRN ÚDAJŮ O PŘÍPRAVKU

1. NÁZEV PŘÍPRAVKU

ZODAC® GTT

2. SLOŽENÍ KVALITATIVNÍ I KVANTITATIVNÍ

Cetirizini dihydrochloridum 10 mg v 1 ml roztoku (= 20 kapek)

3. LÉKOVÁ FORMA

Kapky.

Popis přípravku: čirý, bezbarvý až slabě nažloutlý roztok.

4. KLINICKÉ ÚDAJE

4.1. Indikace

Symptomatická léčba alergické rýmy a konjunktivitidy (včetně celoroční a sezónní) a kožních alergických projevů provázených svěděním a vyrážkou, zejména při urtikarii.

4.2. Dávkování a způsob podání

Dospělí a děti nad 12 let obvykle užívají 10 mg cetirizinu (20 kapek) v jedné denní dávce.

Děti od 6 do 12 let obvykle užívají 10 mg cetirizinu (20 kapek) 1x denně nebo 5 mg cetirizinu (10 kapek) 2x denně.

Děti od 2 do 6 let obvykle užívají 5 mg cetirizinu (10 kapek) 1x denně nebo 2,5 mg cetirizinu (5 kapek) 2x denně.

Pacienti s ledvinným selháním: při snížení funkce ledvin je třeba úměrně snížit dávkování cetirizinu, při clerance kreatininu 11 – 31 ml/min. se podává 5 mg cetirizinu (10 kapek) denně.

Hemodialyzovaným pacientům se podává 5 mg cetirizinu (10 kapek) denně.

Pacientům s jaterní insuficiencí: je třeba úměrně snížit dávkování cetirizinu, obvykle se podává 5 mg cetirizinu (10 kapek) denně.

U geriatrických pacientů: vzhledem k věku není nutné dávky upravovat. Dávkování je třeba upravit v případě snížené funkce ledvin, obvykle se podává 5 mg cetirizinu (10 kapek) denně.

Zodac gtt je možné užívat nezávisle na jídle, kapky se zapíjejí dostatečným množstvím nedráždivé tekutiny.

4.3. Kontraindikace

Známá přecitlivělost k cetirizinu, jiné složce přípravku nebo hydroxyzinu. Děti do 2 let.

4.4. Zvláštní upozornění

Opatrnosti je třeba u pacientů s ledvinným selháním, jaterní insuficiencí a u geriatrických pacientů.

Kapky neobsahují žádný zbytkový cukr (jako sladidlo je použitý sacharin), kapky jsou vhodné pro diabetiky.

Během léčby se nedoporučuje nadměrně pít alkoholické nápoje.

4.5. Interakce

Při současném užívání cetirizinu s teofylinem může být snížena clearance cetirizinu (až o 16 %) s klinickými projevy nežádoucích účinků cetirizinu.

4.6. Těhotenství a kojení

Při pokusech na zvířatech nebyla prokázána embryotoxicita ani teratogenita. S používáním u lidí není dostatek zkušeností.

Vzhledem k nedostatku zkušeností se jeho používání u těhotných a kojících žen nedoporučuje.

4.7. Možnost snížení pozornosti při řízení motorových vozidel a obsluze strojů

Nejsou popsány sedativní účinky přípravku jako u klasických antihistaminik. Studie u zdravých dobrovolníků neprokázaly žádný vliv po podání 20 – 25 mg cetirizinu na bdělost nebo reakční dobu. Přesto je třeba individuálně posoudit nutnost zvýšené opatrnosti u osob vykonávajících činnost vyžadující pozornost, motorickou koordinaci a rychlé rozhodování (např. řízení motorových vozidel, ovládání strojů, práce ve výškách, apod.).

4.8. Nežádoucí účinky

Cetirizin je všeobecně dobře snášen. S užíváním cetirizinu mohou být ojediněle spojeny bolesti hlavy, ospalost, závratě, suchost v ústech, zažívací obtíže (dyspepsie, bolesti břicha, plynatost).

4.9. Předávkování

Při dávkách cetirizinu (více než 50 mg) byla pozorována ospalost, u dětí může předávkování naopak vyvolat neklid a podrážděnost; mohou být pozorovány příznaky anticholinergního účinku (retence moče, výrazná suchost v ústech, zácpa).
Ošetření při předávkování zahrnuje standardní postup, léčba je symptomatická a podpůrná se zaměřením na udržení vitálních funkcí. Specifické antidotum není známo. Při hemodialýze může být odstraněna pouze malá část podané dávky cetirizinu

(cca 9 %).

5. FARMAKOLOGICKÉ VLASTNOSTI

Farmakoterapeutická skupina

Antihistaminikum

5.1. Farmakodynamické vlastnosti

Cetirizin je antihistaminikum II. generace s prodlouženým účinkem. Selektivně inhibuje periferní H_1-receptory, ale výrazněji neovlivňuje cholinergní, adrenergní ani serotoninové receptory. V terapeutických dávkách nemá sedativní účinek na CNS. Inhibuje migraci zánětlivých buněk, především eozinofilů. Tlumí uvolňování histaminu ze žírných buněk a bazofilních leukocytů i v průběhu pozdní fáze alergické reakce.

5.2. Farmakokinetické vlastnosti

Biologická dostupnost cetirizinu po požití kapek je rychlá a úplná. Potrava nemá vliv na vstřebávání cetirizinu, prodlužuje však dobu dosažení maximální koncentrace na 1,7 hodiny a maximální koncentraci snižuje o 23 %. Maximální koncentrace po požití kapek je dosaženo za 30-60 minut, dosažené maximální koncentrace u dětí jsou vyšší než u dospělých. Vztah mezi dávkou a plazmatickou koncentrací je lineární.
Antihistaminový účinek se dostavuje za 20-60 minut po požití, přetrvává po dobu 24 hodin.
Vazba na plazmatické bílkoviny je 93 %. Minimálně proniká do mozkomíšního moku, vazba na mozkové H_1 receptory je nevýznamná. Distribuční objem (V_d) je 0,5 až 0,8 l/kg.
Narozdíl od ostatních antihistaminik se jen minimálně metabolizuje v játrech, O-dealkylovaný metabolit nemá antihistaminovou aktivitu.
Eliminační poločas je 7,4 až 9 hodin, u pacientů se středně závažnou renální insuficiencí se prodlužuje na 19 až 21 hodin. U dětí je celková tělesná clearance cetirizinu asi o 33 % vyšší než u dospělých, eliminační poločas je zkrácen na 6,2 hodiny. Přibližně 60 % podané dávky se vyloučí močí v nezměněné formě během 24 hodin, dalších 10 % v průběhu následujících 4 dní; u dětí se vyloučí močí 40 % podané dávky během 24 hodin. Stolicí se vyloučí asi 10 % podané dávky během 5 dní po požití.

5.3. Preklinická data ve vztahu k bezpečnosti přípravku

Studie na zvířatech prokázaly, že dávky 216x vyšší než maximální dávka pro člověka nejsou teratogenní. Cetirizin nepůsobí teratogenně v průběhu organogeneze.

6. FARMACEUTICKÉ ÚDAJE

6.1. Seznam všech pomocných látek (kvalitativně)

Methylparabenum, Propylparabenum, Glycerolum 85%, Propylenglycolum, Saccharinum natricum dihydricum, Natrii acetas trihydricus, Acidum aceticum 99%,

Aqua purificata

6.2. Inkompatibility

Není známá inkompatibilita perorálně užívaného cetirizinu s další látkou.

6.3. Doba použitelnosti

2 roky

6.4. Uchovávání

Při teplotě do 25°C.

6.5. Druh obalu

Hnědá skleněná lahvička uzavřená kapátkem z LDPE a bezpečnostním uzávěrem s dětskou pojistkou HDPE, příbalová informace v jazyce českém, papírová skládačka

Velikost balení: 20 ml

6.6. Návod k použití

Přípravek se užívá perorálně

Návod pro otevírání lékovky s bezpečnostním uzávěrem

Lékovka je opatřena bezpečnostním uzávěrem zabraňujícím otevření dětmi. Otevře se tak, že se uzávěr stlačí pevně dolů a odšroubuje se proti směru hodinových ručiček. Po použití je třeba uzávěr opět pevně zašroubovat.

7. DRŽITEL ROZHODNUTÍ O REGISTRACI

Léčiva a. s., Praha, Česká republika

8. REGISTRAČNÍ ČÍSLO

24/154/01-C

9. DATUM REGISTRACE / DATUM PRODLOUŽENÍ REGISTRACE

10. DATUM POSLEDNÍ REVIZE TEXTU

STÁTNÍ ÚSTAV
PRO KONTROLU LÉČIV
SCHVÁLENO
18.4.2001

Příloha č. 2 k rozhodnutí o registraci č.j. 3316/00

Příbalová informace

Informace pro použití, čtěte pozorně

ZODAC® GTT

(Cetirizini dihydrochloridum)

kapky

Výrobce / Držitel rozhodnutí o registraci

Léčiva a.s., Praha, Česká republika

Složení

Léčivá látka: Cetirizini dihydrochloridum 10 mg v 1 ml roztoku (= 20 kapek)

Pomocné látky: Methylparaben, propylparaben, glycerol 85%, propylenglykol, dihydrát sodné soli sacharinu, trihydrát octanu sodného, kyselina octová 99%, čištěná voda

Indikační skupina

Antihistaminikum (lék tlumící reakci z přecitlivělosti)

Charakteristika

Cetirizin, účinná látka přípravku Zodac gtt, je antihistaminikum s prodlouženým účinkem. Antihistaminika blokují působení histaminu, jednoho z působků, který se v organismu uvolňuje při reakci z přecitlivělosti (alergie). Cetirizin tlumí jak „časnou" fázi alergické reakce zprostředkovanou histaminem, tak i pohyb buněk zánětu, zejména eozinofilů a uvolňování působků spojených s „pozdní" fází alergické reakce.

Zodac gtt je vysoce účinné antihistaminikum a antialergikum s minimálním výskytem ospalosti po běžné léčebné dávce. Vzhledem k prodlouženému účinku je možné Zodac gtt u dospělých a starších dětí podávat v jedné denní dávce.

Indikace

Zodac gtt se užívá ke zmírnění obtíží při alergické rýmě a alergickém zánětu spojivek (včetně celoroční a sezónní) a kožních alergických projevů provázených svěděním a vyrážkou, zejména při kopřivce.

Kontraindikace

Zodac gtt se nesmí podávat u pacientů se známou přecitlivělostí na cetirizin, jinou složku přípravku nebo hydroxyzin a dětem do 2 let. Těhotným a kojícím ženám se jeho podávání vzhledem k nedostatku zkušeností nedoporučuje.

Nežádoucí účinky

Zodac gtt je všeobecně dobře snášen, s jeho užíváním mohou být ojediněle spojeny bolesti hlavy, ospalost, závratě, suchost v ústech, zažívací obtíže (dyspepsie, bolesti břicha, plynatost). Při případném výskytu těchto nežádoucích účinků nebo jiných neobvyklých reakcí se o dalším užívání přípravku či podávání dítěti poraďte s lékařem.

Vzácně se mohou vyskytnout projevy přecitlivělosti na přípravek (kopřivka, otok měkkých tkání, dušnost). V tomto případě je nutné ihned přerušit užívání přípravku a poradit se s lékařem.

Interakce

Účinky přípravku Zodac gtt a jiných léků současně užívaných se mohou navzájem ovlivňovat. Současné užívání přípravku Zodac gtt s některými bronchodilatancii (léky na rozšíření průdušek) obsahujícími účinnou látku teofylin může vyvolat nežádoucí účinky léčby přípravkem Zodac gtt.

Váš lékař má být proto informován o všech lécích, které užíváte Vy nebo dítě na lékařský předpis i bez něj. Bez porady s lékařem neužívejte ani dítěti nepodávejte současně s přípravkem Zodac gtt žádný volně prodejný lék. Jestliže Vám další lékař bude předepisovat nějaký jiný lék, informujte ho, že Vy nebo dítě užíváte Zodac gtt.

Interakce cetirizinu s alkoholem (při hladině alkoholu v krvi 0,8 g/l) nebyly dosud popsány. Přesto se doporučuje nepožívat nadměrně alkoholické nápoje během užívání přípravku Zodac gtt.

Dávkování

Dávkování vždy určuje lékař. Potrava významně neovlivňuje vstřebávání přípravku Zodac gtt a může tedy být užíván nezávisle na jídle.

Dospělí a děti nad 12 let obvykle užívají 20 kapek přípravku Zodac gtt (= 10 mg cetirizinu) 1x denně.

Děti od 6 do 12 let užívají 20 kapek (= 10 mg cetirizinu) 1x denně nebo 10 kapek (= 5 mg cetirizinu) 2x denně, ráno a večer.

Dětem od 2 do 6 let se podává 10 kapek (= 5 mg cetirizinu) 1x denně nebo 5 kapek (= 2,5 mg cetirizinu) 2x denně, ráno a večer.

Starším nemocným nebo pacientům se závažným onemocněním jater a ledvin může lékař dávkování upravit.

Při náhodném vynechání dávky užijte lék (podejte lék dítěti) ihned, jakmile si vzpomenete. V případě, že by měla být užita další dávka, dávkování nezdvojujte

a pokračujte podle původního plánu léčby.

Kapky se zapíjejí malým množstvím nedráždivé tekutiny.

Návod pro otevírání lékovky s bezpečnostním uzávěrem

Lékovka je opatřena bezpečnostním uzávěrem zabraňujícím otevření dětmi. Otevřete jej tak, že uzávěr stlačíte pevně dolů a odšroubujete proti směru hodinových ručiček. Po použití je třeba uzávěr opět pevně zašroubovat.

Upozornění

U přípravku nejsou popsány tlumící účinky. Přesto se doporučuje nepřekročit doporučenou denní dávku, pokud budete řídit motorové vozidlo nebo obsluhovat stroje.

Zodac gtt kapky neobsahují žádný zbytkový cukr (použitým sladidlem je sacharin). Kapky jsou vhodné pro diabetiky.

Předávkování

Při předávkování může být hlavním příznakem ospalost. U dětí však může předávkování vyvolat i podrážděnost a neklid. Při předávkování (zvláště dětí) je nutno okamžitě vyhledat lékaře. Specifický protilék není dosud znám.

Uchovávání

Při teplotě do 25°C.

Varování

Přípravek nesmí být používán po uplynutí doby použitelnosti vyznačené na obalu.

Přípravek musí být uchováván mimo dosah dětí.

Při užití nadměrné dávky nebo náhodném požití kapek dítětem vyhledejte lékaře.

Balení

20 ml roztoku

Datum poslední revize

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV

Šrobárova 48, 100 41 Praha 10, Česká republika

Tel. : (02) 72 185 111; Fax : (02) 717 32 377; E-mail : SUKL@sukl.cz

Léčiva a.s.
Dolní Měcholupy 130
102 37 Praha 10

Č. J.	VYŘIZUJE/LINKA	DATUM
3315/00	MUDr. B. Vojtová/731	18.4.2001

ROZHODNUTÍ
o registraci léčivého přípravku

Státní ústav pro kontrolu léčiv se sídlem v Praze 10, Šrobárova 48 (dále jen „Ústav"), jako orgán příslušný k rozhodnutí podle § 9 odst. 1 písm.a) bod 1 zákona č. 79/1997 Sb., o léčivech a o změnách a doplnění některých souvisejících zákonů, ve znění pozdějších předpisů (dále jen „zákon"), rozhodl podle § 25 a 26 zákona po provedeném registračním řízení takto:

Léčivý přípravek :

ZODAC SIR lék. forma: **sir.**

o jehož registraci byla podána žádost firmou:

Léčiva a.s., Praha, ČR

která byla doručena Ústavu dne **31.1.2000** se registruje a přiděluje se mu registrační číslo:

24/153/01-C

1. Výdej léčivého přípravku je vázán na lékařský předpis.
2. Léčivý přípravek neobsahuje omamnou látku nebo psychotropní látku uvedenou v přílohách zákona č. 167/1998 Sb., o návykových látkách a o změně některých dalších zákonů, ve znění pozdějších předpisů.
3. Zprávu o nežádoucích účincích registrovaného léčivého přípravku dle § 26 odst. 5 písm. d) bude držitel rozhodnutí o registraci písemně předkládat Ústavu po 5 letech (spolu s žádostí o prodloužení registrace).
4. Pokud byl při výrobě přípravku použit materiál z přežvýkavců, držitel rozhodnutí o registraci doloží do 30.11.2001 zabezpečení přípravku vzhledem k riziku přenosu BSE.
5. Přílohami tohoto rozhodnutí, které jsou jeho nedílnou součástí, je identifikační list přípravku (Příloha č. 1, která sestává z 1 strany), příbalová informace pro používání léčivého přípravku a zacházení s ním (Příloha č. 2, která sestává ze 3 stran) a schválený souhrn údajů o léčivém přípravku (Příloha č. 3, která sestává ze 4 stran).

O d ů v o d n ě n í

Dne **31.1.2000** byla Ústavu doručena žádost firmy:

Léčiva a.s., Praha, ČR

o registraci léčivého přípravku:

ZODAC SIR lék. forma: **sir.**

V rámci registračního řízení Ústav posuzoval, zda léčivý přípravek splňuje požadavky na registraci stanovené právními předpisy. Po provedení tohoto posouzení Ústav konstatuje, že nebyly shledány důvody pro zamítnutí žádosti a jsou splněny požadavky na registraci léčivého přípravku. Na základě zjištění těchto skutečností rozhodl Ústav o registraci způsobem, který je uveden ve výroku tohoto rozhodnutí.

Č. J.
3315/00

DATUM
18.4.2001

Poučení o odvolání

Proti tomuto rozhodnutí je možno podat podle ustanovení § 53 a násl. zákona č.71/1967 Sb., o správním řízení (správní řád) u Ústavu odvolání, a to ve lhůtě 15 dnů ode dne jeho doručení. O odvolání rozhoduje Ministerstvo zdravotnictví.

Státní ústav pro kontrolu léčiv v Praze -6-

MUDr. Milan Šmíd, CSc.
ředitel ústavu

Příloha č.1 k rozhodnutí o registraci č.j. 3315/00

Identifikační list

Registrační číslo přípravku: 24/153/01-C

Název léčivého přípravku	Doplněk názvu	Kód SÚKL	ZEM	VYR	STAV
ZODAC SIR	SIR 1X100ML/0.1GM	58835	CZ	LEX	R

Ve sloupci označeném STAV je pod zkratkou B uveden registrovaný přípravek před provedením změny, pod zkratkou R přípravek po provedení změny. Pod zkratkami ZEM a VYR je uvedeno místo/a výroby, kde dochází k propouštění přípravku a příslušný subjekt:

LEX CZ: LÉČIVA A.S., PRAHA, Česká republika

Příloha č. 2 k rozhodnutí o registraci č.j. 3315/00

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV
SCHVÁLENO
14. 4. 2004

Příbalová informace

Informace pro použití, čtěte pozorně

ZODAC® SIR

(Cetirizini dihydrochloridum)

sirup

Výrobce / Držitel rozhodnutí o registraci

Léčiva a.s., Praha, Česká republika

Složení

Léčivá látka: Cetirizini dihydrochloridum 5 mg v 5 ml sirupu

Pomocné látky: Methylparaben, propylparaben, glycerol 85%, propylenglykol, sorbitol 70% nekrystalizující, dihydrát sodné soli sacharinu, trihydrát octanu sodného, kyselina octová 99%, banánové aroma, čištěná voda

Indikační skupina

Antihistaminikum (lék tlumící reakci z přecitlivělosti)

Charakteristika

Cetirizin, účinná látka přípravku Zodac sir, je antihistaminikum s prodlouženým účinkem. Antihistaminika blokují působení histaminu, jednoho z působků, který se v organismu uvolňuje při reakci z přecitlivělosti (alergie). Cetirizin tlumí jak „časnou" fázi alergické reakce zprostředkovanou histaminem, tak i pohyb buněk zánětu, zejména eozinofilů a uvolňování působků spojených s „pozdní" fází alergické reakce.

Zodac sir je vysoce účinné antihistaminikum a antialergikum s minimálním výskytem ospalosti po běžné léčebné dávce. Vzhledem k prodlouženému účinku je možné Zodac sir u dospělých a starších dětí podávat v jedné denní dávce.

Indikace

Zodac sir se užívá ke zmírnění obtíží při alergické rýmě a alergickém zánětu spojivek (včetně celoroční a sezónní) a kožních alergických projevů provázených svěděním a vyrážkou, zejména při kopřivce.

Kontraindikace

Zodac sir se nesmí podávat u pacientů se známou přecitlivělostí na cetirizin, jinou složku přípravku nebo hydroxyzin a dětem do 2 let. Těhotným a kojícím ženám se jeho podání vzhledem k nedostatku zkušeností nedoporučuje.

Nežádoucí účinky

Zodac sir je všeobecně dobře snášen, s jeho užíváním mohou být ojediněle spojeny bolesti hlavy, ospalost, závratě, suchost v ústech, zažívací obtíže (dyspepsie, bolesti břicha, plynatost). Při případném výskytu těchto nežádoucích účinků nebo jiných neobvyklých reakcí se o dalším užívání přípravku či podávání dítěti poraďte s lékařem.

Vzácně se mohou vyskytnout projevy přecitlivělosti na přípravek (kopřivka, otok měkkých tkání, dušnost). V tomto případě je nutné ihned přerušit užívání přípravku a poradit se s lékařem.

Interakce

Účinky přípravku Zodac sir a jiných léků současně užívaných se mohou navzájem ovlivňovat. Současné užívání přípravku Zodac sir s některými bronchodilatancii (léky na rozšíření průdušek) obsahujícími účinnou látku teofylin může vyvolat nežádoucí účinky léčby přípravkem Zodac sir.

Váš lékař má být proto informován o všech lécích, které užíváte Vy nebo dítě na lékařský předpis i bez něj. Bez porady s lékařem neužívejte ani dítěti nepodávejte současně s přípravkem Zodac sir žádný volně prodejný lék. Jestliže Vám další lékař bude předepisovat nějaký jiný lék, informujte ho, že Vy nebo dítě užíváte Zodac sir.

Interakce cetirizinu s alkoholem (při hladině alkoholu v krvi 0,8 g/l) nebyly dosud popsány. Přesto se doporučuje nepožívat nadměrně alkoholické nápoje během užívání přípravku Zodac sir.

Dávkování

Dávkování vždy určuje lékař. Potrava významně neovlivňuje vstřebávání přípravku Zodac sir a může tedy být užíván nezávisle na jídle.

Dospělí a děti nad 12 let obvykle užívají 2 odměrné lžičky přípravku Zodac sir (= 10 mg cetirizinu) 1x denně.

Děti od 6 do 12 let užívají 2 odměrné lžičky (= 10 mg cetirizinu) 1x denně nebo 1 odměrnou lžičku (= 5 mg cetirizinu) 2x denně, ráno a večer.

Dětem od 2 do 6 let se podává 1 odměrná lžička (= 5 mg cetirizinu) 1x denně nebo 1/2 odměrné lžičky (= 2,5 mg cetirizinu) 2x denně, ráno a večer.

Starším nemocným nebo pacientům se závažným onemocněním jater a ledvin může lékař dávkování upravit.

Při náhodném vynechání dávky užijte lék (podejte lék dítěti) ihned, jakmile si vzpomenete. V případě, že by měla být užita další dávka, dávkování nezdvojujte

a pokračujte podle původního plánu léčby.

K odměření dávky je přiložena odměrná lžička se dvěma ryskami, označenými 1/4 (=1/4 odměrky, odpovídá 1,25 ml) a 1/2 (=1/2 odměrky, odpovídá 2,5 ml); lžička naplněná po okraj obsahuje 5 ml.

Sirup se zapíjí malým množstvím nedráždivé tekutiny.

Návod pro otevírání lékovky s bezpečnostním uzávěrem

Lékovka je opatřena bezpečnostním uzávěrem zabraňujícím otevření dětmi. Otevřete jej tak, že uzávěr stlačíte pevně dolů a odšroubujete proti směru hodinových ručiček. Po použití je třeba uzávěr opět pevně zašroubovat.

Upozornění

U přípravku nejsou popsány tlumící účinky. Přesto se doporučuje nepřekročit doporučenou denní dávku, pokud budete řídit motorové vozidlo nebo obsluhovat stroje.

Zodac sir obsahuje maximálně 0,12 g cukru v 5 ml sirupu (použitými sladidly jsou sorbitol a sacharin). Při dodržení doporučeného dávkování je sirup vhodný pro diabetiky.

Předávkování

Při předávkování může být hlavním příznakem ospalost. U dětí však může předávkování vyvolat i podrážděnost a neklid. Při předávkování (zvláště dětí) je nutno okamžitě vyhledat lékaře. Specifický protilék není dosud znám.

Uchovávání

Při teplotě do 25°C.

Varování

Přípravek nesmí být používán po uplynutí doby použitelnosti vyznačené na obalu.

Přípravek musí být uchováván mimo dosah dětí.
Při užití nadměrné dávky nebo náhodném požití sirupu dítětem vyhledejte lékaře.

Balení

100 ml sirupu

Datum poslední revize

209/25.4.01

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV SCHVÁLENO
18. 4. 2001

Příloha č. 3 k rozhodnutí o registraci č.j. 3315/00

SOUHRN ÚDAJŮ O PŘÍPRAVKU

1. NÁZEV PŘÍPRAVKU

ZODAC® SIR

2. SLOŽENÍ KVALITATIVNÍ I KVANTITATIVNÍ

Cetirizini dihydrochloridum 5 mg v 5 ml sirupu

3. LÉKOVÁ FORMA

Sirup.

Popis přípravku: čirý, bezbarvý až slabě nažloutlý sirup.

4. KLINICKÉ ÚDAJE

4.1. Indikace

Symptomatická léčba alergické rýmy a konjunktivitidy (včetně celoroční a sezónní) a kožních alergických projevů provázených svěděním a vyrážkou, zejména při urtikarii.

4.2. Dávkování a způsob podání

Dospělí a děti nad 12 let obvykle užívají 10 mg cetirizinu (2 odměrné lžičky) v jedné denní dávce.

Děti od 6 do 12 let obvykle užívají 10 mg cetirizinu (2 odměrné lžičky) 1x denně nebo 5 mg cetirizinu (1 odměrnou lžičku) 2x denně.

Děti od 2 do 6 let obvykle užívají 5 mg cetirizinu (1 odměrnou lžičku) 1x denně nebo 2,5 mg cetirizinu (1/2 odměrné lžičky) 2x denně.

Pacienti s ledvinným selháním: při snížení funkce ledvin je třeba úměrně snížit dávkování cetirizinu, při clerance kreatininu 11 – 31 ml/min. se podává 5 mg cetirizinu (1 odměrná lžička) denně.

Hemodialyzovaným pacientům se podává 5 mg cetirizinu (1 odměrná lžička) denně.

Pacientům s jaterní insuficiencí: je třeba úměrně snížit dávkování cetirizinu, obvykle se podává 5 mg cetirizinu (1 odměrná lžička) denně.

U geriatrických pacientů: vzhledem k věku není nutné dávky upravovat. Dávkování je třeba upravit v případě snížené funkce ledvin, obvykle se podává 5 mg cetirizinu (1 odměrná lžička) denně.

Zodac sir je možné užívat nezávisle na jídle, sirup se zapíjí dostatečným množstvím nedráždivé tekutiny.

K odměření dávky je přiložena odměrná lžička se dvěma ryskami, označenými 1/4 (=1/4 odměrky, odpovídá 1,25 ml) a 1/2 (=1/2 odměrky, odpovídá 2,5 ml); lžička

naplněná po okraj obsahuje 5 ml.

4.3. Kontraindikace

Známá přecitlivělost k cetirizinu, jiné složce přípravku nebo hydroxyzinu. Děti do 2 let.

4.4. Zvláštní upozornění

Opatrnosti je třeba u pacientů s ledvinným selháním, jaterní insuficiencí a u geriatrických pacientů.

5 ml sirupu obsahuje maximálně 0,12 g zbytkového cukru (použitými sladidly jsou sorbitol a sacharin). Při dodržení doporučeného dávkování je tento sirup vhodný pro diabetiky.

Během léčby se nedoporučuje nadměrně pít alkoholické nápoje.

4.5. Interakce

Při současném užívání cetirizinu s teofylinem může být snížena clearance cetirizinu (až o 16 %) s klinickými projevy nežádoucích účinků cetirizinu.

4.6. Těhotenství a kojení

Při pokusech na zvířatech nebyla prokázána embryotoxicita ani teratogenita. S používáním u lidí není dostatek zkušeností.

Vzhledem k nedostatku zkušeností se jeho používání u těhotných a kojících žen nedoporučuje.

4.7. Možnost snížení pozornosti při řízení motorových vozidel a obsluze strojů

Nejsou popsány sedativní účinky přípravku jako u klasických antihistaminik. Studie u zdravých dobrovolníků neprokázaly žádný vliv po podání 20 – 25 mg cetirizinu na bdělost nebo reakční dobu. Přesto je třeba individuálně posoudit nutnost zvýšené opatrnosti u osob vykonávajících činnost vyžadující pozornost, motorickou koordinaci a rychlé rozhodování (např. řízení motorových vozidel, ovládání strojů, práce ve výškách, apod.).

4.8. Nežádoucí účinky

Cetirizin je všeobecně dobře snášen. S užíváním cetirizinu mohou být ojediněle spojeny bolesti hlavy, ospalost, závratě, suchost v ústech, zažívací obtíže (dyspepsie, bolesti břicha, plynatost).

4.9. Předávkování

Při dávkách cetirizinu (více než 50 mg) byla pozorována ospalost, u dětí může předávkování naopak vyvolat neklid a podrážděnost; mohou být pozorovány příznaky anticholinergního účinku (retence moče, výrazná suchost v ústech, zácpa).
Ošetření při předávkování zahrnuje standardní postup, léčba je symptomatická

a podpůrná se zaměřením na udržení vitálních funkcí. Specifické antidotum není známo. Při hemodialýze může být odstraněna pouze malá část podané dávky cetirizinu (cca 9 %).

5. FARMAKOLOGICKÉ VLASTNOSTI

Farmakoterapeutická skupina

Antihistaminikum

5.1. Farmakodynamické vlastnosti

Cetirizin je antihistaminikum II. generace s prodlouženým účinkem. Selektivně inhibuje periferní H_1-receptory, ale výrazněji neovlivňuje cholinergní, adrenergní ani serotoninové receptory. V terapeutických dávkách nemá sedativní účinek na CNS. Inhibuje migraci zánětlivých buněk, především eozinofilů. Tlumí uvolňování histaminu ze žírných buněk a bazofilních leukocytů i v průběhu pozdní fáze alergické reakce.

5.2. Farmakokinetické vlastnosti

Biologická dostupnost cetirizinu po požití sirupu je rychlá a úplná. Potrava nemá vliv na vstřebávání cetirizinu, prodlužuje však dobu dosažení maximální koncentrace na 1,7 hodiny a maximální koncentraci snižuje o 23 %. Maximální koncentrace po požití sirupu je dosaženo za 30-60 minut, dosažené maximální koncentrace u dětí jsou vyšší než u dospělých. Vztah mezi dávkou a plazmatickou koncentrací je lineární.
Antihistaminový účinek se dostavuje za 20-60 minut po požití, přetrvává po dobu 24 hodin.
Vazba na plazmatické bílkoviny je 93 %. Minimálně proniká do mozkomíšního moku, vazba na mozkové H_1 receptory je nevýznamná. Distribuční objem (V_d) je 0,5 až 0,8 l/kg.
Narozdíl od ostatních antihistaminik se jen minimálně metabolizuje v játrech, O-dealkylovaný metabolit nemá antihistaminovou aktivitu.
Eliminační poločas je 7,4 až 9 hodin, u pacientů se středně závažnou renální insuficiencí se prodlužuje na 19 až 21 hodin. U dětí je celková tělesná clearance cetirizinu asi o 33 % vyšší než u dospělých, eliminační poločas je zkrácen na 6,2 hodiny. Přibližně 60 % podané dávky se vyloučí močí v nezměněné formě během 24 hodin, dalších 10 % v průběhu následujících 4 dní; u dětí se vyloučí močí 40 % podané dávky během 24 hodin. Stolicí se vyloučí asi 10 % podané dávky během 5 dní po požití.

5.3. Preklinická data ve vztahu k bezpečnosti přípravku

Studie na zvířatech prokázaly, že dávky 216x vyšší než maximální dávka pro člověka nejsou teratogenní. Cetirizin nepůsobí teratogenně v průběhu organogeneze.

6. FARMACEUTICKÉ ÚDAJE

6.1. Seznam všech pomocných látek (kvalitativně)

Methylparabenum, Propylparabenum, Glycerolum 85%, Propylenglycolum, Sorbitolum 70% non cristallisabile, Saccharinum natricum dihydricum, Natrii acetas trihydricus, Acidum aceticum 99%, Aroma musae, Aqua purificata

6.2. Inkompatibility

Není známá inkompatibilita perorálně užívaného cetirizinu s další látkou.

6.3. Doba použitelnosti

2 roky

6.4. Uchovávání

Při teplotě do 25°C.

6.5. Druh obalu

Hnědá skleněná lahvička s bezpečnostním uzávěrem s dětskou pojistkou z PE/PP, odměrná lžička, příbalová informace v jazyce českém, papírová skládačka

Velikost balení: 100 ml

6.6. Návod k použití

Přípravek se užívá perorálně

Návod pro otevírání lékovky s bezpečnostním uzávěrem

Lékovka je opatřena bezpečnostním uzávěrem zabraňujícím otevření dětmi. Otevře se tak, že se uzávěr stlačí pevně dolů a odšroubuje se proti směru hodinových ručiček. Po použití je třeba uzávěr opět pevně zašroubovat.

7. DRŽITEL ROZHODNUTÍ O REGISTRACI

Léčiva a. s., Praha, Česká republika

8. REGISTRAČNÍ ČÍSLO

24/153/01-C

9. DATUM REGISTRACE / DATUM PRODLOUŽENÍ REGISTRACE

10. DATUM POSLEDNÍ REVIZE TEXTU

24/153/01-C
14/0376/00-S
VP

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZODAC SIR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 1 mg cetirizine dihydrochloride.
Excipients:
one ml solution contains 300 mg sorbitol (70% non-crystallizing solution);
one ml solution contains 1.35 mg methylparaben;
one ml solution contains 0.15 mg propylparaben.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Syrup.
Description of the preparation: clear, colorless to faintly yellowish syrup.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults and pediatric patients over 2 years:

- cetirizine is indicated for relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis;
- cetirizine is indicated for relief of the symptoms of chronic idiopathic urticaria..

4.2. Posology and method of administration

Children between 2 and 6 years: 2.5 mg twice daily (2.5 ml syrup twice daily = $^1/_2$ measuring spoon twice daily).
Children between 6 and 12 years: 5 mg twice daily (5 ml syrup twice daily = full measuring spoon twice daily).
Adults and children over 12 years: 10 mg once daily (10 ml syrup = 2 measuring spoons once daily).
Thy syrup can used without preparation/modification.
Elderly patients: based on available clinical data it is presumed that it is not necessary to reduce the dose for elderly patients with normal renal function
Patients with moderate to severe impairment of renal function: no data are available on the benefit/safety ratio of the medicinal preparation in patients with renal function impairment. Since kidneys are the main route of elimination of cetirizine (see section 5.2) the dosing intervals must be adjusted individually in cases where no alternative therapy can be used.
Refer, please, to the following table and adjust the dosage according to the information reported there.
In order to be able to use this table it is necessary to determine the creatinine clearance (CL_{cr}) of the patient in ml/min. The value of CL_{cr} (ml/min) can be calculated from serum creatinine (mg/dl) using the following formula:

$$CL_{cr} = \frac{140 - \text{ager (years)} \times \text{bodily weight [kg]}}{72 \times \text{serum creatinine [mg/dl]}}$$

(x 0.85 for women)

Adjustment of the dose for adult patients with renal function impairment

Group	*Creatinine clearance [ml/min]*	*Dosage and frequency*
Normal function	>= 80	10 mg once daily
Mild disturbance	50-79	10 mg once daily
Moderate impairment	30-49	5 mg once daily
Severe impairment	< 30	5 mg once in 2 days
End-stage kidney disease - dialyzed patients	< 10	Contraindicated

The dose in pediatric patients with renal function impairment must be adjusted individually based on the renal clearance of each patient, his or her age, and bodily weight.

Patients with impaired liver function: it is not necessary to adjust the dose in patients with isolated liver damage.

Patients with combined liver function and renal function impairment: it is recommended that the dosage be adjusted (see above, Patients with moderate to severe impairment of renal function).

4.3. Contraindications

Hypersensitivity to active substance or any of the excipients of this preparation, to hydroxyzine or any piperarazine derivative.
Patients with severe renal impairment with creatinine clearance less than 10 ml/min.
Patients with the rare hereditary fructose intolerance should not use this preparation.

4.4. Special warnings and precautions for use

No clinically relevant interactions with alcohol have been demonstrated for therapeutic doses (for alcohol blood levels of 0.5 g/l). Caution is nevertheless advised when alcohols is consumed simultaneously by the patient.
Caution is also advised in patients with epilepsy or at risk of convulsions.
Administration of the preparation is not recommended in children and infants aged less then 2 years of age.
Methylparaben and propylparaben can cause allergic reactions (that can be delayed/retarded).

4.5. Interaction with other medicinal products and other forms of interaction

No interaction with this antihistamine are expected as a result of pharmacokinetic and pharmacodynamic properties of cetirizine and its tolerance profile. Interaction studies of the type "drug-drug", particularly with pseudoephedrine, or theophylline dosed as 400 mg/day, have not found pharmacodynamic or statistically significant pharmacokinetic interactions.
In spite of reduced rate of absorption when used with foods the amount of absorption is not reduced when the preparation is used with meals.

4.6. Fertility, pregnancy and lactation

There is limited data available concerning the use of cetirizine during pregnancy. Animal studies have not shown any direct or indirect harmful effects on pregnancy, embryonic / fetal development, delivery or post-partum development. Caution is advised when the preparation is administered to pregnant or nursing women as cetirizine is excreted in breast milk.

4.7. Effects on ability to drive and use machine

Objective measurements of the ability to drive, of sleep latency and performance in assembly line settings have not shown any clinically relevant effects for the recommended dose of 10 mg. Patients planning to take part in activities where they will drive, participate in potentially dangerous activities or use machines should not exceed the recommended dose and should consider the possible reaction of their organism to the preparation. Simultaneous consumption of alcohol or use of other substances with depressive action on CNS by these sensitive patients can

cause additional reduction of wakefulness (vigilance) and reduce their performance.

4.8. Undesirable effects

Clinical studies have demonstrated that cetirizine used in recommended doses exhibits mild undesirable effects on CNS including drowsiness, fatigue, dizziness, and headache. Paradox stimulation of CNS has been reported in some cases.
Although cetirizine is a selective antagonist of peripheral H_1 receptors and does not exhibit relative anticholinergic action there have been isolated reports of urination complaints, accommodation disturbances and dry mouth.
Other reported cases included abnormal liver function with increased levels of liver enzymes accompanied by increased bilirubin level. Most of these symptoms resolved after discontinuation of cetirizine dihydrochloride.

Clinical trials

Double-blind controlled clinical or pharmacokinetic studies comparing cetirizine and placebo or other antihistamines in recommended doses (10 mg daily for cetirizine) that provided quantified data on safety included more than 3,200 patients treated with cetirizine. Based on this data set of patients using 10 mg of cetirizine in placebo-controlled studies the following undesirable effects have been reported (with occurrence rates of 1.0% or higher):

Undesirable effect (WHO-ART)	*Cetirizine 10 mg (n=3,260)*	*Placebo (n=3,061)*
Body as a whole - General disorders		
Fatigue	1.63%	0.95%.
Central nervous system and peripheral nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastrointestinal disorders		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
Psychiatric disorders		
Drowsiness	9.63%	5.00%
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	1.29%	1.34%

Though drowsiness was statistically more common in the placebo group most cases included mild to moderate drowsiness. Objective tests in other studies have demonstrated that recommended doses administered to healthy volunteers have no impact on daily activities.
Undesirable effects with occurrence rates of 1% or higher in children aged 6 months to 12years included in clinical or pharmacokinetic placebo-controlled studies were as follows:

Undesirable effect (WHO-ART)	*Cetirizine 10 mg (n=1,656)*	*Placebo (n=1,294)*
Gastrointestinal disorders		
Diarrhea	1.0%	0.6%
Psychiatric disorders		
Drowsiness	1.8%	1.4%
Respiratory. thoracic and mediastinal disorders		
Rhinitis	1.4%	1.1%
Body as a whole - General disorders		
Fatigue	1.0%	0.3%

Post-marketing experience

In addition to undesirable effects reported as part of clinical trials and reported above, the following isolated cases of undesirable effects were reported as part of post-marketing

experience (after marketing of the preparation). Occurrence rates of these effects based on reports obtained after marketing of the preparations were specified as uncommon: >=1/1,000 to <1/100, rare: >=1/10,000 to <1/1,000, or very rare: <1/10,000.

Blood and lymphatic system disorders
Very rare: thrombocytopenia.
Immune system disorders
Rare: hypersensitivity.
Very rare: anaphylactic shock.
Psychiatric disorders
Uncommon: upset (restlessness).
Rare: aggression, confusion, depression, hallucinations, insomnia.
Very rare: tics
Nervous system disorders
Uncommon: paresthesia.
Rare: cramps, motor disorders.
Very rare: appetite disorder, syncope, tremor, dystonia, dyskinesia.
Eye disorders
Very rare: lens accommodation disorder, blurred vision, involuntary eyeball motions.
Cardiac disorders
Rare: tachycardia.
Gastrointestinal disorders
Uncommon: diarrhea.
Hepatobiliary disorders
Rare: abnormal liver function (increased level of transaminases, alkaline phosphatase, gamma-GT and bilirubin).
Skin and subcutaneous tissue disorders
Uncommon: itching, rash.
Rare: urticaria.
Very rare: angioneurotic edema, localized skin eruptions.
Renal and urinary disorders
Very rare: dysuria, enuresis.
General disorders and administration site conditions
Uncommon: asthenia, malaise.
Rare: edema.
Investigations
Rare: weight gain.

4.9. Overdose

Symptoms
Symptoms observed in overdose with cetirizine are associated mainly with effects on CNS or with phenomena that could suggest anticholinergic effect.
Undesirable effects reported after use of at least five recommended daily doses are confusion, diarrhea, dizziness, fatigue, headache, malaise, dilated pupils, itching, nervousness, sedation, drowsiness, bluntness, tachycardia, tremor and urine retention.
Recommended measures
There is no known cetirizine antidote.
In cases of overdose, symptomatic or supportive treatment is recommended.
In case that the period of time after use of the preparation is short it is appropriate to consider gastric lavage.
Cetirizine is not removed effectively with dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: piperazine derivatives.
ATC code: R06AE07.
Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1 receptors. In vitro studies of receptor binding have not shown any other measurable affinity other than for H_1 receptors.
In addition to its anti-H_1 effects, cetirizine has also been shown to exhibit anti-allergic action: when dosed 10 mg once or twice daily it inhibits the late phase of migration of eosinophils into the skin and the conjunctiva of patients with atopy exposed to allergens.
Studies with healthy volunteers show that cetirizine doses of 5 and 10 mg exhibits strong inhibitory action on the "wheal and flare" reaction (eruption with surrounding reddening) caused by very high levels of histamine in the skin, but no correlation with the efficacy of cetirizine has been shown.
In the course of a study in children aged 5 to 12 years lasting 35 days no tolerance to the anti-histamine effect of cetirizine was observed (inhibition of "wheal and flare"). After therapy with repeated doses of cetirizine was discontinued the skin was observed to resume its normal reactivity to histamine within 3 days.
In the course of a six-week, placebo-controlled study in which 186 patients with allergic rhinitis and concurrent moderate to severe asthma were included, 10 mg of cetirizine administered once daily resulted in improved symptoms of rhinitis and did not affect pulmonary function. This study supports the safety of cetirizine when administered to patients with allergy suffering from mild to moderately severe asthma.
In a placebo-controlled study, high daily doses of cetirizine (60 mg) administered for seven days did not cause any statistically significant extension of QT interval.
Cetirizine used in recommended dosages demonstrated improved quality of life in patients with perennial or seasonal allergic rhinitis.

5.2. Pharmacokinetic properties

Maximum steady-state level is approximately 300 ng/ml, and is reached in 1.0 ± 0.5 hours. Cetirizine administered as daily doses of 10 mg for 10 days did not show any accumulation. The distribution curves of pharmacokinetic parameters, such as maximum plasmatic level (C_{max}) or area under the curve (AUC), were unimodal in human volunteers. Ingestion of food does not result in reduced amount of absorbed cetirizine, but the rate of absorption is reduced.
Bioavailability of cetirizine is comparable for solution, capsules and tablets.
Apparent distribution volume is 0.50 L/kg. Plasmatic protein binding of cetirizine is 93 ± 0.3%. Cetirizine does not affect warfarin binding to plasma proteins.
Cetirizine does not undergo extensive metabolism during the first liver passage. About two thirds of the dose are eliminated in urine as unchanged substance. Terminal half-life is approximately 10 hours.
The kinetics of cetirizine is linear over the range of 5 to 60 mg.
Specific population groups
Elderly patients: When 16 elderly patients were compared with normal patients, the administration of one oral dose of 10 mg resulted in increased half-life by about 50% and reduced clearance by about 40%. This reduced cetirizine clearance was presumably associated with reduced renal function in these elderly volunteers.
Children, infants and nursed babies: children aged 6-12 years had cetirizine half-lives of about 6 hours, and children aged 2-6 years of 5 hours. The half-life of infants and nursed babies aged 6 to 24 months is reduced to 3.1 hours.
Patients with renal function impairment: the pharmacokinetics of the drug in patients with mild

disturbance of renal function (creatinine clearance higher than 40 ml/min) was similar to that observed in healthy volunteers. Patients with moderate renal function impairment had, compared to healthy volunteers, a threefold increase of the half-live and a 70% reduction of clearance. Patients undergoing hemodialysis (creatinine clearance below 7 ml/min) who were administered a single oral dose of 10 mg had threefold increases of the half-life when compared with normal volunteers, and their clearance was reduced by 70%. Cetirizine is not effectively removed with hemodialysis.
Dosages employed in patients with moderately or severely impaired renal function must be adjusted (see section 4.2).
Patients with liver impairment: patients with chronic liver disorders (hepatocellular, cholestatic and biliary cirrhosis) who received a single dose of 10 or 20 mg cetirizine had a 50% extension of the half-life and a 40% reduction of clearance when compared with healthy volunteers. Adjustment of dosage is necessary only in patients with liver damage who are simultaneously suffering from renal function impairment.

5.3. Preclinical safety data

Non-clinical data based on conventional pharmacology studies of safety, studies of toxicity after repeated doses, studies on genotoxicity, evaluation of carcinogenic potential, and studies of reproduction toxicity have not revealed any special risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methylparaben, propylparaben, glycerol 85%, propylene glycol, sorbitol 70% non-crystallizing, saccharin sodium dihydrate, sodium acetate trihydrate, acetic acid 99 percent (M/M), banana flavor, purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This drug does not require any special storage conditions.

6.5. Nature of container and package size

Brown glass vial with child-resistant closure PE/PP, measuring spoon, box.
Package size: 100 ml.

6.6. Special precautions for disposal and other handling

No special requirements.
Instruction for opening the vial with child-resistant closure:
The vial is provided with a child-resistant closure preventing its opening by children. It is opened by pressing the closure firmly down and unscrewing it counterclockwise. The closure must be again firmly screwed in after use.

7. MARKETING AUTHORIZATION HOLDER

Zentiva, k.s., Prague, Czech Republic

8. MARKETING AUTHORIZATION NUMBER

24/153/01-C

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE

AUTHORISATION REGISTRACE

18/04/2001 / 28/01/2009

10. DATE OF REVISION OF THE TEXT

21/10/2009 (ref. no.. 92472/2009)
2006/10/11/V
2009/01/28/X
2009/09/01/M
2009/10/21/V

24/154/01-C
14/0375/00-S
VP

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZODAC GTT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 10 mg cetirizine dihydrochloride, 1 drop of the solution contains 0.5 mg cetirizine dihydrochloride.
Excipients: one ml solution contains 1.35 mg methylparaben, one ml solution contains 0.15 mg propylparaben
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral drops, solution.
Description of the preparations: clear, colourless to faintly yellowish solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults and paediatric patients over 2 years:

- cetirizine is indicated to relieve nasal and ocular symptoms of seasonal and perennial allergic rhinitis;
- cetirizine is indicated for relief of the symptoms of chronic idiopathic urticaria.

4.2. Posology and method of administration

Children between 2 and 6 years: 2.5 mg twice daily (5 drops twice daily).
Children between 6 and 12 years: 5 mg twice daily (10 drops twice daily).
Adults and children over 12 years: 10 mg once daily (20 drops).
The solution is used orally - either undiluted as drops applied to a teaspoon, or diluted in a glass of water. When using diluted solution it is important, particularly with children, to use only such amounts of water to dilute the drops that the patient is able to drink (swallow) the whole volume of the solution at once. The diluted solution should be used without delay.
Elderly patients: based on available clinical data it is presumed no dose reduction is necessary for elderly patients with normal renal function.
Patients with moderate to severe impairment of renal function: no data are available on the benefit/safety ratio of the medicinal preparation when used in patients with renal function impairment. Since kidneys are the main elimination route of cetirizine (see section 5.2) the dosing intervals must be adjusted individually in cases where no alternative therapy can be used. Refer, please, to the following table and adjust the dosage according to the information reported therein.
In order to be able to use this table it is necessary to determine creatinine clearance (CL_{cr}) of the patient in ml/min. The value of CL_{cr} (ml/min) can be calculated from serum creatinine (mg/dl) using the following formula:

$$CL_{cr} = \frac{140 - \text{age (years)} \times \text{bodily weight [kg]}}{72 \times \text{serum creatinine [mg/dl]}}$$

(x 0.85 for women)

Adjustment of the dose for adult patients with renal function impairment

Group	*Creatinine clearance [ml/min]*	*Dosage and frequency*
Normal function	>= 80	10 mg once daily
Mild disturbance	50-79	10 mg once daily
Moderate impairment	30-49	5 mg once daily
Severe impairment	< 30	5 mg once in 2 days
End-stage kidney disease - dialyzed patients	< 10	Contraindicated

The dose in paediatric patients with renal function impairment must be adjusted individually based on each patient's renal clearance, his or her age, and bodily weight.

Patients with impaired liver function: it is not necessary to adjust the dose in patients with isolated liver damage.

Patients with combined liver function and renal function impairment: it is recommended that the dosage be adjusted (see above, Patients with moderate to severe impairment of renal function).

4.3. Contraindications

Hypersensitivity to active substance or any of the excipients of this preparation, to hydroxyzine or any piperarazine derivative.

Patients with severe renal impairment with creatinine clearance less than 10 ml/min.

4.4. Special warnings and precautions for use

No clinically relevant interactions with alcohol have been demonstrated for therapeutic doses (for alcohol blood levels of 0.5 g/l). Caution is nevertheless advised when alcohols is used simultaneously by the patient.

Caution is also advised in patients with epilepsy or at risk of convulsions.

Administration of the preparation is not recommended in children and infants less then 2 years of age.

Methylparaben and propylparaben can cause allergic reactions (that can be delayed).

4.5. Interaction with other medicinal products and other forms of interaction

No interactions with this antihistamine are expected as a result of pharmacokinetic and pharmacodynamic properties of cetirizine and its tolerance profile. Interactions studies of the type "drug-drug", particularly with pseudoephedrine, or theophylline dosed as 400 mg/day, have not found any pharmacodynamic or statistically significant pharmacokinetic interactions.

In spite of reduced rate of absorption when used with foods the overall amount of absorption is not reduced when the preparation is used with meals.

4.6. Fertility, pregnancy and lactation

There is limited data available concerning the use of cetirizine during pregnancy. Animal studies have not shown any direct or indirect harmful effect on pregnancy, embryonic / fetal development, delivery or post-partum development. Caution is advised when the preparation is administered to pregnant or nursing women as cetirizine is excreted in breast milk.

4.7. Effects on ability to drive and use machine

Objective measurements of the ability to drive, sleep latency and performance in assembly line settings have not shown any clinically relevant effects for the recommended dose of 10 mg. Patients anticipating to take part in activities where they will drive, participate in potentially dangerous activities or use machines should not exceed the recommended dose, and should consider the possible reaction of their organism to the preparation. Simultaneous consumption of alcohol or use of other substances with depressive action on CNS by these sensitive patients can

cause additional reduction of wakefulness (vigilance) and reduce their performance.

4.8. Undesirable effects

Clinical studies have demonstrated that cetirizine used in recommended doses exhibits mild undesirable effects on CNS including drowsiness, fatigue, dizziness, and headache. Paradox stimulation of CNS has been reported in some cases.
Although cetirizine is a selective antagonist of the peripheral H_1 receptors and does not exhibit relative anticholinergic action there have been isolated reports of urination complaints, accommodation disturbances and dry mouth.
Other reported cases included abnormal liver function with increased levels of liver enzymes accompanied by increased bilirubin level. Most of these symptoms resolved after discontinuation of cetirizine dihydrochloride.

+Clinical trials

Double-blind controlled clinical or pharmacokinetic studies comparing cetirizine with placebo or other antihistamines in recommended doses (10 mg daily for cetirizine) that have been used as quantified data for safety included more than 3,200 patients treated with cetirizine. Based on this data set obtained with the use of 10 mg of cetirizine in placebo-controlled studies the following undesirable effects have been reported (with occurrence rates of 1.0% or higher):

Undesirable effect (WHO-ART)	*Cetirizine 10 mg (n=3,260)*	*Placebo (n=3,061)*
Body as a whole - General disorders		
Fatigue	1.63%	0.95%.
Central nervous system and peripheral nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastrointestinal disorders		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
Psychiatric disorders		
Drowsiness*	9.63%	5.00%
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	1.29%	1.34%

Though drowsiness was statistically more common in the placebo group most cases included mild to moderate drowsiness. Objective tests in other studies have demonstrated that recommended doses administered to healthy volunteers had no impact on daily activities.
Undesirable effects with occurrence rates of 1% or higher in children aged 6 months to 12years included in clinical or pharmacokinetic placebo-controlled studies were as follows:

Undesirable effect (WHO-ART)	*Cetirizine 10 mg (n=1,656)*	*Placebo (n=1,294)*
Gastrointestinal disorders		
Diarrhea	1.0%	0.6%
Psychiatric disorders		
Drowsiness	1.8%	1.4%
Respiratory. thoracic and mediastinal disorders		
Rhinitis	1.4%	1.1%
Body as a whole - General disorders		
Fatigue	1.0%	0.3%

Post-marketing experience

In addition to undesirable effects reported as part of clinical trials and reported above, the following isolated cases of undesirable effects were reported as part of post-marketing

experience (after marketing of the preparation). Occurrence rates of these effects based on reports obtained after marketing of the preparations were specified as uncommon: >=1/1,000 to <1/100, rare: >=1/10,000 to <1/1,000, or very rare: <1/10,000.

Blood and lymphatic system disorders
Very rare: thrombocytopenia.
Immune system disorders
Rare: hypersensitivity.
Very rare: anaphylactic shock.
Psychiatric disorders
Uncommon: upset (restlessness).
Rare: aggression, confusion, depression, hallucinations, insomnia.
Very rare: tics
Nervous system disorders
Uncommon: paresthesia.
Rare: cramps, motor disorders.
Very rare: appetite disorder, syncope, tremor, dystonia, dyskinesia.
Eye disorders
Very rare: lens accommodation disorders, blurred vision, involuntary eyeball motions.
Cardiac disorders
Rare: tachycardia.
Gastrointestinal disorders
Uncommon: diarrhea.
Hepatobiliary disorders
Rare: abnormal liver function (increased levels of transaminases, alkaline phosphatase, gamma-GT and bilirubin).
Skin and subcutaneous tissue disorders
Uncommon: itching, rash.
Rare: urticaria.
Very rare: angioneurotic edema, localized skin eruptions.
Renal and urinary disorders
Very rare: dysuria, enuresis.
General disorders and administration site conditions
Uncommon: asthenia, malaise.
Rare: edema.
Investigations
Rare: weight gain.

4.9. Overdose

Symptoms
Symptoms observed in overdose with cetirizine are associated mainly with effects on CNS or with phenomena that could suggest anticholinergic effect.
Undesirable effects reported after use of at least five recommended daily doses are confusion, diarrhea, dizziness, fatigue, headache, malaise, dilated pupils, itching, nervousness, sedation, drowsiness, bluntness, tachycardia, tremor and urine retention.
Recommended measures
There is no known cetirizine antidote.
In cases of overdose, symptomatic or supportive treatment is recommended.
In case that the period of time after use of the preparation is short it is appropriate to consider gastric lavage.
Cetirizine is not removed effectively with dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: piperazine derivatives.
ATC code: R06AE07.
Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1 receptors. In vitro studies of receptor binding have not shown any other measurable affinity other than for H_1 receptors.
In addition to its anti-H_1 effects, cetirizine has also been shown to exhibit anti-allergic action: when dosed 10 mg once or twice daily it inhibits the late phase of migration of eosinophils into the skin and the conjunctiva of patients with atopy exposed to allergens.
Studies on healthy volunteers show that cetirizine doses of 5 and 10 mg exhibits strong inhibitory action on the "wheal and flare" reaction (eruption with surrounding reddening) caused by very high levels of histamine in the skin, but no correlation with the efficacy of cetirizine has been shown.
In the course of a study in children aged 5 to 12 years lasting 35 days no tolerance to the anti-histamine effect of cetirizine was observed (inhibition of "wheal and flare"). After discontinuation of therapy with repeated doses of cetirizine the skin was observed to resume its normal reactivity to histamine within 3 days.
Over the course of a six-week, placebo-controlled study in which 186 patients with allergic rhinitis and concurrent moderate to severe asthma were included, 10 mg of cetirizine administered once daily resulted in improved symptoms of rhinitis and did not affect pulmonary function. This study supports the safety of cetirizine when administered to patients with allergy with mild to moderately severe asthma.
Cetirizine used in recommended dosages demonstrated improved quality of life in patients with perennial or seasonal allergic rhinitis.

5.2. Pharmacokinetic properties

Maximum steady-state level is approximately 300 ng/ml, and is reached after 1.0 ± 0.5 hours. Cetirizine administered as daily doses of 10 mg for 10 days did not show any accumulation. The distribution curves of pharmacokinetic parameters, such as maximum plasmatic level (C_{max}) or area under the curve (AUC), were unimodal in human volunteers. Ingestion of food does not result in reduced amount of absorbed cetirizine, but the rate of absorption is reduced.
Bioavailability of cetirizine is comparable for its forms as solution, capsules and tablets.
Apparent distribution volume is 0.50 L/kg. Plasmatic protein binding of cetirizine is 93 ± 0.3%.
Cetirizine does not affect warfarin binding to plasma proteins.
Cetirizine does not undergo extensive metabolism during first liver passage. About two thirds of the dose are eliminated in urine as unchanged substance. Terminal half-life is approximately 10 hours.
The kinetics of cetirizine is linear over the range of 5 to 60 mg.
Specific population groups
Elderly patients: When 16 elderly patients were compared with normal patients, the administration of one oral dose of 10 mg resulted in increased half-life of the drug by about 50% and reduced clearance by about 40% in the elderly. This reduced cetirizine clearance was presumably associated with reduced renal function in these elderly volunteers.
Children, infants and nursed babies: children aged 6-12 years had cetirizine half-lives of about 6 hours, and children aged 2-6 years of 5 hours. The half-life of the drug is reduced to 3.1 hours in infants and nursed babies aged 6 to 24 months.
Patients with impaired renal function: the pharmacokinetics of the drug in patients with mild renal function disturbance (creatinine clearance above 40 ml/min) was similar to that in healthy volunteers. Patients with moderate disturbance of renal function had, compared to healthy

volunteers, a threefold increase of the half-life, and their clearance was reduced by 70%. Patients undergoing hemodialysis (creatinine clearance below 7 ml/min) who were administered a single oral dose of 10 mg had threefold increases of half-life when compared with normal volunteers, and their clearance was reduced by 70%. Cetirizine is not effectively removed with hemodialysis.
Dosages employed in patients with moderately or severely impaired renal function must be adjusted (see section 4.2).
Patients with liver impairment: patients with chronic liver disorders (hepatocellular, cholestatic, or biliary cirrhosis) who received a single dose of 10 or 20 mg cetirizine had a 50% extension of their half-life and a 40% reduction of clearance when compared with healthy volunteers. Adjustment of dosage is necessary only in patients with liver damage with coincident renal function impairment.

5.3. Preclinical safety data

Non-clinical data based on conventional pharmacology studies of safety, studies of toxicity after repeated doses, studies on genotoxicity, evaluations of carcinogenic potential, and studies of reproduction toxicity have not revealed any special risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methylparaben (E218), propylparaben (E216), glycerol 85%, propylene glycol, saccharin sodium dihydrate, sodium acetate trihydrate, acetic acid 99 percent (M/M), purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

This drug does not require any special storage conditions.

6.5. Nature of container and package size

Brown glass vial closed with a LDPE stopper and child-resistant HDPE closure, box.
Package size: 20 ml.

6.6. Special precautions for disposal and other handling

No special requirements.
Instruction for opening the vial with child-resistant closure: The vial is provided with a child-resistant closure preventing its opening by children. It is opened by pressing the closure firmly down and unscrewing it counterclockwise. The closure must be again firmly screwed in after use.

7. MARKETING AUTHORIZATION HOLDER

Zentiva, k.s., Prague, Czech Republic

8. MARKETING AUTHORIZATION NUMBER

24/154/01-C

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/04/2001 / 28/01/2009

10. DATE OF REVISION OF THE TEXT

21/10/2009 (ref. no. 92468/2009)
2006/10/11/V
2009/01/28/X
2009/09/01/M
2009/10/21/V

MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY

Toto rozhodnutie nadobudlo právoplatnosť
dňa 5. 1. 2001
v Bratislave 5. 1. 2001
Podpis

Číslo: R-699/2000-SF

V Bratislave: 29.11.2000

R o z h o d n u t i e

Ministerstvo zdravotníctva Slovenskej republiky ako príslušný orgán podľa ustanovenia § 60 písm. b) zákona Národnej rady Slovenskej republiky č. 140/1998 Z. z. o liekoch a zdravotníckych pomôckach, o zmene zákona NR SR č. 455/1991 Zb. o živnostenskom podnikaní (živnostenský zákon) v znení neskorších predpisov a o zmene a doplnení zákona NR SR č. 220/1996 Z. z. o reklame v znení neskorších predpisov, žiadosti č. R-0668/2000 zo dňa 08.06.2000 o registráciu lieku ***ZODAC^{R} SIR sir,*** *držiteľa rozhodnutia o registrácii Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, výrobcu Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, v zastúpení organizačnou zložkou Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava, rozhodlo*

t a k t o :

Žiadosti o registráciu lieku

ZODAC^{R} SIR sir

s obsahom 5 mg dihydrochloridu cetirizínu v 5 ml sirupu, v obale: hnedá sklenená liekovka so závitomvým uzáverom s detskou poistkou, sa vyhovuje. Povoľuje sa uvedenie lieku do obehu a zapísanie do zoznamu registrovaných liekov pod registračným číslom

14/0376/00/-S

a kódom Štátneho ústavu pre kontrolu liečiv pre balenie ***1 x 100 ml 15926,*** *pretože liek spĺňa podmienky ustanovené zákonom NR SR č. 140/1998 Z. z.. Liek sa zatrieďuje do skupiny liekov, ktorých* ***výdaj je viazaný na lekársky predpis.*** *Schvaľuje sa označenie vonkajšieho a vnútorného obalu (príloha č. 1), písomná informácia pre používateľov lieku (príloha č. 2), súhrn charakteristických vlastností lieku (príloha č. 3), ktoré sú súčasťou tohto rozhodnutia*

Čas použiteľnosti lieku ***ZODAC^{R} SIR sir, 1 x 100 ml je dva roky***

Rozhodnutie je platné 5 rokov od nadobudnutia právoplatnosti

O d ô v o d n e n i e

Pri preskúmaní žiadosti o registráciu lieku, držiteľa rozhodnutia o registrácii Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, výrobcu Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, v zastúpení organizačnou zložkou Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava, č. R-0668/2000 zo dňa 08.06.2000, bolo zistené, že produkt spĺňa požiadavky na kvalitný, bezpečný a účinný liek, preto bolo rozhodnuté tak ako je uvedené vo výroku tohto rozhodnutia.

P o u č e n i e: Proti tomuto rozhodnutiu je možno podať rozklad v lehote 15 dní od jeho doručenia na Ministerstvo zdravotníctva Slovenskej republiky (§ 61 ods.1 zákona č. 71/1967 Zb. o správnom konaní).

MINISTERSTVO ZDRAVOTNÍCTVA 40 SLOVENSKEJ REPUBLIKY

Roman K o v á č
m i n i s t e r

Rozhodnutie dostanú:

1. Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava
2. Štátny ústav pre kontrolu liečiv, Kvetná 11, 825 08 Bratislava
3. Ministerstvo zdravotníctva SR, Limbová 2, 833 41 Bratislava

SÚHRN CHARAKTERISTICKÝCH VLASTNOSTÍ LIEKU

16.11.2006

1. NÁZOV LIEKU
ZODAC® SIR

2. KVALITATÍVNE A KVANTITATÍVNE ZLOŽENIE LIEKU
Cetirizini dihydrochloridum (dihydrochlorid cetirizínu) 5 mg v 5 ml sirupu

3. LIEKOVÁ FORMA
Sirup
Opis prípravku: číry, bezfarebný až slabo žltkastý roztok sladkej banánovej chuti.

4. KLINICKÉ ÚDAJE
4.1. Terapeutické indikácie
Symptomatická liečba alergickej nádchy a konjunktivitídy (vrátane celoročnej a sezónnej) a kožných prejavov sprevádzaných svrbením a vyrážkou, najmä pri urtikárii.

4.2. Dávkovanie a spôsob podávania
Dospelí a deti od 12 rokov zvyčajne užívajú 10 mg cetirizínu (2 odmerné lyžičky) v jednej dennej dávke.
Deti od 6 do 12 rokov zvyčajne užívajú 10 mg cetirizínu (2 odmerné lyžičky) 1x denne alebo 5 mg cetirizínu (1 odmernú lyžičku) 2x denne.
Deti od 2 do 6 rokov zvyčajne užívajú 5 mg cetirizínu (1 odmernú lyžičku) 1x denne alebo 2,5 mg cetirizínu (1/2 odmernej lyžičky) 2x denne.
Pacienti so zlyhaním obličiek: pri znížení funkcie obličiek treba úmerne znížiť dávkovanie cetirizínu, pri klírensi kreatinínu 11 - 31 ml/min sa podáva 5 mg cetirizínu (1 odmerná lyžička) denne.
Hemodialyzovaným pacientom sa podáva 5 mg cetirizínu (1 odmerná lyžička) denne.
Pacienti s pečeňovou insuficienciou: treba úmerne znížiť dávkovanie cetirizínu, zvyčajne sa podáva 5 mg cetirizínu (1 odmerná lyžička) denne.
U geriatrických pacientov: vzhľadom na vek nie je nutné dávky upravovať. Dávkovanie treba upraviť v prípade zníženej funkcie obličiek, zvyčajne sa podáva 5 mg cetirizínu (1 odmerná lyžička) denne.
Zodac sir sa môže užívať nezávisle od jedla, sirup sa zapíja dostatočným množstvom nedráždivej tekutiny.
Na odmeranie dávky je priložená odmerná lyžička s dvomi ryskami, označenými 1/4 (= 1/4 odmerky, zodpovedá 1,25 ml) a 1/2 (= 1/2 odmerky, zodpovedá 2,5 ml); lyžička naplnená po okraj obsahuje 5 ml.

4.3. Kontraindikácie
Známa precitlivenosť na cetirizín, inú zložku prípravku alebo hydroxyzín. Deti do 2 rokov.
Neodporúča sa podávať počas tehotenstva ani v období dojčenia.

4.4. Špeciálne upozornenia
Opatrnosť je potrebná u pacientov so zlyhaním obličiek, insuficienciou pečene a u geriatrických pacientov.
Zodac sir obsahuje maximálne 0,12 g zvyškového cukru v 5 ml sirupu (použité sladidlá sú sorbitol a sacharín). Ak sa dodrží odporučené dávkovanie, je tento sirup vhodný pre diabetikov.
Počas liečby sa neodporúča nadmerne piť nealkoholické nápoje.

4.5. Liekové a iné interakcie
Pri súčasnom užívaní cetirizínu s teofylínom sa môže znížiť klírens cetirizínu (až o 16%) s klinickými prejavmi nežiaducich účinkov cetirizínu.

4.6. Používanie v gravidite a počas laktácie
Pri pokusoch na zvieratách sa nepreukázala embryotoxicita ani teratogenita.
S používaním u ľudí nie je dostatok skúseností.
Vzhľadom na nedostatok skúseností sa jeho používanie u tehotných a dojčiacich žien neodporúča.

4.7. Ovplyvnenie schopnosti viesť motorové vozidlá a obsluhovať stroje
Nie sú opísané sedatívne účinky prípravku ako pri klasických antihistaminikách. Štúdie u zdravých dobrovoľníkov nepreukázali po podaní 20 - 25 mg cetirizínu žiadny vplyv na bdelosť alebo reakčnú dobu. Napriek tomu treba individuálne posúdiť nutnosť zvýšenej opatrnosti u osôb vykonávajúcich činnosť vyžadujúcu pozornosť, motorickú koordináciu a rýchle rozhodovanie (napr. vedenie motorových vozidiel, ovládanie strojov, práca vo výškach a pod.).

4.8. Nežiaduce účinky
Cetirizín sa všeobecne dobre znáša. S užívaním cetirizínu sa ojedinele môžu spájať bolesti hlavy, ospanlivosť, závraty, suchosť v ústach, tráviace ťažkosti (dyspepsia, bolesti brucha, plynatosť).

4.9. Predávkovanie
Pri dávkach cetirizínu (viac ako 50 mg) sa pozorovala ospanlivosť, u detí môže predávkovanie naopak vyvolať nepokoj a podráždenosť; môžu sa pozorovať príznaky anticholínergného účinku (retencia moču, výrazná suchosť v ústach, zápcha).
Ošetrenie pri predávkovaní zahŕňa štandardný postup, liečba je symptomatická a podporná so zameraním na udržanie vitálnych funkcií. Špecifické antidotum nie je známe. Hemodialýzou je možné odstrániť len malú časť podanej dávky cetirizínu (cca 9%).

5. FARMAKOLOGICKÉ VLASTNOSTI
5.1. Farmakodynamické vlastnosti
Farmakoterapeutická skupina - Antihistaminikum. ATC skupina: B06AE07- antihistaminiká na celkové podávanie - piperazínové deriváty - cetirizín.

Cetirizín je antihistaminikum II. generácie s predĺženým účinkom. Selektívne inhibuje periférne H_1 - receptory, ale výraznejšie neovplyvňuje cholínergické. adrenergické ani serotonínové receptory. V terapeutických dávkach nemá sedatívny účinok na CNS. Inhibuje migráciu zápalových buniek, predovšetkým

eozinofilov. Tlmí uvoľňovanie histamínu zo žírnych buniek a bazofilných leukocytov aj v priebehu neskorej fázy alergickej reakcie.

5.2. Farmakokinetické vlastnosti
Biologická dostupnosť cetirizínu po požití sirupu je rýchla a úplná. Potrava nemá vplyv na vstrebávanie cetirizínu, predlžuje však dobu dosiahnutia maximálnej koncentrácie na 1,7. Maximálna koncentrácia po požití kvapiek sa dosiahne o 30 - 60 minút, u detí sú dosiahnuté maximálne koncentrácie vyššie ako u dospelých. Vzťah medzi dávkou a plazmatickou koncentráciou je lineárny.
Antihistamínový účinok sa dostavuje 20 - 60 minút po požití, pretrváva počas 24 hodín.
Väzba na plazmatické bielkoviny je 93%. Minimálne preniká do mozgovomiechového moku, väzba na mozgové H_1 receptory je nevýznamná. Distribučný objem (V_d) je 0,5 až 0,8 l/kg.
Na rozdiel od ostatných antihistaminík sa len minimálne metabolizuje v pečeni, O-dealkylovaný metabolit nemá antihistamínovú aktivitu.
Eliminačný polčas je 7,4 až 9 hodín, u pacientov so stredne závažnou renálnou insuficienciou sa predlžuje na 19 až 21 hodín. U detí je celkový telesný klírens cetirizínu asi o 33% vyšší ako u dospelých, eliminačný polčas je skrátený na 6,2 hodín. Približne 60% podanej dávky sa vylúči močom v nezmenenej forme počas 24 hodín, ďalších 10% v priebehu nasledujúcich štyroch dní; u detí sa vylúči močom 40% podanej dávky počas 24 hodín. Stolicou sa vylúči asi 10% podanej dávky počas piatich dní po požití.

5.3. Predklinické údaje o bezpečnosti
Štúdie na zvieratách preukázali, že dávky 216x vyššie ako maximálna dávka pre človeka nie sú teratogénne. Cetirizín nepôsobí teratogénne v priebehu organogenézy.

6. FARMACEUTICKÉ INFORMÁCIE

6.1. Zoznam pomocných látok
Methylparabenum, propylparabenum, glycerolum 85%, propylenglycolum, sorbitolum 70% non cristallisabile, saccharinum natricum, natrii acetas, acidum aceticum 99%, aroma musae, aqua purificata.

6.2. Inkompatibility
Inkompatibilita perorálne užívaného cetirizínu s ďalšou látkou nie je známa.

6.3. Čas použiteľnosti
2 roky

6.4. Upozornenie na podmienky a spôsob skladovania
V suchu, pri teplote 10 - 25°C, chrániť pred svetlom.

6.5. Vlastnosti a zloženie obalu a veľkosť balenia
Obal: hnedá sklenená liekovka so závitovým uzáverom s detskou poistkou, odmerná lyžička, písomná informácia v slovenskom jazyku, papierová skladačka.
Veľkosť balenie: 100 ml

6.6. Upozornenia na spôsob zaobchádzania s liekom
Prípravok sa užíva perorálne.

Návod na otváranie liekovky s bezpečnostným uzáverom
Liekovka je opatrená bezpečnostným uzáverom, ktorý bráni otvoreniu deťmi. Otvorí sa tak, že sa uzáver stlačí silno nadol a odskrutkuje sa proti smeru hodinových ručičiek. Po použití treba uzáver opäť silno zaskrutkovať.

7. DRŽITEĽ ROZHODNUTIA O REGISTRÁCII
Léčiva a.s., Praha, Česká republika

8. REGISTRAČNÉ ČÍSLO

9. DÁTUM REGISTRÁCIE/DÁTUM PREDĹŽENIA REGISTRÁCIE

9. DÁTUM POSLEDNEJ REVÍZIE TEXTU
November 2000

16.11.2020

Písomná informácia pre používateľa

Informácia o použití, čítajte pozorne!

ZODAC® SIR

(cetirizini dihydrochloridum)
sirup

Držiteľ rozhodnutia o registrácii:
Léčiva a.s., Praha, Česká republika

Zloženie:
Liečivo: cetirizini dihydrochloridum (dihydrochlorid cetirizínu) 5 mg v 5 ml sirupu
Pomocné látky: methylparabenum (metylparabén), propylparabenum (propylparabén), glycerolum (glycerol), propylenglycolum (propylénglykol), sorbitolum 70% noncristallisabile (sorbitol 70% nekryštalizujúci), saccharinum natricum (sodná soľ sacharínu), natrii acetas (octan sodný), acidum aceticum (kyselina octová), aroma musae (banánová aróma), aqua purificata (čistená voda).

Farmakoterapeutická skupina:
Antihistaminikum (liek tlmiaci reakciu z precitlivenosti)

Charakteristika:
Cetirizín, účinná látka prípravku Zodac sir, je antihistaminikum s predĺženým účinkom. Antihistaminiká blokujú pôsobenie histamínu, jedného z pôsobkov, ktorý sa v organizme uvoľňuje pri reakcii z precitlivenosti (alergia). Cetirizín tlmí tak "skorú" fázu alergickej reakcie sprostredkovanú histamínom, ako aj pohyb buniek zápalu, najmä eozinofilov a uvoľňovanie pôsobkov spojených s "neskorou" fázou alergickej reakcie.
Zodac sir je vysoko účinné antihistaminikum a antialergikum s minimálnym výskytom ospanlivosti po bežnej liečebnej dávke. Vzhľadom na predĺžený účinok sa prípravok Zodac sir môže podávať dospelým a starším deťom v jedinej dennej dávke.

Indikácie:
Zodac sir sa užíva na zmiernenie ťažkostí pri alergickej nádche a alergickom zápale spojoviek (vrátane celoročnej a sezónnej) a kožných prejavov sprevádzaných svrbením a vyrážkou, najmä pri žihľavke.

Kontraindikácie:
Zodac sir sa nesmie podávať pacientom so známou precitlivenosťou na cetirizín, inú zložku prípravku alebo hydroxyzín, tehotným a dojčiacim ženám a deťom do 2 rokov.

Nežiaduce účinky:
Zodac sir sa všeobecne dobre znáša, s jeho užívaním sa ojedinele môžu spájať bolesti hlavy, ospanlivosť, závraty, suchosť v ústach, tráviace ťažkosti (dyspepsia, bolesti brucha, plynatosť). Pri prípadnom výskyte týchto nežiaducich účinkov alebo iných nezvyčajných reakcií sa o ďalšom užívaní prípravku či podávaní dieťaťu poraďte s lekárom.

Zriedkavo sa môžu vyskytnúť prejavy precitlivenosti na prípravok (žihľavka, opuch mäkkých tkanív, dýchavica). V tomto prípade je nutné ihneď prerušiť užívanie prípravku a poradiť sa s lekárom.

Interakcie:
Účinky prípravku Zodac sir a iných súčasne užívaných liekov sa môžu navzájom ovplyvňovať. Súčasné užívanie prípravku Zodac sir s niektorými bronchodilatanciami (lieky na rozšírenie priedušiek) obsahujúcimi účinnú látku teofylín môže vyvolať nežiaduce účinky liečby prípravkom Zodac sir.
Informujte preto vášho lekára o všetkých liekoch, ktoré vy alebo vaše dieťa užívate na lekársky predpis aj bez neho. Bez súhlasu lekára neužívajte ani nepodávajte dieťaťu súčasne s prípravkom Zodac sir žiadny voľnopredajný liek . Ak vám ďalší lekár bude predpisovať nejaký iný liek, informujte ho, že vy alebo dieťa užívate Zodac sir.
Interakcie cetirizínu s alkoholom (pri hladine alkoholu v krvi 0,8 g/l) doposiaľ neboli opísané. Napriek tomu sa počas užívania prípravku Zodac sir neodporúča požívať nadmerne alkoholické nápoje.

Dávkovanie a spôsob podávania:
Dávkovanie určuje vždy lekár. Potrava významne neovplyvňuje vstrebávanie prípravku Zodac sir a môže sa teda užívať nezávisle od jedla.
Dospelí a deti od 12 rokov užívajú zvyčajne 2 odmerné lyžičky prípravku Zodac sir (= 10 mg cetirizínu) 1x denne.
Deti od 6 do 12 rokov užívajú 2 odmerné lyžičky (=10 mg cetirizínu) 1x denne alebo 1 odmernú lyžičku (= 5 mg cetirizínu) 2x denne, ráno a večer.
Deťom od 2 do 6 rokov sa podáva 1 odmerná lyžička (= 5 mg cetirizínu) 1x denne alebo 1/2 odmernej lyžičky (= 2,5 mg cetirizínu) 2x denne, ráno a večer.
Starším chorým alebo pacientom so závažným ochorením pečene a obličiek môže lekár dávkovanie upraviť.
Pri náhodnom vynechaní dávky užite liek (podajte liek dieťaťu) ihneď, ako si spomeniete. V prípade, že by sa mala užiť ďalšia dávka, dávkovanie nezdvojnásobujte a pokračujte podľa pôvodného plánu liečby.
Na odmeranie dávky je priložená odmerná lyžička s dvomi ryskami, označenými 1/4 (= 1/4 odmerky, zodpovedá 1,25 ml) a 1/2 (=1/2 odmerky, zodpovedá 2,5 ml); lyžička naplnená po okraj obsahuje 5 ml.
Sirup sa zapíja malým množstvom nedráždivej tekutiny.

Návod na otváranie liekovky s bezpečnostným uzáverom
Liekovka je opatrená bezpečnostným uzáverom, ktorý bráni otvoreniu deťmi. Otvoríte ho tak, že uzáver stlačíte silno nadol a odskrutkujete proti smeru hodinových ručičiek. Po použití treba uzáver opäť silno zaskrutkovať.

Upozornenie:
U prípravku nie sú opísané tlmivé účinky. Napriek tomu sa odporúča neprekročiť odporučenú dennú dávku, pokiaľ budete viesť motorové vozidlo alebo obsluhovať stroje.
Zodac sir obsahuje maximálne 0,12 g cukru v 5 ml sirupu (použité sladidlá sú sorbitol a sacharín). Ak sa dodrží odporučené dávkovanie, je sirup vhodný pre diabetikov.

Predávkovanie:

Pri predávkovaní môže byť hlavným príznakom ospanlivosť. U detí však predávkovanie môže vyvolať aj podráždenosť a nepokoj. Pri predávkovaní (najmä detí) je nutné ihneď vyhľadať lekára. Špecifický protiliek doposiaľ nie je známy.

Varovanie:
Prípravok sa nesmie používať po uplynutí času použiteľnosti uvedenom na obale.
Pri užití nadmernej dávky alebo ak sirup náhodne požije dieťa, vyhľadajte lekára.

Balenie:
100 ml sirupu

Uchovávanie:
V suchu, pri teplote 10-25° C, chrániť pred svetlom.
Uchovávajte mimo dosahu detí!

Dátum poslednej revízie:
November 2000

Vzor označenia vonkajšieho obalu

16.11.2020

100 ml

ZODAC SIR

(Cetirizini dihydrochloridum)

sirup

Antihistaminikum

Cetirizini dihydrochloridum 5 mg v 5 ml sirupu

Obsahuje methylparaben, propylparaben , sorbitol a sodnú soľ sacharinu

Nepoužívať pri precitlivenosti na parabény

Na vnútorné užitie

Výdaj len na lekársky predpis

Písomná informácia pre používateľa priložená

Odmerná lyžička naplnená po okraj obsahuje 5 ml sirupu

Zodac sir obsahuje maximálne 0,12 g cukru v 5 ml sirupu

Uchovávajte v suchu pri teplote 10 - 25 °C!

Chráňte pred svetlom

Ukladajte mimo dosahu detí!

Nepoužitý liek vráťte do lekárne

Č. reg.:

Č. šarže:

Použ. do:

Léčiva a.s.
102 37 Praha 10

Dolní Měcholupy 130,
Česká republika

EAN kód

Vzor označenia vnútorného obalu

100 ml

ZODAC SIR

(Cetirizini dihydrochloridum)

sirup

Antihistaminikum

Cetirizini dihydrochloridum 5 mg v 5 ml sirupu

Obsahuje methylparaben, propylparaben , sorbitol a sodnú soľ sacharinu

Nepoužívať pri precitlivenosti na parabény

Na vnútorné užitie

Výdaj len na lekársky predpis

Písomná informácia pre používateľa priložená

Odmerná lyžička naplnená po okraj obsahuje 5 ml sirupu

Zodac sir obsahuje maximálne 0,12 g cukru v 5 ml sirupu

Uchovávajte v suchu pri teplote 10 - 25 °C!

Chráňte pred svetlom

Ukladajte mimo dosahu detí!

Nepoužitý liek vráťte do lekárne

Č. reg.:

Údaj č. šarže

Údaj dátumu skončenia použiteľnosti

Logo LÉČIVA

Thomson Reuters Newport Premium
Launched Drug Forms Detail

Dose Form	Strength	Active Ingredient	Trade Name	Marketer	Name	Launch Country	Pack Launch Date
Liquid	5MG	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Russia	31-Jan-2006
Liquid	.1% 100ML	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Slovakia	30-Sep-2002
Liquid	.1% 100ML	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Czech Republic	31-Oct-2001
Liquid/Drops	1% 20ML	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Czech Republic	31-Oct-2001
Liquid/Drops	1% 20ML	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Slovakia	30-Sep-2002
Liquid/Drops	10MG	cetirizine hydrochloride	ZODAC	ZENTIVA	Sanofi-Aventis	Russia	31-Jan-2006

MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY

MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY 40

Toto rozhodnutie nadobudlo právoplatnosť
dňa 5. 2. 2001
v Bratislave 7. 2. 2001
Podpis

Číslo: R-700/2000-SF

V Bratislave: 29.11.2000

R o z h o d n u t i e

Ministerstvo zdravotníctva Slovenskej republiky ako príslušný orgán podľa ustanovenia § 60 písm. b) zákona Národnej rady Slovenskej republiky č. 140/1998 Z. z. o liekoch a zdravotníckych pomôckach, o zmene zákona NR SR č. 455/1991 Zb. o živnostenskom podnikaní (živnostenský zákon) v znení neskorších predpisov a o zmene a doplnení zákona NR SR č. 220/1996 Z. z. o reklame v znení neskorších predpisov, žiadosti č. R-0667/2000 zo dňa 08.06.2000 o registráciu lieku ***ZODAC^{R} GTT gtt por,*** *držiteľa rozhodnutia o registrácii Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, výrobcu Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, v zastúpení organizačnou zložkou Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava, rozhodlo*

t a k t o :

Žiadosti o registráciu lieku

ZODAC^{R} GTT gtt por

s obsahom 10 mg dihydrochloridu cetirizínu v 1 ml roztoku, v obale: hnedá sklenená liekovka uzavretá kvapkadlom a závitovým uzáverom s detskou poistkou, sa vyhovuje. Povoľuje sa uvedenie lieku do obehu a zapísanie do zoznamu registrovaných liekov pod registračným číslom

14/0375/00/-S

a kódom Štátneho ústavu pre kontrolu liečiv pre balenie ***1 x 20 ml 15927,*** *pretože liek spĺňa podmienky ustanovené zákonom NR SR č. 140/1998 Z. z.. Liek sa zatrieďuje do skupiny liekov, ktorých* ***výdaj je viazaný na lekársky predpis.*** *Schvaľuje sa označenie vonkajšieho a vnútorného obalu (príloha č. 1), písomná informácia pre používateľov lieku (príloha č. 2), súhrn charakteristických vlastností lieku (príloha č. 3), ktoré sú súčasťou tohto rozhodnutia*

Čas použiteľnosti lieku ***ZODAC^{R} GTT gtt por, 1 x 20 ml*** *je* ***dva roky***

Rozhodnutie je platné 5 rokov od nadobudnutia právoplatnosti

O d ô v o d n e n i e

Pri preskúmaní žiadosti o registráciu lieku, držiteľa rozhodnutia o registrácii Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, výrobcu Léčiva a.s., Dolní Měcholupy 130, 102 37 Praha 10, Česká republika, v zastúpení organizačnou zložkou Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava, č. R-0667/2000 zo dňa 08.06.2000, bolo zistené, že produkt spĺňa požiadavky na kvalitný, bezpečný a účinný liek, preto bolo rozhodnuté tak ako je uvedené vo výroku tohto rozhodnutia.

P o u č e n i e: Proti tomuto rozhodnutiu je možno podať rozklad v lehote 15 dní od jeho doručenia na Ministerstvo zdravotníctva Slovenskej republiky (§ 61 ods.1 zákona č. 71/1967 Zb. o správnom konaní).

MINISTERSTVO ZDRAVOTNÍCTVA SR

Roman K o v á č
m i n i s t e r

Rozhodnutie dostanú:

1. Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava
2. Štátny ústav pre kontrolu liečiv, Kvetná 11, 825 08 Bratislava
3. Ministerstvo zdravotníctva SR, Limbová 2, 833 41 Bratislava

SÚHRN CHARAKTERISTICKÝCH VLASTNOSTÍ LIEKU

1. NÁZOV LIEKU
ZODAC® GTT

2. KVALITATÍVNE A KVANTITATÍVNE ZLOŽENIE LIEKU
Cetirizini dihydrochloridum (dihydrochlorid cetirizínu) 10 mg v 1 ml roztoku
(= 20 kvapiek)

3. LIEKOVÁ FORMA
Perorálne roztokové kvapky.
Opis prípravku: číry, bezfarebný až slabo žltkastý roztok sladkej chuti.

4. KLINICKÉ ÚDAJE
4.1. Terapeutické indikácie
Symptomatická liečba alergickej nádchy a konjunktivitídy (vrátane celoročnej a sezónnej) a kožných prejavov sprevádzaných svrbením a vyrážkou, najmä pri urtikárii.

4.2. Dávkovanie a spôsob podávania
Dospelí a deti od 12 rokov zvyčajne užívajú 10 mg cetirizínu (20 kvapiek) v jednej dennej dávke.
Deti od 6 do 12 rokov zvyčajne užívajú 10 mg cetirizínu (20 kvapiek) 1x denne alebo 5 mg cetirizínu (10 kvapiek) 2x denne.
Deti od 2 do 6 rokov zvyčajne užívajú 5 mg cetirizínu (10 kvapiek) 1x denne alebo 2,5 mg cetirizínu (5 kvapiek) 2x denne.
Pacienti so zlyhaním obličiek: pri znížení funkcie obličiek treba úmerne znížiť dávkovanie cetirizínu, pri klírensi kreatinínu 11 - 31 ml/min sa podáva 5 mg cetirizínu (10 kvapiek) denne.
Hemodialyzovaným pacientom sa podáva 5 mg cetirizínu (10 kvapiek) denne.
Pacienti s pečeňovou insuficienciou: treba úmerne znížiť dávkovanie cetirizínu, zvyčajne sa podáva 5 mg cetirizínu (10 kvapiek) denne.
U geriatrických pacientov: vzhľadom na vek nie je nutné dávky upravovať. Dávkovanie treba upraviť v prípade zníženej funkcie obličiek, zvyčajne sa podáva 5 mg cetirizínu (10 kvapiek) denne.
Zodac gtt sa môže užívať nezávisle od jedla, kvapky sa zapíjajú dostatočným množstvom nedráždivej tekutiny.

4.3. Kontraindikácie
Známa precitlivenosť na cetirizín, inú zložku prípravku alebo hydroxyzín. Deti do 2 rokov.
Neodporúča sa podávať počas tehotenstva ani v období dojčenia.

4.4. Špeciálne upozornenia
Opatrnosť je potrebná u pacientov so zlyhaním obličiek, insuficienciou pečene a u geriatrických pacientov.
Kvapky neobsahujú žiadny zvyškový cukor (ako sladidlo je použitý sacharín), sú vhodné pre diabetikov.
Počas liečby sa neodporúča nadmerne piť nealkoholické nápoje.

4.5. Liekové a iné interakcie
Pri súčasnom užívaní cetirizínu s teofylínom sa môže znížiť klírens cetirizínu (až o 16%) s klinickými prejavmi nežiaducich účinkov cetirizínu.

4.6. Používanie v gravidite a počas laktácie
Pri pokusoch na zvieratách sa nepreukázala embryotoxicita ani teratogenita.
S používaním u ľudí nie je dostatok skúseností.
Vzhľadom na nedostatok skúseností sa jeho používanie u tehotných a dojčiacich žien neodporúča.

4.7. Ovplyvnenie schopnosti viesť motorové vozidlá a obsluhovať stroje
Nie sú opísané sedatívne účinky prípravku ako pri klasických antihistaminikách. Štúdie u zdravých dobrovoľníkov nepreukázali po podaní 20 - 25 mg cetirizínu žiadny vplyv na bdelosť alebo reakčnú dobu. Napriek tomu treba individuálne posúdiť nutnosť zvýšenej opatrnosti u osôb vykonávajúcich činnosť vyžadujúcu pozornosť, motorickú koordináciu a rýchle rozhodovanie (napr. vedenie motorových vozidiel, ovládanie strojov, práca vo výškach a pod.).

4.8. Nežiaduce účinky
Cetirizín sa všeobecne dobre znáša. S užívaním cetirizínu sa ojedinele môžu spájať bolesti hlavy, ospanlivosť, závraty, suchosť v ústach, tráviace ťažkosti (dyspepsia, bolesti brucha, plynatosť).

4.9. Predávkovanie
Pri dávkach cetirizínu (viac ako 50 mg) sa pozorovala ospanlivosť, u detí môže predávkovanie naopak vyvolať nepokoj a podráždenosť; môžu sa pozorovať príznaky anticholínergného účinku (retencia moču, výrazná suchosť v ústach, zápcha).
Ošetrenie pri predávkovaní zahŕňa štandardný postup, liečba je symptomatická a podporná so zameraním na udržanie vitálnych funkcií. Špecifické antidotum nie je známe. Hemodialýzou je možné odstrániť len malú časť podanej dávky cetirizínu (cca 9%).

5. FARMAKOLOGICKÉ VLASTNOSTI

5.1. Farmakodynamické vlastnosti
Farmakoterapeutická skupina - Antihistaminikum. ATC skupina: B06AE07- antihistaminiká na celkové podávanie - piperazínové deriváty - cetirizín.

Cetirizín je antihistaminikum II. generácie s predĺženým účinkom. Selektívne inhibuje periférne H_1 - receptory, ale výraznejšie neovplyvňuje cholínergické. adrenergické ani serotonínové receptory. V terapeutických dávkach nemá sedatívny účinok na CNS. Inhibuje migráciu zápalových buniek, predovšetkým eozinofilov. Tlmí uvoľňovanie histamínu zo žírnych buniek a bazofilných leukocytov aj v priebehu neskorej fázy alergickej reakcie.

5.2. Farmakokinetické vlastnosti

Biologická dostupnosť cetirizínu po požití kvapiek je rýchla a úplná. Potrava nemá vplyv na vstrebávanie cetirizínu, predlžuje však dobu dosiahnutia maximálnej koncentrácie na 1,7 hodiny. Maximálna koncentrácia po požití kvapiek sa dosiahne o 30 - 60 minút, u detí sú dosiahnuté maximálne koncentrácie vyššie ako u dospelých. Vzťah medzi dávkou a plazmatickou koncentráciou je lineárny.
Antihistamínový účinok sa dostavuje 20 - 60 minút po požití, pretrváva počas 24 hodín.
Väzba na plazmatické bielkoviny je 93%. Minimálne preniká do mozgovomiechového moku, väzba na mozgové H_1 receptory je nevýznamná.
Distribučný objem (V_d) je 0,5 až 0,8 l/kg.
Na rozdiel od ostatných antihistaminík sa len minimálne metabolizuje v pečeni, O-dealkylovaný metabolit nemá antihistamínovú aktivitu.
Eliminačný polčas je 7,4 až 9 hodín, u pacientov so stredne závažnou renálnou insuficienciou sa predlžuje na 19 až 21 hodín. U detí je celkový telesný klírens cetirizínu asi o 33% vyšší ako u dospelých, eliminačný polčas je skrátený na 6,2 hodín. Približne 60% podanej dávky sa vylúči močom v nezmenenej forme počas 24 hodín, ďalších 10% v priebehu nasledujúcich štyroch dní; u detí sa vylúči močom 40% podanej dávky počas 24 hodín. Stolicou sa vylúči asi 10% podanej dávky počas piatich dní po požití.

5.3. Predklinické údaje o bezpečnosti

Štúdie na zvieratách preukázali, že dávky 216x vyššie ako maximálna dávka pre človeka nie sú teratogénne. Cetirizín nepôsobí teratogénne v priebehu organogenézy.

6. FARMACEUTICKÉ INFORMÁCIE

6.1. Zoznam pomocných látok

Methylparabenum, propylparabenum, glycerolum 85%, propylenglycolum, saccharinum natricum, natrii acetas, acidum aceticum 99%, aqua purificata.

6.2. Inkompatibility

Inkompatibilita perorálne užívaného cetirizínu s ďalšou látkou nie je známa.

6.3. Čas použiteľnosti

2 roky

6.4. Upozornenie na podmienky a spôsob skladovania

V suchu, pri teplote 10 - 25°C, chrániť pred svetlom.

6.5. Vlastnosti a zloženie obalu a veľkosť balenia

Obal: hnedá sklenená liekovka uzavretá kvapkadlom a závitovým uzáverom s detskou poistkou, písomná informácia pre používateľa v slovenskom jazyku, papierová skladačka.
Veľkosť balenia: 20 ml

6.6. Upozornenia na spôsob zaobchádzania s liekom

Prípravok sa užíva perorálne.

Návod na otváranie liekovky s bezpečnostným uzáverom
Liekovka je opatrená bezpečnostným uzáverom, ktorý bráni otvoreniu deťmi. Otvorí sa tak, že sa uzáver stlačí silno nadol a odskrutkuje sa proti smeru hodinových ručičiek. Po použití treba uzáver opäť silno zaskrutkovať.

7. DRŽITEĽ ROZHODNUTIA O REGISTRÁCII
Léčiva a.s., Praha, Česká republika

8. REGISTRAČNÉ ČÍSLO

9. DÁTUM REGISTRÁCIE/DÁTUM PREDĹŽENIA REGISTRÁCIE

9. DÁTUM POSLEDNEJ REVÍZIE TEXTU
November 2000

16.11.2020

Písomná informácia pre používateľa

Informácia o použití, čítajte pozorne!

ZODAC® GTT

(cetirizini dihydrochloridum)
perorálne roztokové kvapky

Držiteľ rozhodnutia o registrácii:
Léčiva a.s., Praha, Česká republika

Zloženie:
Liečivo: cetirizini dihydrochloridum (dihydrochlorid cetirizínu) 10 mg v 1 ml roztoku (= 20 kvapiek)
Pomocné látky: methylparabenum (metylparabén), propylparabenum (propylparabén), glycerolum (glycerol), propylenglycolum (propylénglykol), saccharinum natricum (sodná soľ sacharínu), natrii acetas (octan sodný), acidum aceticum (kyselina octová), aqua purificata (čistená voda).

Farmakoterapeutická skupina:
Antihistaminikum (liek tlmiaci reakciu z precitlivenosti)

Charakteristika:
Cetirizín, účinná látka prípravku Zodac gtt, je antihistaminikum s predĺženým účinkom. Antihistaminiká blokujú pôsobenie histamínu, jedného z pôsobkov, ktorý sa v organizme uvoľňuje pri reakcii z precitlivenosti (alergia). Cetirizín tlmí tak "skorú" fázu alergickej reakcie sprostredkovanú histamínom, ako aj pohyb buniek zápalu, najmä eozinofilov a uvoľňovanie pôsobkov spojených s "neskorou" fázou alergickej reakcie.
Zodac gtt je vysoko účinné antihistaminikum a antialergikum s minimálnym výskytom ospanlivosti po bežnej liečebnej dávke. Vzhľadom na predĺžený účinok sa prípravok Zodac gtt môže podávať dospelým a starším deťom v jedinej dennej dávke.

Indikácie:
Zodac gtt sa užíva na zmiernenie ťažkostí pri alergickej nádche a alergickom zápale spojoviek (vrátane celoročnej a sezónnej) a kožných prejavov sprevádzaných svrbením a vyrážkou, najmä pri žihľavke.

Kontraindikácie:
Zodac gtt sa nesmie podávať pacientom so známou precitlivenosťou na cetirizín, inú zložku prípravku alebo hydroxyzín, tehotným a dojčiacim ženám a deťom do 2 rokov.

Nežiaduce účinky:
Zodac gtt sa všeobecne dobre znáša, s jeho užívaním sa ojedinele môžu spájať bolesti hlavy, ospanlivosť, závraty, suchosť v ústach, tráviace ťažkosti (dyspepsia, bolesti brucha, plynatosť). Pri prípadnom výskyte týchto nežiaducich účinkov alebo iných nezvyčajných reakcií sa o ďalšom užívaní prípravku či podávaní dieťaťu poraďte s lekárom.

Zriedkavo sa môžu vyskytnúť prejavy precitlivenosti na prípravok (žihľavka, opuch mäkkých tkanív, dýchavica). V tomto prípade je nutné ihneď prerušiť užívanie prípravku a poradiť sa s lekárom.

Interakcie:
Účinky prípravku Zodac gtt a iných súčasne užívaných liekov sa môžu navzájom ovplyvňovať. Súčasné užívanie prípravku Zodac gtt s niektorými bronchodilatanciami (lieky na rozšírenie priedušiek) obsahujúcimi účinnú látku teofylín môže vyvolať nežiaduce účinky liečby prípravkom Zodac gtt.
Informujte preto vášho lekára o všetkých liekoch, ktoré vy alebo vaše dieťa užívate na lekársky predpis aj bez neho. Bez súhlasu lekára neužívajte ani nepodávajte dieťaťu súčasne s prípravkom Zodac gtt žiadny voľnopredajný liek . Ak vám ďalší lekár bude predpisovať nejaký iný liek, informujte ho, že vy alebo dieťa užívate Zodac gtt.
Interakcie cetirizínu s alkoholom (pri hladine alkoholu v krvi 0,8 g/l) doposiaľ neboli opísané. Napriek tomu sa počas užívania prípravku Zodac gtt neodporúča požívať nadmerne alkoholické nápoje.

Dávkovanie a spôsob podávania:
Dávkovanie určuje vždy lekár. Potrava významne neovplyvňuje vstrebávanie prípravku Zodac gtt a môže sa teda užívať nezávisle od jedla.
Dospelí a deti od 12 rokov užívajú zvyčajne 20 kvapiek prípravku Zodac gtt (= 10 mg cetirizínu) 1x denne.
Deti od 6 do 12 rokov užívajú 20 kvapiek (=10 mg cetirizínu) 1x denne alebo 10 kvapiek (= 5 mg cetirizínu) 2x denne, ráno a večer.
Deťom od 2 do 6 rokov sa podáva 10 kvapiek (= 5 mg cetirizínu) 1x denne alebo 5 kvapiek (= 2,5 mg cetirizínu) 2x denne, ráno a večer.
Starším chorým alebo pacientom so závažným ochorením pečene a obličiek môže lekár dávkovanie upraviť.
Pri náhodnom vynechaní dávky užite liek (podajte liek dieťaťu) ihneď, ako si spomeniete. V prípade, že by sa mala užiť ďalšia dávka, dávkovanie nezdvojnásobujte a pokračujte podľa pôvodného plánu liečby.
Kvapky sa zapíjajú malým množstvom nedráždivej tekutiny.

Návod na otváranie liekovky s bezpečnostným uzáverom
Liekovka je opatrená bezpečnostným uzáverom, ktorý bráni otvoreniu deťmi. Otvoríte ho tak, že uzáver stlačíte silno nadol a odskrutkujete proti smeru hodinových ručičiek. Po použití treba uzáver opäť silno zaskrutkovať.

Upozornenie:
U prípravku nie sú opísané tlmivé účinky. Napriek tomu sa odporúča neprekročiť odporučenú dennú dávku, pokiaľ budete viesť motorové vozidlo alebo obsluhovať stroje.
Zodac gtt neobsahuje žiadny zvyškový cukor (použitým sladidlom je sacharín). Kvapky sú vhodné pre diabetikov.

Predávkovanie:

Pri predávkovaní môže byť hlavným príznakom ospanlivosť. U detí však predávkovanie môže vyvolať aj podráždenosť a nepokoj. Pri predávkovaní (najmä detí) je nutné ihneď vyhľadať lekára. Špecifický protiliek doposiaľ nie je známy.

Varovanie:
Prípravok sa nesmie používať po uplynutí času použiteľnosti uvedenom na obale.
Pri užití nadmernej dávky alebo ak kvapky náhodne požije dieťa, vyhľadajte lekára.

Balenie:
20 ml roztoku

Uchovávanie:
V suchu, pri teplote 10-25° C, chrániť pred svetlom.
Uchovávajte mimo dosahu detí!

Dátum poslednej revízie:
November 2000

Vzor označenia vonkajšieho obalu

16.11.2020

20 ml

ZODAC GTT

(Cetirizini dihydrochloridum)

perorálne roztokové kvapky

Antihistaminikum

Cetirizini dihydrochloridum 10 mg v 1 ml (20 kvapiek)

Obsahuje methylparaben, propylparaben a sodnú soľ sacharinu

Nepoužívať pri precitlivenosti na parabény

Na vnútorné užitie

Výdaj len na lekársky predpis

Písomná informácia pre používateľa priložená

Uchovávajte v suchu pri teplote 10 - 25 °C!

Chráňte pred svetlom

Ukladajte mimo dosahu detí!

Nepoužitý liek vráťte do lekárne

Č. reg.:

Č. šarže:

Použ. do:

Léčiva a.s.
102 37 Praha 10

Dolní Měcholupy 130,
Česká republika

EAN kód

Vzor označenia vnútorného obalu

20 ml

ZODAC

(Cetirizini dihydrochloridum)

perorálne roztokové kvapky

Antihistaminikum

Cetirizini dihydrochloridum 10 mg v 1 ml (20 kvapiek)

Obsahuje methylparaben, propylparaben a sodnú soľ sacharinu

Nepoužívať pri precitlivenosti na parabény

Na vnútorné užitie

Údaj č. šarže

Údaj dátumu skončenia použiteľnosti

Logo LÉČIVA

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the Notice of Opposition:

Submission number	858234
Application number	EP05758582.0
Patent number	EP1768649
Date of receipt	23 June 2010
Your reference	B0199PI-EP
Opponent	Zentiva k.s.
Title	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Documents submitted

package-data.xml	ep-opposition-data.xml
ep-oppo.pdf (6 p.)	OPPO.pdf\B0199PI-OPPOSITION AGAINST EP1768649B1-final.pdf (11 p.)
Published-Evidence-1.pdf\EP0605203 A2.pdf (14 p.)	Published-Evidence-2.pdf\US5891913 A.pdf (8 p.)
Published-Evidence-3.pdf\D10 Hanbook parabenes.pdf (4 p.)	Published-Evidence-4.pdf\Wang DY 2001.pdf (6 p.)
Other-evidence-1.pdf\Registrace Zodac 20001129 SK.pdf (11 p.)	Other-evidence-2.pdf\Registrace Zodac sir 20001129 SK.pdf (11 p.)
Other-evidence-3.pdf\Registrace Zodac gtt 20010418 CZ.pdf (10 p.)	Other-evidence-4.pdf\Registrace Zodac sir 20010418 CZ.pdf (10 p.)
Other-evidence-5.pdf\cetirizinliquidlaunch.pdf (1 p.)	Other-evidence-6.pdf\SmPC Zodac gtt 2010 ENG.pdf (7 p.)
Other-evidence-7.pdf\SmPC Zodac sir 2010 ENG.pdf (7 p.)	

Submitted by	CN=C. Westerholm 5880,O=Borenius & Co. Oy Ab,C=FI
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Correction by the EPO of errors in debit instructions filed by eOLF
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Date
29-06-2010

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

Communication of a notice of opposition

You are hereby informed of a notice of opposition to the European patent specified above (see attached copy in the enclosure). The documents specified as patent documents in the notice of opposition are available for inspection via the Register Plus online service at **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (see OJ EPO 2009, 434).

If oral proceedings are to take place, parties are advised to check the electronic file via the Register Plus online service in advance of the hearing to ensure they are in possession of all relevant documents.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (R. 79(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (R. 77 EPC).

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Enclosure: Notice of opposition

O I - Zentiva k.s.
(with literature)

STATE INSTITUTE FOR DRUG CONTROL
Šrobárova 48, 100 41 Prague 10, Czech Republic
Tel. (02) 72 185 111, fax (02) 717 32 377, e-mail: SUKL@sukl.cz

Léčiva a.s.
Dolní Měcholupy 130
102 37 Prague 10

File No.	PROCESSED BY/EXTENSION	DATE
3316/00	B. Vojtová, MD/731	18-Apr-2001

DECISION
on marketing authorization of a medicinal product

The State Institute for Drug Control, with its registered office in Prague 10, Šrobárova 48 (hereinafter the "Institute"), as the administrative body competent to decide, pursuant to Section 9 paragraph 1 letter a) of Act No. 79/1997 Coll., on Pharmaceuticals and on Amendments and Supplements to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter the "Act"), has decided, pursuant to sections 25 and 26 of the Act, after the marketing authorization procedure, as follows:

Medicinal product:

ZODAC GTT drug form: **drops**

for which an application for marketing authorization was submitted by:

Léčiva a.s., Prague, CR

delivered to the Institute on **31-Jan-2000** is authorized under the allocated registration No:

24/154/01-C

1. Distribution of the medicinal product is prescription bound.
2. The medicinal product does not contain any narcotic or psychotropic substance listed in Supplements of the Act No. 167/1998 Coll., on Dependency Producing Substances and on Amendments to Some Other Acts, as amended.
3. The Marketing Authorization Holder will submit the report on adverse effects of a registered medicinal substance pursuant to Section 26 paragraph 5 letter d) in writing to the Institute after 5 years (together with an application for marketing authorization renewal).
4. If material obtained from ruminants was used for product manufacture, the Marketing Authorization Holder will document before the date of 30-Nov-2001 how the product is secured as regards the risk of BSE transmission.
5. Representing an integral part of this Decision, its Supplements are: Product Identification Sheet (Supplement No.1 consisting of 1 page), Patient Information Leaflet for product use and handling (Supplement No.2 consisting of 3 pages), and the approved Summary of product Characteristics (Supplement No.3 consisting of 4 pages).

Rationale:

On **31-1-2000** the Institute received the application of the company:

Léčiva a.s., Prague, CR

For marketing authorization of the medicinal product:

ZODAC GTT drug form: **drops**

Within the scope of marketing authorization procedure the Institute has assessed if the medicinal product meets the requirements for marketing authorization set by legal regulations. Having performed the assessment, the Institute states, that no grounds for refusal have been found and the requirements for authorization of a medicinal products have been met. Based on these findings, the Institute has decided about the marketing authorization as stated in the announcement of this Decision.

File No.	DATE
3316/00	18-Apr-2001

Advice on repeal:

Pursuant to the provisions of Section 53 and following provisions of Act No. 71/1967 Coll., on administrative procedure (the Administrative Code), repeal from this Decision may be filed with the Institute within the period of 15 days of its delivery. The repeal shall be decided on by the Ministry of Health.

Milan Šmíd, MD, Ph.D.
Director of the Institute

Supplement No. 1 to the Decision on Marketing Authorization, File No. 3316/00

Identification Sheet

Product registration number: 24/154/01-C

Name of medicinal product	Name appendix	SUKL (State Institute for Drug Control) code	Country	Producer	Status
ZODAC GTT	GTT 1x20ML/0.2GM	58834	CZ	LEX	R

In the column marked as Status, a registered product before the variation is performed is listed under B, a product after the variation is listed under R. Below the titles Country and Producer, the site/s of manufacture where the product is released and the relevant subject:

LEX CZ: LÉČIVA A.S., PRAGUE, Czech Republic

are listed.

SUMMARY OF PRODUCT CHARACTERISTICS

1. PRODUCT NAME

ZODAC® GTT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Cetirizine dihydrochloride 10 mg in 1 ml of solution (= 20 drops)

3. DRUG FORM
Drops.
Product description: clear, colorless to slightly yellow solution.

4. CLINICAL PARTICULARS
4.1 Indications
Symptomatic treatment of allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

4.2. Dosage and Administration
Adults and children over 12 years of age usually use 10 mg of cetirizine (20 drops) in one daily dose.

Children from 6 to 12 years of age usually use 10 mg of cetirizine (20 drops) 1x daily or 5 mg of cetirizine (10 drops) 2x daily.

Children from 2 to 6 years of age usually use 5 mg of cetirizine (10 drops) 1x daily or 2.5 mg of cetirizine (5 drops) 2x daily.

Patients with kidney failure: in decreased kidney function it is necessary to adequately decrease cetirizine dosage, in creatinine clearance of 11 – 31 ml/min, 5 mg of cetirizine (10 drops) is administered daily.

Hemodialysis patients are administered 5 mg of cetirizine (10 drops) daily.

Patients with liver insufficiency: it is necessary to adequately decrease cetirizine dosage; usually, 5 mg of cetirizine (10 drops) is administered daily.

In geriatric patients: No dose adjustment is necessary as regards age. Dosage must be adjusted in case of decreased kidney function, usually 5 mg of cetirizine (10 drops) is administered daily.

Zodac gtt may be used regardless of food; drops are taken with a sufficient amount of non-irritating liquid.

4.3. Contraindications

Known hypersensitivity to cetirizine, another product component, or hydroxyzine.

Children under 2 years of age.

4.4. Special Warnings

Caution is necessary in patients with kidney failure, liver insufficiency, and geriatric patients.

Drops do not contain any residual sugar (saccharin is used as sweetener), they are suitable for diabetics.

Excessive consumption of alcoholic beverages during treatment is not recommended.

4.5. Interactions

In simultaneous use of cetirizine and theophylline, cetirizine clearance may be decreased (by up to 16%) with the occurrence of clinical symptoms of cetirizine adverse effects.

4.6. Pregnancy and Breastfeeding

Animal experiments have documented neither embryotoxicity nor teratogenicity. Experience with use in humans is insufficient.

With regard to insufficient experience, product use in pregnant and breastfeeding women is not recommended.

4.7. Possibility of Decreased Attentiveness when Driving Motor Vehicles and Operating Machinery

Sedative effects of the product similar to those of classical antihistamines have not been described. Studies in healthy individuals have not shown any impact on alertness or reaction time after administration of 20 – 25 mg of cetirizine. In spite of that, the need for increased caution should be assessed individually in persons performing activities necessitating attention, motor coordination, and rapid decision making (e.g. driving motor vehicles, operating machinery, working in heights, etc.).

4.8. Adverse Effects

Cetirizine is generally well tolerated. In isolated cases, headache, sleepiness, vertigo, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with cetirizine use.

4.9.Overdose

In cetirizine doses (exceeding 50 mg) sleepiness has been observed; in children, in contrast, overdose may cause restlessness and irritation; the signs of its anticholinergic effect may be observed (urine retention, marked mouth dryness, constipation).

Treatment of overdose comprises the standard approach; therapy is symptomatic and supportive, focused on maintaining vital functions. Specific antidote is not known. Only a small fraction of the administered dose of cetirizine may be removed by hemodialysis (about 9%).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Cetirizine is a 2nd generation antihistamine with prolonged effect. It selectively inhibits peripheral H_1 receptors, but does not markedly influence cholinergic, adrenergic, or serotonin receptors. In therapeutic doses it is devoid of any sedative effect on the CNS. It inhibits migration of inflammatory cells, especially eosinophils. It suppresses histamine release from mast cells and basophil leukocytes even during the late phase of allergic reaction.

5.2. Pharmacokinetic Properties

Cetirizine bioavailability after ingestion of drops is rapid and complete. Food does not influence cetirizine absorption but it prolongs the time necessary to reach the maximum plasma concentration to 1.7 hours and decreases the maximum concentration by 23% Maximum concentration after ingestion of drops is reached in 30 – 60 minutes, maximum concentrations in children are higher than those in adults. Relationship between the dose and plasma concentration is linear. Antihistamine effect occurs in 20 – 60 minutes after ingestion and lasts for 24 hours.

The degree of plasma protein binding is 93%. Penetration into cerebrospinal fluid is minimal, binding to brain H_1 receptors is insignificant. Distribution volume (V_d) is 0.5 to 0.8 l/kg.

In contrast to other antihistamines, cetirizine metabolism in the liver is minimal. Its O-dealkylated metabolite lacks antihistamine activity.

Cetirizine elimination half-life is 7.4 to 9 hours, in patients with moderate kidney insufficiency it is prolonged to 19 to 21 hours. In children, the total body clearance of cetirizine exceeds that in adults by about 33%, elimination half-life is shortened to 6.2 hours. Approximately 60% of the administered dose is eliminated unchanged with urine within 24 hours, other 10% during the following 4 days; in children, 40% of the administered dose is eliminated with urine within 24 hours. About 10% of the administered dose is eliminated with stools within 5 days after ingestion.

5.3. Preclinical Data Regarding Product Safety

Animal studies have shown that doses exceeding 216-fold the maximum human daily dose are not teratogenic. Cetirizine does not show teratogenic effects during organogenesis.

6. PHARMACEUTICAL DATA

6.1. List of All Inactive Substances (Qualitatively)

Methylparaben, propylparaben, 85% glycerol, propylene glycol, sodium saccharin dihydrate, sodium acetate trihydrate, 99% acetic acid, purified water.

6.2. Incompatibilities

Incompatibility of orally used cetirizine with any other substance is not known.

6.3. Shelf Life

2 years

6.4. Storage

At temperature up to 25 °C.

6.5. Packaging Type

Brown glass vial closed with a LDPE dropper and a HDPE childproof screw cap, Patient Information Leaflet in Czech, paper folding box.

Package size: 20 ml

6.6. Instructions for Use

Product is used orally.

Instructions for Opening a Vial with a Safety Cap

The vial is provided with a safety cap, which prevents children from opening it. You may open it by pressing the cap strongly downwards and turning counter-clockwise. After use the cap must be screwed on tightly again.

7. MARKETING AUTHORIZATION HOLDER

Léčiva a.s., Prague, Czech Republic

8. REGISTRATION NUMBER

24/154/01-C

9. DATE OF MARKETING AUTHORIZATION / MARKETING AUTHORIZATION RENEWAL

10. DATE OF THE LAST TEXT REVISION

Supplement No. 2 to the Marketing Authorization Decision File No. 3316/00

STÁTNÍ ÚSTAV
PRO KONTROLU LÉČIV
SCHVÁLENO
18. 4. 2011

STATE INSTITUTE FOR DRUG CONTROL
APPROVED

Patient Information Leaflet

Information on use, read carefully

ZODAC® GTT

(cetirizine dihydrochloride)

drops

Producer / Marketing Authorization Holder

Léčiva a.s., Prague, Czech Republic

Composition

Active substance: cetirizine dihydrochloride 10 mg in 1 ml of solution (=20 drops)

Inactive Substances: Methylparaben, propylparaben, 85% glycerol, propylene glycol, sodium saccharin dihydrate, sodium acetate trihydrate, 99% acetic acid, purified water.

Pharmacotherapeutic group

Antihistamine (medicinal product suppressing hypersensitivity reaction)

Characteristic

Cetirizine, the active substance of Zodac gtt, is an antihistamine with prolonged effect. Antihistamines block the effect of histamine, one of the agents released in the organism during hypersensitivity reaction (allergy). Cetirizine suppresses both the "early" phase of allergic reaction mediated by histamine, and the migration of inflammatory cells, especially eosinophils, and the release of agents linked with the "late" phase of allergic reaction.

Zodac gtt is a highly efficient antihistamine and anti-allergic agent with a minimum occurrence of sleepiness after regular therapeutic dose. With regard to its prolonged effect, Zodac gtt may be administered to adults and older children in one daily dose.

Indications

Zodac gtt is used for alleviation of complaints in allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

Contraindications

Zodac gtt may not be administered to patients with known hypersensitivity to cetirizine, another product component, or hydroxyzine, and to children under 2 years of age. With regard to insufficient experience, its administration to pregnant or breastfeeding women is not recommended.

Adverse Effects

Zodac gtt is generally well tolerated. In isolated cases, headache, sleepiness, dizziness, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with its use. If any of these adverse effects or other unusual reactions eventually develop, consult a physician about further use of the product or its administration to a child.

Rarely, reactions of hypersensitivity to the product might occur (hives, soft tissue edema, shortness of breath). In that case it is necessary to discontinue product use immediately and consult a physician.

Interactions

The effects of Zodac gtt and other simultaneously used medicines may mutually interact. Simultaneous use of Zodac gtt and some bronchodilators (medicines for widening the bronchi) containing the active substance theophylline may cause the occurrence of adverse effects of Zodac gtt treatment.

Therefore, your physician should be informed about all medicines you or your child are using, whether they are prescription or non-prescription medicines. Do not use or give your child any over-the-counter medicine simultaneously with Zodac gtt without having consulted your physician. If another physician prescribes you another medicine, inform him/her that you or your child are using Zodac gtt.

Interaction of cetirizine with alcohol (in blood alcohol level of 0.8 g/l) have not been described yet. However, excessive consumption of alcoholic beverages when using Zodac gtt is not recommended.

Dosage

Dosage is always determined by a physician. Food does not significantly influence the absorption of Zodac gtt, and so Zodac gtt may be taken independently of food.

Adults and children over 12 years of age usually use 20 drops of Zodac gtt (=10 mg of cetirizine) 1x daily.

Children from 6 to 12 years of age use 20 drops (=10 mg of cetirizine) 1x daily or 10 drops (5 mg of cetirizine) 2x daily, in the morning and in the evening.

Children from 2 to 6 years of age are administered 10 drops (=5 mg of cetirizine) 1x daily or 5 drops (=2.5 mg of cetirizine) 2x daily, in the morning and in the evening.

The physician may adjust the dosage for elderly patients or patients with serious liver and/or kidney disease.

If you accidentally omit a dose, use the product (administer it to the child) as soon as you remember. In case another dose should be already taken, do not double the dose but continue the treatment according to the original treatment plan.

Drops are taken with a small amount of non-irritating liquid.

Instructions for Opening a Vial with a Safety Cap

Vial is provided with a safety cap, which prevents children from opening it. Open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

Note

No sedative effects of the product similar have been described. In spite of that, you should not exceed the recommended daily dose if you are going to drive a motor vehicle or operate machinery.

Zodac gtt does not contain any residual sugar (the used sweetener is saccharin). Drops are suitable for diabetics.

Overdose

The main symptom of overdose may be sleepiness. In children, however, overdose may cause also irritation restlessness. In case of overdose (especially in children) it is necessary to see a physician immediately. Specific antidote is not yet known.

Storage

At temperature up to 25 °C.

Warning

Product may not be used after expiration date stated on the packaging.

Product must be stored out of reach of children.

In case of using an excessive dose or accidental ingestion of drops by a child, see a physician.

Package size

20 ml of solution

Date of the Last Revision

STATE INSTITUTE FOR DRUG CONTROL
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Léčiva a.s.
Dolní Měcholupy 130
102 37 Prague 10

File No.	PROCESSED BY/EXTENSION	DATE
3315/00	B. Vojtová, MD/731	18-Apr-2001

DECISION
on marketing authorization of a medicinal product

The State Institute for Drug Control, with its registered office in Prague 10, Šrobárova 48 (hereinafter the "Institute"), as the administrative body competent to decide, pursuant to Section 9 paragraph 1 letter a) of Act No. 79/1997 Coll., on Pharmaceuticals and on Amendments and Supplements to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter the "Act"), has decided, pursuant to sections 25 and 26 of the Act, after the marketing authorization procedure, as follows:

Medicinal product:

ZODAC SIR drug form: **syrup**

for which an application for marketing authorization was submitted by:

Léčiva a.s., Prague, CR

delivered to the Institute on **31-Jan-2000** is authorized under the allocated registration No:

24/153/01-C

1. Distribution of the medicinal product is prescription bound.
2. The medicinal product does not contain any narcotic or psychotropic substance listed in Supplements of the Act No. 167/1998 Coll., on Dependency Producing Substances and on Amendments to Some Other Acts, as amended.
3. The Marketing Authorization Holder will submit the report on adverse effects of a registered medicinal substance pursuant to Section 26 paragraph 5 letter d) in writing to the Institute after 5 years (together with an application for marketing authorization renewal).
4. If material obtained from ruminants was used for product manufacture, the Marketing Authorization Holder will document before the date of 30-Nov-2001 how the product is secured as regards the risk of BSE transmission.
5. Representing an integral part of this Decision, its Supplements are: Product Identification Sheet (Supplement No.1 consisting of 1 page), Patient Information Leaflet for product use and handling (Supplement No.2 consisting of 3 pages), and the approved Summary of product Characteristics (Supplement No.3 consisting of 4 pages).

Rationale:

On **31-1-2000** the Institute received the application of the company:

Léčiva a.s., Prague, CR

For marketing authorization of the medicinal product:

ZODAC SIR drug form: **syrup**

Within the scope of marketing authorization procedure the Institute has assessed if the medicinal product meets the requirements for marketing authorization set by legal regulations. Having performed the assessment, the Institute states, that no grounds for refusal have been found and the requirements for authorization of a medicinal products have been met. Based on these findings, the Institute has decided about the marketing authorization as stated in the announcement of this Decision.

File No.	DATE
3315/00	18-Apr-2001

Advice on repeal:

Pursuant to the provisions of Section 53 and following provisions of Act No. 71/1967 Coll., on administrative procedure (the Administrative Code), repeal from this Decision may be filed with the Institute within the period of 15 days of its delivery. The repeal shall be decided on by the Ministry of Health.

Milan Šmíd, MD, Ph.D.
Director of the Institute

Supplement No. 1 to the Decision on Marketing Authorization, File No. 3315/00

Identification Sheet

Product registration number: 24/153/01-C

Name of medicinal product	Name appendix	SUKL (State Institute for Drug Control) code	Country	Producer	Status
ZODAC SIR	SIR 1x100ML/0.1GM	58835	CZ	LEX	R

In the column marked as Status, a registered product before the variation is performed is listed under B, a product after the variation is listed under R. Below the titles Country and Producer, the site/s of manufacture where the product is released and the relevant subject:

LEX CZ: LÉČIVA A.S., PRAGUE, Czech Republic

are listed.

Supplement No. 2 to the Marketing Authorization Decision File No. 3315/00

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV SCHVÁLENO

STATE INSTITUTE FOR DRUG CONTROL
APPROVED

Patient Information Leaflet

Information on use, read carefully

ZODAC® SIR

(cetirizine dihydrochloride)

syrup

Producer / Marketing Authorization Holder

Léčiva a.s., Prague, Czech Republic

Composition

Active substance: cetirizine dihydrochloride 5 mg in 5 ml of syrup

Inactive Substances: Methylparaben, propylparaben, 85% glycerol, propylene glycol, noncrystallizing 70% sorbitol, sodium saccharin dihydrate, sodium acetate trihydrate, 99% acetic acid, banana flavor, purified water.

Pharmacotherapeutic group

Antihistamine (medicinal product suppressing hypersensitivity reaction)

Characteristic

Cetirizine, the active substance of Zodac sir, is an antihistamine with prolonged effect. Antihistamines block the effect of histamine, one of the agents released in the organism during hypersensitivity reaction (allergy). Cetirizine suppresses both the "early" phase of allergic reaction mediated by histamine, and the migration of inflammatory cells, especially eosinophils, and the release of agents linked with the "late" phase of allergic reaction.

Zodac sir is a highly efficient antihistamine and anti-allergic agent with a minimum occurrence of sleepiness after regular therapeutic dose. With regard to its prolonged effect, Zodac sir may be administered to adults and older children in one daily dose.

Indications

Zodac sir is used for alleviation of complaints in allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

Contraindications

Zodac sir may not be administered to patients with known hypersensitivity to cetirizine, another product component, or hydroxyzine, and to children under 2 years of age. With regard to insufficient experience, its administration to pregnant or breastfeeding women is not recommended.

Adverse Effects

Zodac sir is generally well tolerated. In isolated cases, headache, sleepiness, dizziness, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with its use. If any of these adverse effects or other unusual reactions eventually develop, consult a physician about further use of the product or its administration to a child.

Rarely, reactions of hypersensitivity to the product might occur (hives, soft tissue edema, shortness of breath). In that case it is necessary to discontinue product use immediately and consult a physician.

Interactions

The effects of Zodac sir and other simultaneously used medicines may mutually interact. Simultaneous use of Zodac sir and some bronchodilators (medicines for widening the bronchi) containing the active substance theophylline may cause the occurrence of adverse effects of Zodac sir treatment.

Therefore, your physician should be informed about all medicines you or your child are using, whether they are prescription or non-prescription medicines. Do not use or give your child any over-the-counter medicine simultaneously with Zodac sir without having consulted your physician. If another physician prescribes you another medicine, inform him/her that you or your child are using Zodac sir.

Interaction of cetirizine with alcohol (in blood alcohol level of 0.8 g/l) have not been described yet. However, excessive consumption of alcoholic beverages when using Zodac sir is not recommended.

Dosage

Dosage is always determined by a physician. Food does not significantly influence the absorption of Zodac sir, and so Zodac sir may be taken independently of food.

Adults and children over 12 years of age usually use 2 measuring spoons of Zodac sir (=10 mg of cetirizine) 1x daily.

Children from 6 to 12 years of age use 2 measuring spoons (=10 mg of cetirizine) 1x daily or 1 measuring spoon (5 mg of cetirizine) 2x daily, in the morning and in the evening.

Children from 2 to 6 years of age are administered 1 measuring spoon (=5 mg of cetirizine) 1x daily or ½ measuring spoon (=2.5 mg of cetirizine) 2x daily, in the morning and in the evening.

The physician may adjust the dosage for elderly patients or patients with serious liver or kidney disease.

If a dose is accidentally omitted, use the product (administer it to the child) as soon as you remember. In case another dose should be already taken, do not double the dose but continue the treatment according to the original treatment plan.

For measuring the dose, a measuring spoon graduated at 2 levels marked as 1/4 (= ¼ of a measuring spoon, which corresponds to 1.25 ml) and ½ (= ½ of a measuring spoon, which corresponds to 2.5 ml) is provided; measuring spoon full to the brim contains 5 ml.
Syrup is taken with a small amount of non-irritating liquid.

Instructions for Opening a Vial with a Safety Cap

Vial is provided with a safety cap, which prevents children from opening it. Open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

Note

No sedative effects of the product similar have been described. In spite of that, you should not exceed the recommended daily dose if you are going to drive a motor vehicle or operate machinery.

Zodac contains 0.12 g of sugar in 5 ml of syrup (the used sweeteners are sorbitol and saccharin). If the recommended dosage is observed, syrup is suitable for diabetics.

Overdose

The main symptom of overdose may be sleepiness. In children, however, overdose may cause also irritation and restlessness. In case of overdose (especially in children) it is necessary to see a physician immediately. Specific antidote is not yet known.

Storage

At temperature up to 25 °C.

Warning

Product may not be used after expiration date stated on the packaging.

Product must be stored out of reach of children.

In case of using an excessive dose or accidental ingestion of syrup by a child, see a physician.

Package size

100 ml of syrup

Date of the Last Revision

SUMMARY OF PRODUCT CHARACTERISTICS

1. PRODUCT NAME

ZODAC® SIR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Cetirizine dihydrochloride 5 mg in 5 ml of syrup

3. DRUG FORM
Syrup.
Product description: clear, colorless to slightly yellow syrup.

4. CLINICAL PARTICULARS

4.1 Indications
Symptomatic treatment of allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

4.2. Dosage and Administration
Adults and children over 12 years of age usually use 10 mg of cetirizine (2 measuring spoons) in one daily dose.

Children from 6 to 12 years of age usually use 10 mg of cetirizine (2 measuring spoons) 1x daily or 5 mg of cetirizine (1 measuring spoon) 2x daily.

Children from 2 to 6 years of age usually use 5 mg of cetirizine (1 measuring spoon) 1x daily or 2.5 mg of cetirizine (1/2 a measuring spoon) 2x daily.

Patients with kidney failure: in decreased kidney function it is necessary to adequately decrease cetirizine dosage, in creatinine clearance of 11 – 31 ml/min, 5 mg of cetirizine (1 measuring spoon) is administered daily.

Hemodialysis patients are administered 5 mg of cetirizine (1 measuring spoon) daily.

Patients with liver insufficiency: it is necessary to adequately decrease cetirizine dosage; usually, 5 mg of cetirizine (1 measuring spoon) is administered daily.

In geriatric patients: No dose adjustment is necessary as regards age. Dosage must be adjusted in case of decreased kidney function, usually 5 mg of cetirizine (1 measuring spoon) is administered daily.

Zodac sir may be used regardless of food; syrup is taken with a sufficient amount of non-irritating liquid.

For measuring the doses, a measuring spoon graduated at 2 levels marked as 1/4 (= ¼ of a measuring spoon, which corresponds to 1.25 ml) and ½ (= ½ of a measuring spoon, which corresponds to 2.5 ml) is provided; measuring spoon full to the brim contains 5 ml.

4.3. Contraindications

Known hypersensitivity to cetirizine, another product component, or hydroxyzine.

Children under 2 years of age.

4.4. Special Warnings

Caution is necessary in patients with kidney failure, liver insufficiency, and geriatric patients.

5 ml of syrup contain at maximum 0.12 g of residual sugar (the used sweeteners are sorbitol and saccharin). If recommended dosage is observed, the product is suitable for diabetics.

Excessive consumption of alcoholic beverages during treatment is not recommended.

4.5. Interactions

In simultaneous use of cetirizine and theophylline, cetirizine clearance may be decreased (by up to 16%) with the occurrence of clinical symptoms of cetirizine adverse effects.

4.6. Pregnancy and Breastfeeding

Animal experiments have documented neither embryotoxicity nor teratogenicity. Experience with use in humans is insufficient.

With regard to insufficient experience, product use in pregnant and breastfeeding women is not recommended.

4.7. Possibility of Decreased Attentiveness when Driving Motor Vehicles and Operating Machinery

Sedative effects of the product similar to those of classical antihistamines have not been described. Studies in healthy individuals have not shown any impact on alertness or reaction time after administration of 20 – 25 mg of cetirizine. In spite of that, the need for increased caution should be assessed individually in persons performing activities necessitating attention, motor coordination, and rapid decision making (e.g. driving motor vehicles, operating machinery, working in heights, etc.).

4.8. Adverse Effects

Cetirizine is generally well tolerated. In isolated cases, headache, sleepiness, vertigo, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with cetirizine use.

4.9. Overdose

In cetirizine doses (exceeding 50 mg) sleepiness has been observed; in children, in contrast, overdose may cause restlessness and irritation; the signs of its anticholinergic effect may be observed (urine retention, marked mouth dryness, constipation).

Treatment of overdose comprises the standard approach; therapy is symptomatic and supportive, focused on maintaining vital functions. Specific antidote is not known. Only a

small fraction of the administered dose of cetirizine may be removed by hemodialysis (about 9%).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group

Antihistamine

5.1. Pharmacodynamic Properties

Cetirizine is a 2nd generation antihistamine with prolonged effect. It selectively inhibits peripheral H_1 receptors, but does not markedly influence cholinergic, adrenergic, or serotonin receptors. In therapeutic doses it is devoid of any sedative effect on the CNS. It inhibits migration of inflammatory cells, especially eosinophils. It suppresses histamine release from mast cells and basophil leukocytes even during the late phase of allergic reaction.

5.2. Pharmacokinetic Properties

Cetirizine bioavailability after ingestion of syrup is rapid and complete. Food does not influence cetirizine absorption but it prolongs the time necessary to reach the maximum plasma concentration to 1.7 hours and decreases the maximum concentration by 23% Maximum concentration after ingestion of syrup is reached in 30 – 60 minutes, maximum concentrations in children are higher than those in adults. Relationship between the dose and plasma concentration is linear.

Antihistamine effect occurs in 20 – 60 minutes after ingestion and lasts for 24 hours.

The degree of plasma protein binding is 93%. Penetration into cerebrospinal fluid is minimal, binding to brain H_1 receptors is insignificant. Distribution volume (V_d) is 0.5 to 0.8 l/kg.

In contrast to other antihistamines, cetirizine metabolism in the liver is minimal. Its O-dealkylated metabolite lacks antihistamine activity.

Cetirizine elimination half-life is 7.4 to 9 hours, in patients with moderate kidney insufficiency it is prolonged to 19 to 21 hours. In children, the total body clearance of cetirizine exceeds that in adults by about 33%, elimination half-life is shortened to 6.2 hours. Approximately 60% of the administered dose is eliminated unchanged with urine within 24 hours, other 10% during the following 4 days; in children, 40% of the administered dose is eliminated with urine within 24 hours. About 10% of the administered dose is eliminated with stools within 5 days after ingestion.

5.3. Preclinical Data Regarding Product Safety

Animal studies have shown that doses exceeding 216-fold the maximum human daily dose are not teratogenic. Cetirizine does not show teratogenic effects during organogenesis.

6. PHARMACEUTICAL DATA

6.1. List of All Inactive Substances (Qualitatively)

Methylparaben, propylparaben, 85% glycerol, propylene glycol, noncrystallizing 70% sorbitol, sodium saccharin dihydrate, sodium acetate trihydrate, 99% acetic acid, banana flavor, purified water.

6.2. Incompatibilities

Incompatibility of orally used cetirizine with any other substance is not known.

6.3. Shelf Life

2 years

6.4. Storage

At temperature up to 25 °C.

6.5. Packaging Type

Brown glass vial closed with a PE/PP childproof screw cap, measuring spoon, Patient Information Leaflet in Czech, paper folding box.

Package size: 100 ml

6.6. Instructions for Use

Product is used orally.

Instructions for Opening a Vial with a Safety Cap

The vial is provided with a safety cap, which prevents children from opening it. You may open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

7. MARKETING AUTHORIZATION HOLDER

Léčiva a.s., Prague, Czech Republic

8. REGISTRATION NUMBER

24/153/01-C

9. DATE OF MARKETING AUTHORIZATION / MARKETING AUTHORIZATION RENEWAL

10. DATE OF THE LAST TEXT REVISION

This decision entered into force
on 5-Feb-2001
in Bratislava, 5-Feb-2001
Signature .....

MINISTRY OF HEALTH
OF THE SLOVAK REPUBLIC

Number: R-700/2000-SF ***In Bratislava, 29-Nov-2000***

Decision

The Ministry of Health of the Slovak Republic as the administrative body competent, pursuant to Section 60 Letter b) of Act of the National Council of the Slovak Republic No 140/1998 Coll. on medicines and medical aids, amending Act No 455/1991 Coll. of the National Council of the Slovak Republic on small business activity (Trade Licensing Act) as amended, and amending and supplementing Act of the National Council of the Slovak Republic No 220/1996 Coll. on advertizing as amended, has decided regarding the Application No. R-0667/2000 dated 08-Jun-2000 for marketing authorization of the medicinal product ***ZODAC^{R} GTT gtt por (oral drops),*** *of the Marketing Authorization Holder Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic, of the producer Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic represented by the organizational subsection Léčiva SK, Dvojkrížna 9, 821 06 Bratislava*

as follows:

The application for marketing authorization of the medicinal product

ZODAC^{R} GTT oral drops

containing 10 mg of cetirizine dihydrochloride in 1 ml of solution, in the packaging: brown glass vial closed with a dropper and a childproof screw cap, is approved. Placement of the medicinal product to the market and its entry into the List of Registered Medicinal Product under the registration Number

14/0375/00/-S

and the State Institute for Drug Control code ***15927*** *for the package size of* ***1x20 ml*** *is approved, as the medicinal product meets the requirements of the Act of the National Council of the Slovak Republic No 140/1998 Coll. The medicinal product is classified into the group of medicinal products* ***available on medical prescription only****. Labeling of outer and inner packaging (Supplement No.1), Patient Information Leaflet (Supplement No.2), and Summary of Product Characteristics (Supplement No.3), which constitute an integral part of this decision, are approved.*

Shelf life of the medicinal product ***ZODAC^{R} GTT oral drops, 1x20 ml*** ***is two years***

This Decision expires 5 years after entry into force.

Rationale:

After reviewing the application for marketing authorization of the medicinal product of the of the Marketing Authorization Holder Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic, of the producer Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic represented by the organizational subsection Léčiva SK, Dvojkrížna 9, 821 06 Bratislava, Registration No. R-0667/2000 dating from 08-Jun-2000, it has been found that the product meets the requirements on quality, safety, and efficacy of a medicinal product and, therefore, it has been decided as stated in this Decision

Advice: *Repeal from this Decision may be filed within the period of 15 days from its delivery to the Ministry of Health of the Slovak Republic (Section 61, paragraph 1 of Act No. 71/1967 Coll. on administrative proceedings).*

MINISTERSTVO ZDRAVOTNÍCTVA 40

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m i n i s t e r

Decision will be delivered to:

1. Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava
2. State Institute for Drug Control, Kvetná 11, 825 08 Bratislava
3. Ministry of Health of the Slovak Republic, Limbová 2, 833 41 Bratislava

SUMMARY OF PRODUCT CHARACTERISTICS

1. PRODUCT NAME
ZODAC® GTT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Cetirizine dihydrochloride 10 mg in 1 ml of solution (= 20 drops)

3. DRUG FORM
Oral solution drops.
Product description: clear, colorless to slightly yellow, sweet tasting solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Symptomatic treatment of allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

4.2. Dosage and Administration
Adults and children over 12 years of age usually use 10 mg of cetirizine (20 drops) in one daily dose.
Children from 6 to 12 years of age usually use 10 mg of cetirizine (20 drops) 1x daily or 5 mg of cetirizine (10 drops) 2x daily.
Children from 2 to 6 years of age usually use 5 mg of cetirizine (10 drops) 1x daily or 2.5 mg of cetirizine (5 drops) 2x daily.
Patients with kidney failure: in decreased kidney function it is necessary to adequately decrease cetirizine dosage, in creatinine clearance of 11 – 31 ml/min, 5 mg of cetirizine (10 drops) is administered daily.
Hemodialysis patients are administered 5 mg of cetirizine (10 drops) daily.
Patients with liver insufficiency: it is necessary to adequately decrease cetirizine dosage; usually, 5 mg of cetirizine (10 drops) is administered daily.
In geriatric patients: No dose adjustment is necessary as regards age.
Dosage must be adjusted in case of decreased kidney function, usually 5 mg of cetirizine (10 drops) is administered daily.
Zodac gtt may be used regardless of food; drops are taken with a sufficient amount of non-irritating liquid.

4.3. Contraindications
Known hypersensitivity to cetirizine, another product component, or hydroxyzine.
Children under 2 years of age.
It is not recommended to use the product in pregnancy or during breastfeeding.

4.4. Special Warnings
Caution is necessary in patients with kidney failure, liver insufficiency, and geriatric patients.
Drops do not contain any residual sugar (saccharin is used as sweetener), they are suitable for diabetics.
Excessive consumption of non-alcoholic beverages during treatment is not recommended.

4.5. Drug Interactions and Other Interactions
In simultaneous use of cetirizine and theophylline, cetirizine clearance may decrease (by up to 16%) with the occurrence of clinical symptoms of cetirizine adverse effects.

4.6. Use in Pregnancy and during Breastfeeding
Animal experiments have documented neither embryotoxicity nor teratogenicity.
Experience with use in humans is insufficient.
With regard to insufficient experience, product use in pregnant and breastfeeding women is not recommended.

4.7. Influence on the Ability to Drive Motor Vehicles and Operate Machinery
Sedative effects of the product similar to those observed with classical antihistamines have not been described. Studies in healthy individuals have not shown any impact on alertness or reaction time after administration of 20 – 25 mg of cetirizine. In spite of that, the need for increased caution should be assessed individually in persons performing activities necessitating attention, motor coordination, and rapid decision making (e.g. driving motor vehicles, operating machinery, working in heights, etc.).

4.8. Adverse Effects
Cetirizine is generally well tolerated. In isolated cases, headache, sleepiness, vertigo, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with cetirizine use.

4.9.Overdose
In cetirizine doses (exceeding 50 mg) sleepiness has been observed; in children, in contrast, overdose may cause restlessness and irritation; the signs of its anticholinergic effect may be observed (urine retention, marked mouth dryness, constipation).
Treatment of overdose comprises the standard approach, therapy is symptomatic and supportive, focused on maintaining vital functions. Specific antidote is not known. Only a small fraction of the administered dose of cetirizine may be removed by hemodialysis (about 9%).

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic Properties
Pharmacotherapeutic group – Antihistamine. ATC group: B06AE07-antihistamine for systemic administration – piperazine derivatives – cetirizine.

Cetirizine is a 2nd generation antihistamine with prolonged effect. It selectively inhibits peripheral H_1 receptors, but does not markedly influence cholinergic, adrenergic, or serotonin receptors. In therapeutic doses it is devoid of any sedative effect on the CNS. It inhibits migration of inflammatory cells, especially eosinophils. It suppresses histamine release from mast cells and basophil leukocytes even during the late phase of allergic reaction.

5.2. Pharmacokinetic Properties

Cetirizine bioavailability after ingestion of drops is rapid and complete. Food does not influence cetirizine absorption but it prolongs the time necessary to reach the maximum plasma concentration to 1.7 hours. Maximum concentration after ingestion of drops is reached in 30 – 60 minutes, maximum concentrations in children are higher than those in adults. Relationship between the dose and plasma concentration is linear.
Antihistamine effect occurs in 20 – 60 minutes after ingestion, it lasts for 24 hours. The degree of plasma protein binding is 93%. Penetration into cerebrospinal fluid is minimal, binding to brain H_1 receptors is insignificant.
Distribution volume (V_d) is 0.5 to 0.8 l/kg.
In contrast to other antihistamines, cetirizine metabolism in the liver is minimal. Its O-dealkylated metabolite lacks antihistamine activity.
Cetirizine elimination half-life is 7.4 to 9 hours, in patients with moderate kidney insufficiency it is prolonged to 19 to 21 hours. In children, the total body clearance of cetirizine exceeds that in adults by about 33%, elimination half-life is shortened to 6.2 hours. Approximately 60% of the administered dose is eliminated unchanged with urine within 24 hours, other 10% within the following 4 days; in children, 40% of the administered dose is eliminated with urine within 24 hours. About 10% of the administered dose is eliminated with stools within 5 days after ingestion.

5.3. Preclinical Safety Data

Animal studies have shown that doses exceeding 216-fold the maximum human daily dose are not teratogenic. Cetirizine does not show teratogenic effects during organogenesis.

6. PHARMACEUTICAL INFORMATION

6.1. List of Inactive Substances

Methylparaben, propylparaben, 85% glycerol, propylene glycol, sodium saccharin, sodium acetate, 99% acetic acid, purified water.

6.2. Incompatibilities

Incompatibility of orally used cetirizine with any other substance is not known.

6.3. Shelf Life

2 years

6.4. Warning about Storage Conditions and Storage Method

Store in a dry place, at temperature of 10 – 25 °C, protect from light.

6.5. Properties and Content of Packaging and Package Size

Packaging: brown glass vial closed with a dropper and a childproof screw cap, Patient Information Leaflet in Slovak, paper folding box.
Package size: 20 ml

6.6. Warning about Product Handling

Product is used orally.

Instructions for Opening a Vial with a Safety Cap
The vial is provided with a safety cap, which prevents children from opening it. You may open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

7. MARKETING AUTHORIZATION HOLDER
Léčiva a.s., Prague, Czech Republic

8. REGISTRATION NUMBER

9. DATE OF MARKETING AUTHORIZATION / MARKETING AUTHORIZATION RENEWAL

10. DATE OF THE LAST TEXT REVISION
NOVEMBER 2000

16.11.2004

Patient Information Leaflet

Information on use, read carefully!

ZODAC® GTT
(cetirizine dihydrochloride)
oral solution drops

Marketing Authorization Holder
Léčiva a.s., Prague, Czech Republic

Composition
Active substance: cetirizine dihydrochloride 10 mg in 1 ml of solution (=20 drops)
Inactive Substances: methylparaben, propylparaben, glycerol, propylene glycol, sodium saccharin, sodium acetate, acetic acid, purified water.

Pharmacotherapeutic group:
Antihistamine (medicinal product suppressing hypersensitivity reaction)

Characteristic:
Cetirizine, the active substance of Zodac gtt, is an antihistamine with prolonged effect. Antihistamines block the effect of histamine, one of the agents released in the organism during hypersensitivity reaction (allergy). Cetirizine suppresses both the "early" phase of allergic reaction mediated by histamine, and the migration of inflammatory cells, especially eosinophils, and the release of agents linked with the "late" phase of allergic reaction.
Zodac gtt is a highly efficient antihistamine and anti-allergic agent with a minimum occurrence of sleepiness after regular therapeutic dose. With regard to its prolonged effect, Zodac gtt may be administered to adults and older children in one daily dose.

Indications:
Zodac gtt is used for alleviation of complaints in allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

Contraindications
Zodac gtt may not be administered to patients with known hypersensitivity to cetirizine, another product component, or hydroxyzine, to pregnant or breastfeeding women and to children under 2 years of age.

Adverse Effects
Zodac gtt is generally well tolerated. In isolated cases, headache, sleepiness, dizziness, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with its use. If any of these adverse effects or other unusual reactions eventually develop, consult a physician about further use of the product or its administration to a child.

Rarely, reactions of hypersensitivity to the product might occur (hives, soft tissue edema, shortness of breath). In that case it is necessary to discontinue product use immediately and consult a physician.

Interactions:
The effects of Zodac gtt and other simultaneously used medicines may mutually interact. Simultaneous use of Zodac gtt and some bronchodilators (medicines for widening the bronchi) containing the active substance theophylline may cause the occurrence of adverse effects of Zodac gtt treatment.
Therefore, inform your physician about all medicines you or your child are using, whether they are prescription or non-prescription medicines. Do not use or give your child any over-the-counter medicine simultaneously with Zodac gtt without approval of your physician. If another physician prescribes you another medicine, inform him/her that you or your child are using Zodac gtt.
Interaction of cetirizine with alcohol (in blood alcohol level of 0.8 g/l) have not been described yet. However, excessive consumption of alcoholic beverages when using Zodac gtt is not recommended.

Dosage and Administration:
Dosage is always determined by a physician. Food does not significantly influence the absorption of Zodac gtt, and so Zodac gtt may be taken independently of food.
Adults and children over 12 years of age usually use 20 drops of Zodac gtt (=10 mg of cetirizine) 1x daily.
Children from 6 to 12 years of age use 20 drops (=10 mg of cetirizine) 1x daily or 10 drops (5 mg of cetirizine) 2x daily, in the morning and in the evening.
Children from 2 to 6 years of age are administered 10 drops (=5 mg of cetirizine) 1x daily or 5 drops (=2.5 mg of cetirizine) 2x daily, in the morning and in the evening.
The physician may adjust the dosage for elderly patients or patients with serious liver or kidney disease.
If you accidentally omit a dose, use the dose (administer it to the child) as soon as you remember. In case another dose should be already taken, do not double the dose but continue the treatment according to the original treatment plan.
Drops are taken with a small amount of non-irritating liquid.

Instructions for Opening a Vial with a Safety Cap
Vial is provided with a safety cap, which prevents children from opening it. Open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

Note
No sedative effects of the product similar have been described. In spite of that, you should not exceed the recommended daily dose if you are going to drive a motor vehicle or operate machinery.
Zodac gtt contains no residual sugar (the used sweetener is saccharin). Drops are suitable for diabetics.

Overdose:

The main symptom of overdose may be sleepiness. In children, however, overdose may cause also irritation restlessness. In case of overdose (especially in children) it is necessary to see a physician immediately. Specific antidote is not yet known.

Warning:
Product may not be used after expiration date stated on the packaging. In case of using an excessive dose or accidental ingestion of drops by a child, seek a physician.

Package size:
20 ml of solution

Storage:
In a dry place, at temperature of 10 – 25 °C, protect from light.
Keep out of reach of children!

Date of the Last Revision
November 2000

Outer Packaging Labeling Template

16.11.2020

20 ml

ZODAC GTT

(cetirizine dihydrochloride)
oral solution drops

Antihistamine

Cetirizine dihydrochloride 10 mg in 1 ml (20 drops)

Contains methylparaben, propylparaben, and saccharin sodium salt

Do not use in hypersensitivity to parabens

For internal use

Available on medical prescription only

Patient Information Leaflet is enclosed

Store in a dry place at temperature of 10 – 25 °C!

Protect from light.

Store out of reach of children!

Return any unused product to the pharmacy

Registration number:

Batch No.:

Expiration date:

Léčiva a.s.,
102 37 Prague 10

Dolní Měcholupy 130,
Czech Republic

EAN code

Inner Packaging Labeling Template

16.11.2020

20 ml

ZODAC

(cetirizine dihydrochloride)
oral solution drops

Antihistamine

Cetirizine dihydrochloride 10 mg in 1 ml (20 drops)

Contains methylparaben, propylparaben, and saccharin sodium salt

Do not use in hypersensitivity to parabens

For internal use

Batch No. specification:

Expiration date specification:

LÉČIVA logo

This decision entered into force
on 5-Feb-2001
in Bratislava, 5-Feb-2001
Signature .....

MINISTRY OF HEALTH
OF THE SLOVAK REPUBLIC

Number: R-699/2000-SF ***In Bratislava, 29-Nov-2000***

Decision

The Ministry of Health of the Slovak Republic as the administrative body competent, pursuant to Section 60 Letter b) of Act of the National Council of the Slovak Republic No 140/1998 Coll. on medicines and medical aids, amending Act No 455/1991 Coll. of the National Council of the Slovak Republic on small business activity (Trade Licensing Act) as amended, and amending and supplementing Act of the National Council of the Slovak Republic No 220/1996 Coll. on advertizing as amended, has decided regarding the Application No. R-0668/2000 dated 08-Jun-2000 for marketing authorization of the medicinal product ***ZODAC^{R} SIR syrup,*** *of the Marketing Authorization Holder Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic, of the producer Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic, represented by the organizational subsection Léčiva SK, Dvojkrížna 9, 821 06 Bratislava*

as follows:

The application for marketing authorization of the medicinal product

ZODAC^{R} SIR syrup

containing 5 mg of cetirizine dihydrochloride in 5 ml of syrup, in the packaging: brown glass vial closed with a childproof screw cap, is approved. Placement of the medicinal product to the market and its entry into the List of Registered Medicinal Product under the registration Number

14/0376/00/-S

and the State Institute for Drug Control code ***15926*** *for the package size of* ***1x100 ml*** *is approved, as the medicinal product meets the requirements of the Act of the National Council of the Slovak Republic No 140/1998 Coll. The medicinal product is classified into the group of medicinal products* ***available on medical prescription only****. Labeling of outer and inner packaging (Supplement No.1), Patient Information Leaflet (Supplement No.2), and Summary of Product Characteristics (Supplement No.3), which constitute an integral part of this decision, are approved.*

Shelf life of the medicinal product ***ZODAC^{R} SIR syrup, 1x100 ml is two years***

This Decision expires 5 years after entry into force.

Rationale:

After reviewing the application for marketing authorization of the medicinal product of the of the Marketing Authorization Holder Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic, of the producer Léčiva a.s., Dolní Měcholupy 130, 102 37 Prague 10, Czech Republic represented by the organizational subsection Léčiva SK, Dvojkrížna 9, 821 06 Bratislava, Registration No. R-0668/2000 dating from 08-Jun-2000, it has been found that the product meets the requirements on quality, safety, and efficacy of a medicinal product and, therefore, it has been decided as stated in this Decision

Advice: *Repeal from this Decision may be filed within the period of 15 days from its delivery to the Ministry of Health of the Slovak Republic (Section 61, paragraph 1 of Act No. 71/1967 Coll. on administrative proceedings).*

MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY 40

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Decision will be delivered to:

1. Léčiva SK a.s., Dvojkrížna 9, 821 06 Bratislava
2. State Institute for Drug Control, Kvetná 11, 825 08 Bratislava
3. Ministry of Health of the Slovak Republic, Limbová 2, 833 41 Bratislava

16.11.2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. PRODUCT NAME
ZODAC® SIR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Cetirizine dihydrochloride 5 mg in 5 ml of syrup

3. DRUG FORM
Syrup
Product description: clear, colorless to slightly yellow, sweet, banana flavored solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Symptomatic treatment of allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

4.2. Dosage and Administration
Adults and children over 12 years of age usually use 10 mg of cetirizine (2 measuring spoons) in one daily dose.
Children from 6 to 12 years of age usually use 10 mg of cetirizine (2 measuring spoons) 1x daily or 5 mg of cetirizine (1 measuring spoon) 2x daily.
Children from 2 to 6 years of age usually use 5 mg of cetirizine (1 measuring spoon) 1x daily or 2.5 mg of cetirizine (1/2 of a measuring spoon) 2x daily.
Patients with kidney failure: in decreased kidney function it is necessary to adequately decrease cetirizine dosage, in creatinine clearance of 11 – 31 ml/min, 5 mg of cetirizine (1 measuring spoon) is administered daily.
Hemodialysis patients are administered 5 mg of cetirizine (1 measuring spoon) daily.
Patients with liver insufficiency: it is necessary to adequately decrease cetirizine dosage; usually, 5 mg of cetirizine (1 measuring spoon) is administered daily.
In geriatric patients: No dose adjustment is necessary as regards age.
Dosage must be adjusted in case of decreased kidney function, usually 5 mg of cetirizine (1 measuring spoon) is administered daily.
Zodac sir may be used regardless of food; syrup is taken with a sufficient amount of non-irritating liquid.
For measuring the doses, a measuring spoon graduated at 2 levels marked as 1/4 (= ¼ of a measuring spoon, which corresponds to 1.25 ml) and ½ (= ½ of a measuring spoon, which corresponds to 2.5 ml) is provided; measuring spoon full to the brim contains 5 ml.

4.3. Contraindications
Known hypersensitivity to cetirizine, another product component, or hydroxyzine.
Children under 2 years of age.
It is not recommended to use the product in pregnancy or during breastfeeding.

4.4. Special Warnings

Caution is necessary in patients with kidney failure, liver insufficiency, and geriatric patients.
Zodac sir contains at maximum 0.12 g of residual sugar in 5 ml of syrup (the used sweeteners are sorbitol and saccharin). If recommended dosage is observed, the product is suitable for diabetics.
Excessive consumption of non-alcoholic beverages during treatment is not recommended.

4.5. Drug Interactions and Other Interactions

In simultaneous use of cetirizine and theophylline, cetirizine clearance may decrease (by up to 16%) with the occurrence of clinical symptoms of cetirizine adverse effects.

4.6. Use in Pregnancy and during Breastfeeding

Animal experiments have documented neither embryotoxicity nor teratogenicity.
Experience with use in humans is insufficient.
With regard to insufficient experience, product use in pregnant and breastfeeding women is not recommended.

4.7. Influence on the Ability to Drive Motor Vehicles and Operate Machinery

Sedative effects of the product similar to those observed with classical antihistamines have not been described. Studies in healthy individuals have not shown any impact on alertness or reaction time after administration of 20 – 25 mg of cetirizine. In spite of that, the need for increased caution should be assessed individually in persons performing activities necessitating attention, motor coordination, and rapid decision making (e.g. driving motor vehicles, operating machinery, working in heights, etc.).

4.8. Adverse Effects

Cetirizine is generally well tolerated. In isolated cases, headache, sleepiness, vertigo, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with cetirizine use.

4.9.Overdose

In cetirizine doses (exceeding 50 mg) sleepiness has been observed; in children, in contrast, overdose may cause restlessness and irritation; the signs of its anticholinergic effect may be observed (urine retention, marked mouth dryness, constipation).
Treatment of overdose comprises the standard approach, therapy is symptomatic and supportive, focused on maintaining vital functions. Specific antidote is not known. Only a small fraction of the administered dose of cetirizine may be removed by hemodialysis (about 9%).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group – Antihistamine. ATC group: B06AE07-antihistamine for systemic administration – piperazine derivatives – cetirizine.

Cetirizine is a 2nd generation antihistamine with prolonged effect. It selectively inhibits peripheral H_1 receptors, but does not markedly influence cholinergic, adrenergic, or serotonin receptors. In therapeutic doses it is devoid of any sedative effect on the CNS. It inhibits migration of inflammatory cells, especially eosinophils. It suppresses histamine release from mast cells and basophil leukocytes even during the late phase of allergic reaction.

5.2. Pharmacokinetic Properties

Cetirizine bioavailability after ingestion of syrup is rapid and complete. Food does not influence cetirizine absorption but it prolongs the time necessary to reach the maximum plasma concentration to 1.7 hours. Maximum concentration after ingestion of drops is reached in 30 – 60 minutes, maximum concentrations in children are higher than those in adults. Relationship between the dose and plasma concentration is linear.
Antihistamine effect occurs in 20 – 60 minutes after ingestion, it lasts for 24 hours. The degree of plasma protein binding is 93%. Penetration into cerebrospinal fluid is minimal, binding to brain H_1 receptors is insignificant.
Distribution volume (V_d) is 0.5 to 0.8 l/kg.
In contrast to other antihistamines, cetirizine metabolism in the liver is minimal. Its O-dealkylated metabolite lacks antihistamine activity.
Cetirizine elimination half-life is 7.4 to 9 hours, in patients with moderate kidney insufficiency it is prolonged to 19 to 21 hours. In children, the total body clearance of cetirizine exceeds that in adults by about 33%, elimination half-life is shortened to 6.2 hours. Approximately 60% of the administered dose is eliminated unchanged with urine within 24 hours, other 10% within the following 4 days; in children, 40% of the administered dose is eliminated with urine within 24 hours. About 10% of the administered dose is eliminated with stools within 5 days after ingestion.

5.3. Preclinical Safety Data

Animal studies have shown that doses exceeding 216-fold the maximum human daily dose are not teratogenic. Cetirizine does not show teratogenic effects during organogenesis.

6. PHARMACEUTICAL INFORMATION

6.1. List of Inactive Substances

Methylparaben, propylparaben, 85% glycerol, propylene glycol, noncrystallizing 70% sorbitol, sodium saccharin, sodium acetate, 99% acetic acid, banana flavor, purified water.

6.2. Incompatibilities

Incompatibility of orally used cetirizine with any other substance is not known.

6.3. Shelf Life

2 years

6.4. Warning about Storage Conditions and Storage Method

Store in a dry place, at temperature of 10 – 25 °C, protect from light.

6.5. Properties and Content of Packaging and Package Size
Packaging: brown glass vial closed with childproof screw cap, measuring spoon, Patient Information Leaflet in Slovak, paper folding box.
Package size: 100 ml

6.6. Warning about Product Handling
Product is used orally.

Instructions for Opening a vial with a safety cap
The vial is provided with a safety cap, which prevents children from opening it. You may open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

7. MARKETING AUTHORIZATION HOLDER
Léčiva a.s., Prague, Czech Republic

8. REGISTRATION NUMBER

9. DATE OF MARKETING AUTHORIZATION / MARKETING AUTHORIZATION RENEWAL

10. DATE OF THE LAST TEXT REVISION
NOVEMBER 2000

16.11.2000

Patient Information Leaflet

Information on use, read carefully!

ZODAC® SIR
(cetirizine dihydrochloride)
syrup

Marketing Authorization Holder
Léčiva a.s., Prague, Czech Republic

Composition
Active substance: cetirizine dihydrochloride 5 mg in 5 ml of syrup
Inactive Substances: methylparaben, propylparaben, glycerol, propylene glycol, noncrystallizing 70% sorbitol, sodium saccharin, sodium acetate, acetic acid, banana flavor, purified water.

Pharmacotherapeutic group:
Antihistamine (medicinal product suppressing hypersensitivity reaction)

Characteristic:
Cetirizine, the active substance of Zodac sir, is an antihistamine with prolonged effect. Antihistamines block the effect of histamine, one of the agents released in the organism during hypersensitivity reaction (allergy). Cetirizine suppresses both the "early" phase of allergic reaction mediated by histamine, and the migration of inflammatory cells, especially eosinophils, and the release of agents linked with the "late" phase of allergic reaction.
Zodac sir is a highly efficient antihistamine and anti-allergic agent with a minimum occurrence of sleepiness after regular therapeutic dose. With regard to its prolonged effect, Zodac sir may be administered to adults and older children in one daily dose.

Indications:
Zodac sir is used for alleviation of complaints in allergic rhinitis and conjunctivitis (including perennial and seasonal one) and skin symptoms accompanied with itching and rash, namely in urticaria.

Contraindications
Zodac sir may not be administered to patients with known hypersensitivity to cetirizine, another product component, or hydroxyzine, to pregnant or breastfeeding women and to children under 2 years of age.

Adverse Effects
Zodac sir is generally well tolerated. In isolated cases, headache, sleepiness, dizziness, dry mouth, digestive problems (dyspepsia, abdominal pain, flatulence) may be associated with its use. If any of these adverse effects or other unusual reactions eventually develop, consult a physician about further use of the product or its administration to a child.

Rarely, reactions of hypersensitivity to the product might occur (hives, soft tissue edema, shortness of breath). In that case it is necessary to discontinue product use immediately and consult a physician.

Interactions:
The effects of **Zodac sir** and other simultaneously used medicines may mutually interact. Simultaneous use of Zodac sir and some bronchodilators (medicines for widening the bronchi) containing the active substance theophylline may cause the occurrence of adverse effects of Zodac sir treatment.
Therefore, inform your physician about all medicines you or your child are using, whether they are prescription or non-prescription medicines. Do not use or give your child any over-the-counter medicine simultaneously with Zodac sir without approval of your physician. If another physician prescribes you another medicine, inform him/her that you or your child are using Zodac sir.
Interaction of cetirizine with alcohol (in blood alcohol level of 0.8 g/l) have not been described yet. However, excessive consumption of alcoholic beverages when using Zodac sir is not recommended.

Dosage and Administration:
Dosage is always determined by a physician. Food does not significantly influence the absorption of Zodac sir, and so Zodac sir may be taken independently of food.
Adults and children over 12 years of age usually use 2 measuring spoons of Zodac sir (=10 mg of cetirizine) 1x daily.
Children from 6 to 12 years of age use 2 measuring spoons (=10 mg of cetirizine) 1x daily or 1 measuring spoon (5 mg of cetirizine) 2x daily, in the morning and in the evening.
Children from 2 to 6 years of age are administered 1 measuring spoon (=5 mg of cetirizine) 1x daily or ½ measuring spoon (=2.5 mg of cetirizine) 2x daily, in the morning and in the evening.
The physician may adjust the dosage for elderly patients or patients with serious liver or kidney disease.
If you accidentally omit a dose, use the dose (administer it to the child) as soon as you remember. In case another dose should be already taken, do not double the dose but continue the treatment according to the original treatment plan.
For measuring the dose, a measuring spoon graduated at 2 levels marked as 1/4 (= ¼ of a measuring spoon, which corresponds to 1.25 ml) and ½ (= ½ of a measuring spoon, which corresponds to 2.5 ml) is provided; measuring spoon full to the brim contains 5 ml.
Syrup is taken with a small amount of non-irritating liquid.

Instructions for Opening a Vial with a Safety Cap
Vial is provided with a safety cap, which prevents children from opening it. Open it by pressing the cap strongly downwards and turning counter-clockwise. After use, the cap must be screwed on tightly again.

Note
No sedative effects of the product similar have been described. In spite of that, you should not exceed the recommended daily dose if you are going to drive a motor vehicle or operate machinery.

Zodac sir contains at maximum 0.12 g of sugar in 5 ml of syrup (the used sweeteners are sorbitol and saccharin). If recommended dosage is observed syrup is suitable for diabetics.

Overdose:

The main symptom of overdose may be sleepiness. In children, however, overdose may cause also irritation and restlessness. In case of overdose (especially in children) it is necessary to see a physician immediately. Specific antidote is not yet known.

Warning:
Product may not be used after expiration date stated on the packaging. In case of using an excessive dose or accidental ingestion of syrup by a child, see a physician.

Package size:
100 ml of syrup

Storage:
In a dry place, at temperature of 10 – 25 °C, protect from light.
Keep out of reach of children!

Date of the Last Revision
November 2000

Outer Packaging Labeling Template

16.11.2000

100 ml

ZODAC SIR

(cetirizine dihydrochloride)

syrup

Antihistamine

Cetirizine dihydrochloride 5 mg in 5 ml of syrup

Contains methylparaben, propylparaben, sorbitol, and saccharin sodium salt

Do not use in hypersensitivity to parabens

For internal use

Available on medical prescription only

Patient Information Leaflet is enclosed

Measuring spoon filled to the brim contains 5 ml of syrup.

Zodac sir contains at maximum 0.12 g of sugar in 5 ml of syrup.

Store in a dry place at temperature of 10 – 25 °C!

Protect from light.

Store out of reach of children!

Return any unused product to the pharmacy

Registration number:

Batch No.:

Expiration date:

Léčiva a.s.,
102 37 Prague 10

Dolní Měcholupy 130,
Czech Republic

EAN code

Inner Packaging Labeling Template

100 ml

ZODAC

(cetirizine dihydrochloride)
syrup

Antihistamine

Cetirizine dihydrochloride 5 mg in 5 ml of syrup

Contains methylparaben, propylparaben, and saccharin sodium salt

Do not use in hypersensitivity to parabens

For internal use

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Store in a dry place at temperature of 10 – 25 °C!

Protect from light.

Store out of reach of children!

Return any unused product to the pharmacy

Registration number:

Batch No. specification:

Expiration date specification:

LÉČIVA logo

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Our ref: B0199PI-EP

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*1 European Patent Attorney
*2 European Trade Mark Attorney
*3 European Design Attorney

13 July 2010

Re.: **Opposition against European Patent No. 1768649**
Opponent: Zentiva k.s.

Dear Sirs,

With reference to the Opposition against European Patent No. 1768649 by Zentiva k.s. enclosed please find translations of cited documents D5-D8 according to Article 14(4) EPC and Rule 6(2) EPC.

Yours faithfully,
BORENIUS & Co Oy Ab

Christian Westerholm
(00125420)

Enclosures: Translation into English of;

D5 Marketing authorization for ZODAC®GTT in Slovakia

D6 Marketing authorization for ZODAC®SIR in Slovakia

D7 Marketing authorization for ZODAC®GTT in the Czech Republic

D8 Marketing authorization for ZODAC®SIR in the Czech Republic

Europäisches Patentamt
European Patent Office
Office européen des brevets

Submission in opposition proceedings

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- representing the opponent(s):	Zentiva k.s.
Opponent/representative's reference	B0199PI-EP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1768649
Application No.	EP05758582.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	23 September 2009
Title of the invention	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES
Proprietor of the patent	UCB FARCHIM S.A.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Any annexes (other than citation) to an opposition letter - Letter	B0199PI-OPPOSITION AGAINST EP 1768649B1-filing translations.pdf	OTHER-1.pdf

Evidence filed subsequently:

D5	Other evidence	Marketing authorization for ZODAC GTT in Slovakia original file name: D5 English translation.pdf attached as: Other-evidence-1.pdf
D6	Other evidence	Marketing authorization for ZODAC SIR in Slovakia original file name: D6 English translation.pdf attached as: Other-evidence-2.pdf
D7	Other evidence	Marketing authorization for ZODAC GTT in the Czech Republic original file name: D7 English translation.pdf

		attached as: Other-evidence-3.pdf
D8	Other evidence	Marketing authorization for ZODAC SIR in the Czech Republic original file name: D8 English translation.pdf attached as: Other-evidence-4.pdf

Signatures

Place:	**Helsinki**
Date:	**15 July 2010**
Signed by:	**FI, Borenius & Co. Oy Ab, C. Westerholm 5880**
Association:	**BORENIUS & Co Oy Ab**
Capacity:	**(Representative)**

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European Patent Office
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Acknowledgement of receipt

We hereby acknowledge receipt of the following submission by the opponent:

Submission number	878710
Application number	EP05758582.0
Patent number	EP1768649
Date of receipt	15 July 2010
Your reference	B0199PI-EP
Opponent	Zentiva k.s.
Title	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES
Documents submitted	package-data.xml ep-oppo.pdf (2 p.) Other-evidence-1.pdf\D5 English translation.pdf (11 p.) Other-evidence-3.pdf\D7 English translation.pdf (10 p.) ep-opposition-data.xml OTHER-1.pdf\B0199PI-OPPOSITION AGAINST EP 1768649B1-filing translations.pdf (1 p.) Other-evidence-2.pdf\D6 English translation.pdf (11 p.) Other-evidence-4.pdf\D8 English translation.pdf (10 p.)
Submitted by	CN=C. Westerholm 5880,O=Borenius & Co. Oy Ab,C=FI
Method of submission	Online
Date and time receipt generated	15 July 2010, 11:06 (CEST)
Message Digest	79:CA:E1:21:34:D0:57:96:E1:F1:ED:33:5E:CC:AC:B9:71:C0:D9:C6

Correction by the EPO of errors in debit instructions filed by eOLF

Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

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Office européen des brevets

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Date
20-07-2010

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent 01 of 13.07.10 with literature
- ☐ Copy (copies)

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

☐

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

☐ **Registered letter**

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Date
29-07-2010

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

Communication of further notices of opposition pursuant to Rule 79(2) EPC

No further opposition has been filed.

If oral proceedings are to take place, parties are advised to check the electronic file via the Register Plus online service at **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2) in advance of the hearing to ensure that they are in possession of all relevant documents.

A copy of the communication pursuant to Rule 79(1) EPC sent to the proprietor of the patent is also enclosed for your information.

The patent proprietor's (proprietors') observations on the notice of opposition to the above-mentioned patent will be communicated to the opponent without delay. A time limit for reply will be fixed if the Opposition Division considers this expedient.

If no reply to a communication is received within the time limit set, the proceedings will be resumed forthwith. Your attention is drawn to Article 114(2) EPC.

For the Opposition Division

Enclosures: copy of the communication pursuant to Rule 79(1) EPC (Form 2317A)

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Date
29-07-2010

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

Communication of notices of opposition (R. 79(1) EPC)

Notice of opposition has been filed within the opposition period by:

01. Zentiva k.s./U kabelovny 130/10237 Praha 10/REPUBLIQUE TCHEQUE//

The notice of opposition indicated above has already been communicated to you.

You are requested to file your observations within a period of **four months** from notification of this communication.

You may also file amendments, where appropriate, to the description, claims and drawings within the period specified. One set of these documents is to be filed.

If you introduced documents which have not yet been mentioned during the proceedings, your attention is drawn to Rule 83 EPC.

Enclosures:

For the Opposition Division

UCB Pharma SA - Département Propriété Intellectuelle - Allée de la Recherche 60 - B-1070 Bruxelles
Intellectuele Eigendom Departement - Rechearchdreef 60 - B-1070 Brussel
Intellectual Property Department - Allée de la Recherche 60 - B-1070 Brussels

17.80_EP (WO)

ML/MC

VIA REGISTERED MAIL

EUROPEAN PATENT OFFICE
D-80298 MUNICH (Germany)

EPO - Munich
63
19. Okt. 2010

Our ref.: Case 17.80_EP (WO)
IPD/1010-037

→ *Please quote in all correspondence*

Brussels, October 13, 2010

Your ref.:

Reference: European Patent 1 768649 (Application No.05 758 582.0-2112)
In the Name of UCB Farchim SA. – Notice of opposition

Dear Sirs,

Reference is made to the Official Communication pursuant to R. 79(1) EPC dated July 29, 2010, issued in respect of the above-identified patent.

This is in response to the Communication of the European Patent Office dated July 29, 2010:

We write in reply to the above Communication inviting us to make observations on the notice of opposition filed on the above mentioned patent. A notice of opposition has been filed by Zentiva k.s., Prague, Czech Republic (the *opponent* in the following).

I. REQUESTS

It is our main request that the patent is maintained as granted, i.e. in unamended form.

New claims 1-6 according to the first auxiliary request and new claims 1-3 according to the second auxiliary request are filed enclosed to this submission. It is requested to maintain the patent within the scope of one of these auxiliary requests should the Opposition Division surprisingly come to the conclusion that the opposed patent contravenes Article 100 a) EPC.

Oral proceedings according to Article 116 EPC are requested if the Opposition Division is unable to grant the above requests without them.

II. AUXILIARY REQUESTS

Claim 1 according to the first auxiliary request is restricted to the subject-matter of claim 4 as granted. A new dependent claim 3 has been added based on [0020] of EP 1 768 649 corresponding to p. 4, l. 29 of WO2006/005507.

Claim 1 according to the second auxiliary request is based on [0020] of EP 1 768 649 corresponding to p. 4, l. 29 of WO2006/005507 and has been restricted to levocetirizine. Claims 3-6 as granted were deleted.

III. PRIOR ART CITED BY THE OPPONENT

In the Notice of opposition, documents D1-D11 were cited. The order of the documents as submitted will be maintained also in the following.

IV. GROUNDS FOR OPPOSITION

The only ground for opposition on which the opposition is based is that of Article 100 a) EPC in connection with Articles 52-57 EPC.

In more detail, the opponent has requested to revoke the opposed patent due to a lack of novelty of claims 1, 2, 3, 5 and 7 and due to a lack of inventive step of all claims 1-7.

1. Lack of Novelty - Claim 1

Prior use of the products named ZODAC®GTT and ZODAC®SIR

Claim 1 of the opposed patent allegedly lacks novelty in view of the prior use of two products named ZODAC®GTT and ZODAC®SIR marketed by the opponent in Slovakia and in the Czech Republic before the priority date of the opposed patent (14.7.2004).

The marketing authorizations for both products were granted on November 29, 2000 in Slovakia and on April 18, 2001 in the Czech Republic.

The respective products then were launched in the Czech Republic on October 31, 2001 and in Slovakia on September 30, 2002. The opponent indicated that, thus, the respective medicaments were available on the market before the priority date of the opposed patent, and the compositions of the products were part of the state of the art after the launch of the products since the composition of the products could be analyzed without undue burden.

Opponent submitted documents D9-D11 in order to provide evidence for this alleged prior use. However, one should bear in mind that the standard of proof for a public prior use is high. Public prior use is only adequately substantiated, if specific details are given of what was made available to the public, where, when, how and by whom (T328/87; T93/89; T1002/92, and T212/97).

It is established case law that to be able to determine whether an invention has been made available to the public by prior use, the following circumstances have to be clarified:

(i) When the act prior use occurred

(ii) What was made available to the public through that use

(iii) The circumstances of the act of use, i. e. where, how and by whom the subject matter was made public through that use.

It is important to note that in cases of alleged public prior use, particular substantiation is required in the Notice of opposition, i. e. within the time period for filing an opposition. Thus, if an opponent wishes to rely upon prior use, the notice of opposition must indicate within the opposition period all the facts which make it possible to determine the date of prior use, what has been used, and the circumstances relating to the prior use.

However, it is at least doubtful what was made available to the public through the use of the products named ZODAC®GTT and ZODAC®SIR.

The opponent submitted documents D9 and D10 in order to provide evidence on the constitution and precise composition of products ZODAC®GTT and ZODAC®SIR. The submitted evidence should clearly prove what kind of medicinal product was available to the public before the priority date of the opposed patent, i. e. July 14, 2004.

However, having a view to documents D9 and D10, there is no proof that the composition indicated here indeed reflects the products launched on the market before July 14, 2004. We would like to draw the attention of the Opposition Division to chapter 9. and 10. of D9 and D10, respectively, leaving considerable doubts regarding the question, what was available to the public before July 14, 2004. Chapters 9. and 10. clearly indicate that the publication date of these information sheets is later than July 14, 2004. The original text has been revised 4 (!) times starting on October 11, 2006 to October 21, 2009 for both documents D9 and D10. Furthermore, in point 9. of D9 and D10 it is indicated that there was a renewal of the authorization in January 28, 2009.

Opponent wishes to use the information contained in D9 and D10 to confirm that the exact composition as disclosed therein (methylparaben 1.35 mg, propylparaben 0.15 mg) was identically launched in the time before July 14, 2004. However, since it is not convincing that the summary of product characteristics of D9 and D10 truly and identically reflect the characteristics of ZODAC®SIR and ZODAC®GTT as launched in 2001 and 2002, this evidence is insufficient.

Therefore, opponent has not convincingly shown that the subject matter of claim 1 has been publicly demonstrated before the priority date of the opposed patent.

Unless the opponent will convincingly and without any remaining doubt show what composition the ZODAC®SIR and ZODAC®GTT products had before the priority

date of the opposed patent, claim 1 according to the main and the auxiliary requests is novel in view of these products.

Furthermore, it should be noted that T594/01 as cited by the opponent is not relevant here. The case underlying T594/01 is completely different and cannot be compared with the present situation. In the patent case underlying T594/01, the main claim was related to a process for the preparation of ethylene glycols where, among others, the process was performed "with less than 0.1 wt% of carbon dioxide in the reaction mixture". However, there was no information contained on how to measure the carbon dioxide content indicated in the examples of a prior art document. In this case, the Board held that "normally the uncertainty of a measured experimental value is irrelevant for the assessment of novelty". But only in this precise case, a specific experimental value as disclosed in an example of the prior art still anticipates claimed subject matter since the latter is not distinguishable from the prior art within the margin of experimental error.

That is to say, T594/01 does not indicate that a "lower than" value in general cannot be distinguished from the identified value itself. In particular in the field of pharmaceutical chemistry, there are established and very precise standard methods for determining the content of any ingredient of a pharmaceutical composition. It is quite unrealistic to assume that the data indicated in D9 and D10 are not valid as such but that a large margin of uncertainty regarding the measurement has to be taken into consideration.

Therefore, as a conclusion, claim 1 according to the main request is novel in view of the prior use of products ZODAC®GTT and ZODAC®SIR.

This even more applies to the subject matter of claim 1 according to the first and second auxiliary requests since the quantity of parahydroxybenzoate esters there is restricted to a range of from 0.0001-1.4 mg/ml and 0.01-1.125 mg/ml, respectively.

Therefore, the subject matter of claim 1 according to the main request as well as according to the first and second auxiliary request is clearly novel according to Article 54(1) and (2) EPC.

2. Lack of inventive step - (Article 56 EPC)

The only attack as regards lack of inventive step is based on documents D1 and D3.

D1 was considered to be the closest prior art since it discloses a pharmaceutical composition comprising cetirizine hydrochloride and methyl- as well as propylparaben (see example 5 of D1). Needless to say, D1 does not disclose a liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine and parahydroxybenzoate esters as preservatives in the amount of more than 0 and less than 1.5 mg/ml.

The combined amount of methylparaben and propylparaben of example 5 of D1 (page 11) is 0.3 g/100ml or 3 mg/ml. Therefore, D1 reflects not more and not less than what has been already discussed in the introduction of the present patent and has been mentioned in [0014] of the present patent specification (last sentence).

Further, it is interesting to note that D1 discloses on p. 3, lines 56-57 that different kinds of additives, for example preservatives, buffer agents, pH-controlling agents and the like can be used in amounts determined by those skilled in the art within the same range as adopted for ordinary ophthalmic or nasal solutions. This will have to be discussed later.

In view of the citation of D1, the objective problem underlying the present invention is exactly that mentioned in the description of the patent-in-suit, [0008] stating that "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 (selected from parahydroxybenzoate esters)".

This purpose is achieved by the subject matter of claim 1 according to the main or the first or second auxiliary request.

Opponent referred to D3 (Handbook of Pharmaceutical Excipients) which is allegedly giving the person skilled in the art information regarding the concentrations of methylparabens and propylparabens that should be used for different applications.

However, it is worth to study D3 in detail.

The chapter of D3, discussing methylparaben (p. 340 etc.) indicates that methylparaben is widely used as an anti-microbial preservative in cosmetics, food products and pharmaceutical formulations. Although it is indicated, that it may be used alone, it can be derived from D3 that it is preferably used in combination with other parabens or with other anti-microbial agents, see section 7. of chapter "Methylparaben". Thus, the amounts of methylparaben indicated in the table of section 7. have to be evaluated quite carefully since the amounts of methylparaben indicated therein clearly do not reflect the methylparaben content used as the only preservative. Rather, the amounts of methylparaben have to be seen as intended for use in combination with other preservatives.

It is interesting to note that the first sentence on the right col. on p. 340 of D3 indicates that methylparaben is used together with propylparaben in an overall amount of 2 mg/ml for the "preservation of various parenteral pharmaceutical formulations". There is not any indication that the amounts indicated in the table are sufficient for methylparaben to act efficiently as the only preservative in a pharmaceutical formulation.

Of particular interest is section 10. of chapter "Methylparaben", which was not submitted by opponent but is submitted enclosed to this submission. Here, one can read that

> *"Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens since additive effects occur. Therefore, combinations of methyl, ethyl, propyl- and butylparaben are usually used together".* (emphasis added)

Furthermore, the minimum inhibitory concentrations (MICs) of methylparaben in table I (section 11.) are interesting to read: here, one can easily derive that the minimum inhibitory concentration of methylparaben in, for example, important pharmaceutical formulations such as eye drops, has to be more than 4 mg/ml since a well known and very harmful pathogen such as *pseudomonas aeruginosa* requires a minimum inhibitory concentration of 4000 µg/ml (= 4 mg/ml). As a skilled person knows, infections of the eye with *pseudomonas aeruginosa* may lead to harmful infections of the eye and even to blindness.

By comparing the contents of table I and the table in section 7. of chapter "Methylparaben" it can be easily determined that the minimum inhibitory concentrations as contained in table I do not fit to the concentrations indicated in the table of section 7. That is to say, a skilled person can easily derive from the latter table that the lower limits are only theoretical ones and that they are not suitable to provide a sufficient effect as a preservative alone in view of the best known pathogens which might occur in pharmaceutical compositions.

The same also applies to chapter "Propylparaben" of D3.

Apart from that, a skilled person would not have any motivation to combine D1 and D3 for the following reasons:

In section 14. of chapters "Methylparaben" and "Propylparaben" one can find the information that

> *"although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for these types of formulations...".*

Therefore, it is highly questionable what should prompt a skilled person to combine the teachings of D1, i. e. an ophthalmic composition comprising cetirizine hydrochloride and methyl- and propylparaben in an amount of 3 mg/ml with the teachings of D3 which is on the one hand indicating that not even the concentration of parabens used in D1 is sufficient to defeat well known pathogens and on the other hand indicates in general that parabens should not be used in ophthalmic preparations.

There is no reason to assume that a skilled person would arrive at the subject matter presently claimed by a combination of D1 and D3 without using inadmissible hindsight. A very interesting indication in this respect is the passage on p. 3, line 56 and 57 of D1 (as mentioned by opponent):

> *"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".*

Having a view to D3, a skilled person would be deterred from using parabens in liquid pharmaceutical formulations at all bearing in mind the above teachings.

Further, opponent pointed out that

"For the skilled person in the art preparing a liquid composition it is obvious to have preservatives on the lowest possible level."

This statement ignores the main problem areas which have to be addressed by a skilled person in determining the proper constitution and concentration of preservatives used in a pharmaceutical preparation. Although potential side effects of preservatives always are an issue for a skilled person, product safety usually will be the main topic which has to be addressed, in particular regarding microbial contaminations in liquid pharmaceutical preparations.

D3 thus discloses not to use parabens in certain liquid formulations at all and, in general, in amounts much higher then presently claimed. D3 therefore is clearly teaching away from the subject matter according to the main and the first or second auxiliary request.

Thus, the subject matter of claim 1 according to the main, first and second auxiliary request is based on an inventive step in the meaning of article 56 EPC.

IV. THE SUBJECT MATTER OF DEPENDENT CLAIMS 2-7

Since the subject matter of claim 1 according to the main, first and second auxiliary request is novel and based on an inventive step, this automatically applies to the subject matter of the dependent claims.

V. CONCLUSIONS

Therefore, it is justified to reject the opposition and to maintain the present patent as granted or, as auxiliary requests, in the scope of the first or second auxiliary request.

Respectfully submitted,

Yours faithfully,

Lechien

Monique LECHIEN
European Patent Attorney

Enclosures: - Set of claims according to the first and second auxiliary request (with and without trackchanges)
- Further pages of D3
- Acknowledgement of receipt Form 1037

Methylparaben

1. Nonproprietary Names

BP: Methyl hydroxybenzoate
JP: Methyl parahydroxybenzoate
PhEur: Methylis parahydroxybenzoas
USP: Methylparaben

2. Synonyms

E218; 4-hydroxybenzoic acid methyl ester; *Methyl Chemosept*; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*.

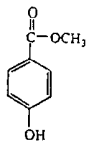
3. Chemical Name and CAS Registry Number

Methyl 4-hydroxybenzoate [99-76-3]

4. Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

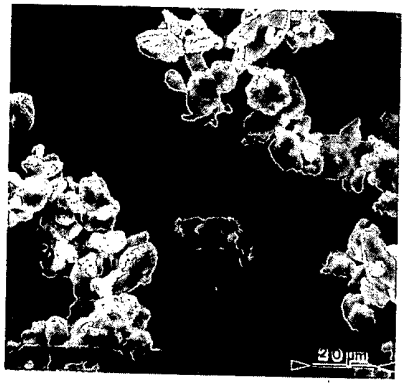
7. Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone, in combination with other parabens, or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative.[1]

The parabens are effective over a wide pH range 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; aqueous solubility however decreases. A mixture of parabens is thus frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of 2-5% propylene glycol, or by using parabens in combination with other antimicrobial agents such as imidurea, *see* Section 10.

Due to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. However, this raises the pH of poorly buffered formulations.

SEM: 1
Excipient: Methylparaben
Supplier: Bate Chemical Co Ltd
Magnification: 600×



Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations, *see* Section 14.

Use	Concentration (%)
IM, IV, SC injections[a]	0.065-0.25
Inhalation solutions	0.025-0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015-0.2
Oral solutions and suspensions	0.015-0.2
Rectal preparations	0.1-0.18
Topical preparations	0.02-0.3
Vaginal preparations	0.1-0.18

[a] *See* Section 14.

8. Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Melting range	125-128°C	125-128°C	125-128°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.10%	—	≤ 0.05%
Sulfated ash	—	≤ 0.1%	—
Chloride	≤ 0.035%	—	—

(Continued)

Test	JP	PhEur	USP
Sulfate	≤ 0.024%	—	—
Heavy metals	≤ 20 ppm	—	—
Readily carbonizable substances	+	—	—
Appearance of solution	—	+	+
Related substances	+	+	—
Assay (dried basis)	≥ 99.0%	99.0-100.5%	99.0-100.5%

10. Typical Properties

Antimicrobial activity: methylparaben exhibits antimicrobial activity between pH 4-8. Preservative efficacy decreases with increasing pH due to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive bacteria than against Gram-negative bacteria.

Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens, since additive effects occur. Therefore, combinations of methyl, ethyl, propyl, and butylparaben are often used together. Activity has also been reported to be enhanced by the addition of other excipients such as: propylene glycol (2-5%);[2] phenylethyl alcohol;[3] and edetic acid.[4] Activity may also be enhanced, due to synergistic effects, by using combinations of parabens with other antimicrobial preservatives such as imidurea.[5]

The hydrolysis product, *p*-hydroxybenzoic acid, has practically no antimicrobial activity.

See also Section 12.

Reported minimum inhibitory concentrations (MICs) for methylparaben are shown in Table I.[4]

Density (true): 1.352 g/cm³[a]
Dissociation constant: pK_a = 8.4 at 22°C
Melting point: 125-128°C
Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil, *see* Table II.
Solubility: *see* Table III

[a] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Aqueous solutions of methylparaben, at pH 3-6, may be sterilized by autoclaving at 120°C for 20 minutes, without decomposition.[8] Aqueous solutions at pH 3-6 are stable (less than 10% decomposition) for up to about 4 years at room temperature, while aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days storage at room temperature).[9]

Predicted rate constants and half-lives at 25°C, for methylparaben dissolved in dilute hydrochloric acid solution at the initial pH shown below:[9]

Initial pH of solution	Rate constant $k \pm \sigma^{[a]}$ (hour^{-1})	Half-life $t_{½} \pm \sigma^{[a]}$ (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47000 ± 12000
4	$(3.27 \pm 0.64) \times 10^{-7}$	88000 ± 17000

[a] Indicates the standard error.

Table I: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. mycoides ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

Table II: Partition coefficients of methylparaben in vegetable o and water.[6,7]

Solvent	Partition coefficient Oil: water
Almond oil	7.5
Castor oil	6.0
Corn oil	4.1
Diethyl adipate	200
Isopropyl myristate	18.0
Lanolin	7.0
Mineral oil	0.1
Peanut oil	4.2
Soybean oil	6.1

Table III: Solubility of methylparaben in various solvents.[4]

Solvent	Solubility at 25°C Unless otherwise stated
Ethanol	1 in 2
Ethanol (95%)	1 in 3
Ethanol (50%)	1 in 6
Ether	1 in 10
Glycerin	1 in 60
Mineral oil	Practically insoluble
Peanut oil	1 in 200
Propylene glycol	1 in 5
Water	1 in 400
	1 in 50 at 50°C
	1 in 30 at 80°C

The predicted amount of methylparaben remaining after autoclaving is shown below for methylparaben dissolved in dilute hydrochloric acid solution at the initial pH shown:[9]

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after autoclaving (%)
1	$(4.96 \pm 0.16) \times 10^{-1}$	84.77 ± 0.46
2	$(4.49 \pm 0.37) \times 10^{-2}$	98.51 ± 0.12
3	$(2.79 \pm 0.57) \times 10^{-3}$	99.91 ± 0.02
4	$(1.49 \pm 0.22) \times 10^{-3}$	99.95 ± 0.01

[a] Indicates the standard error.

Methylparaben should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization.[10,11]

However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.[12]

Incompatibilities with other substances such as bentonite,[13] magnesium trisilicate,[14] talc, tragacanth,[15] sodium alginate,[16] essential oils,[17] sorbitol,[18] and atropine[19] have been reported.

Absorption of methylparaben by plastics has also been reported; the amount absorbed is dependent upon the type of plastic and the vehicle. It has been claimed that low- and high-density polyethylene bottles do not absorb methylparaben.[20]

Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

13. Method of Manufacture

Methylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with methanol.

14. Safety

Methylparaben, and other parabens, are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations. Although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for these types of formulations due to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity.

Hypersensitivity reactions to parabens, generally of the delayed type, and appearing as contact dermatitis have been reported. However, given the widespread use of parabens as preservatives such reactions are relatively uncommon and the classification of parabens in some sources as high-rate sensitizers may thus be somewhat overstated.[21]

Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported.[22-24] Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.[25-27]

Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis, provided they are applied to another unaffected site. This has been termed the paraben paradox.[28]

Concern has been expressed over the use of methylparaben in infant parenteral products since bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinaemic neonates.[29]

Systemically no adverse effects to parabens have been reported. The WHO has set an estimated total acceptable daily intake for methyl, ethyl, and propylparabens at up to 10 mg/kg body-weight.[30]

LD_{50} (dog, oral): 3.0 g/kg[31]
LD_{50} (mouse, IP): 0.96 g/kg
LD_{50} (mouse, SC): 1.20 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Methylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16. Regulatory Status

Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the US at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, ophthalmic preparations, oral capsules, tablets, solutions and suspensions, otic, rectal, topical, and vaginal preparations). Included in medicines licensed in the UK.

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Butylparaben; ethylparaben; methylparaben potassium; methylparaben sodium; propylparaben.

Methylparaben potassium: $C_8H_7KO_3$
Molecular weight: 190.25
CAS number: [26112-07-2]
Synonyms: methyl 4-hydroxybenzoate potassium salt; potassium methyl hydroxybenzoate.
Comments: methylparaben potassium may be used instead of methylparaben because of its greater aqueous solubility.

Methylparaben sodium: $C_8H_7NaO_3$
Molecular weight: 174.14
CAS number: [5026-62-0]
Synonyms: E219; methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; soluble methyl hydroxybenzoate.

Pharmacopeias: Eur and US.
Appearance: a white odorless, or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity: pH = 9.5-10.5 (0.1% aqueous solution).
Solubility: 1 in 50 of ethanol (95%); 1 in 2 of water; practically insoluble in fixed oils.
Comments: methylparaben sodium may be used instead of methylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

19. Comments

In addition to the most commonly used paraben esters, efforts have been made to use some less-common esters, which are listed below.

Name	CAS No.
Benzylparaben	94-18-8
Isobutylparaben	4247-02-3
Isopropylparaben	4191-73-5

20. Specific References

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Jian L, Li Wan Po A. Ciliotox
hydroxybenzoates: a dose-r
study. *J Pharm Pharmacol* 1

Mineral
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mineral oil

Propylparaben

1. Nonproprietary Names

BP: Propyl hydroxybenzoate
JP: Propyl parahydroxybenzoate
PhEur: Propylis parahydroxybenzoas
USP: Propylparaben

2. Synonyms

Chemocide PK; E216; 4-hydroxybenzoic acid propyl ester; *Nipasol M*; propagin; *Propyl chemosept*; propyl *p*-hydroxybenzoate; *Propyl paraseptt*; *Solbrol P*; *Tegosept P*.

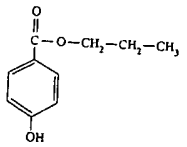
3. Chemical Name and CAS Registry Number

Propyl 4-hydroxybenzoate [94-13-3]

4. Empirical Formula Molecular Weight

$C_{10}H_{12}O_3$ 180.20

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

7. Applications in Pharmaceutical Formulation or Technology

Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used alone, in combination with other paraben esters, or with other antimicrobial agents. In cosmetics it is the second most frequently used preservative.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity although they are most effective against yeasts and molds, *see* Section 10.

Due to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

Propylparaben (0.02%) together with methylparaben (0.18%) has been used for the preservation of various parenteral pharmaceutical formulations, *see* Section 14.

See Methylparaben for further information.

Use	Concentration (%)
IM, IV, SC injections	0.005-0.2
Inhalation solutions	0.015
Intradermal injections	0.02-0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005-0.01
Oral solutions and suspensions	0.01-0.02
Rectal preparations	0.02-0.01
Topical preparations	0.01-0.6
Vaginal preparations	0.02-0.1

8. Description

Propylparaben occurs as a white, crystalline, odorless, and tasteless powder.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
Melting range	96-99°C	96-99°C	95-98°C
Acidity	—	+	+
Loss on drying	≤ 0.5%	—	≤ 0.5%
Residue on ignition	≤ 0.1	—	≤ 0.05%
Sulfated ash	—	≤ 0.1%	—
Appearance of solution	—	+	—
Chloride	≤ 0.035%	—	—
Sulfate	≤ 0.024%	—	—
Heavy metals	≤ 20 ppm	—	—
Related substances	+	+	—
Readily carbonizable substances	+	—	—
Organic volatile impurities	—	—	+
Assay (dried basis)	≥ 99.0%	99.0-100.5%	99.0-100.5%

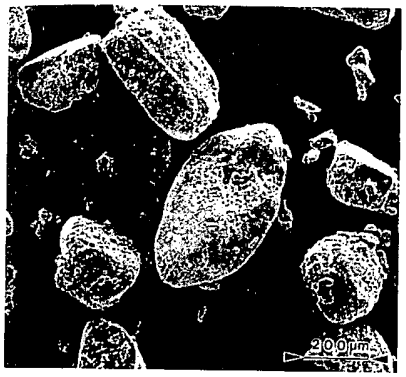
10. Typical Properties

Antimicrobial activity: propylparaben exhibits antimicrobial activity between pH 4-8. Preservative efficacy decreases with increasing pH due to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria. The activity of the parabens increases with increasing chain length of the alkyl moiety; solubility however decreases. Activity may be improved by using combinations of parabens since additive effects occur. Propylparaben has thus been used with methylparaben in parenteral preparations and is used with combinations of other parabens in topical and oral formulations. Activity has also been reported to be improved by the addition of other excipients, *see* Methylparaben for further information.

Reported minimum inhibitory concentrations (MICs) for propylparaben are shown in Table I:[2]

Boiling point: 295°C
Density (bulk): 0.426 g/cm$^{3(a)}$
Density (tapped): 0.706 g/cm$^{3(a)}$
Density(true): 1.288 g/cm$^{3(a)}$
Dissociation constant: pKa = 8.4 at 22°C

SEM: 1
Excipient: Propylparaben
Supplier: Bate Chemical Co Ltd
Magnification: 60×



SEM: 2
Excipient: Propylparaben
Supplier: Bate Chemical Co Ltd
Magnification: 600×

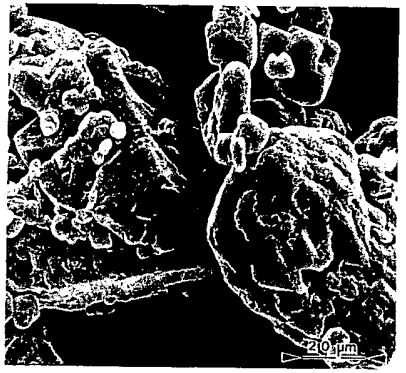


Table I: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. mycoides ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	> 1000
Pseudomonas aeruginosa ATCC 15442	> 1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagrophytes	65

Table II: Partition coefficients for propylparaben in vegetable oil and water.[3]

Solvent	Partition coefficient Oil: water
Corn oil	58.0
Mineral oil	0.5
Peanut oil	51.8
Soybean oil	65.9

Table III: Solubility of propylparaben in various solvents.[2]

Solvent	Solubility at 25°C Unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 1.1
Ethanol (50%)	1 in 5.6
Ether	Freely soluble
Glycerin	1 in 250
Mineral oil	1 in 3330
Peanut oil	1 in 70
Propylene glycol	1 in 3.9
Propylene glycol (50%)	1 in 110
Water	1 in 4350 at 15°C
	1 in 2500
	1 in 225 at 80°C

Flash point: 140°C
Partition coefficients: values for different vegetable oils vary considerably and are affected by the purity of the oil, *see* Table II.
Refractive index: n_D^{14} = 1.5049
Solubility: *see* Table III.

[a] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Aqueous propylparaben solutions at pH 3-6 can be sterilized by autoclaving, without decomposition.[4] At pH 3-6 aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

Predicted rate constants and half-lives at 25°C, for propylparaben dissolved in dilute hydrochloric acid solution at the initial pH shown:[5]

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Half-life $t_{\frac{1}{2}} \pm \sigma^{(a)}$ (day)
1	$(1.255 \pm 0.042) \times 10^{-4}$	230 ± 7.6
2	$(1.083 \pm 0.081) \times 10^{-5}$	2670 ± 200
3	$(8.41 \pm 0.96) \times 10^{-7}$	34 300 ± 3900
4	$(2.23 \pm 0.37) \times 10^{-7}$	130 000 ± 22 000

(a) Indicates the standard error.

The predicted amount of propylparaben remaining after autoclaving is shown below for propylparaben dissolved in dilute hydrochloric acid solution at the pH shown:[5]

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after sterilization (%)
1	$(4.42 \pm 0.10) \times 10^{-1}$	86.30 ± 0.30
2	$(4.67 \pm 0.19) \times 10^{-2}$	98.46 ± 0.06
3	$(2.96 \pm 0.24) \times 10^{-3}$	99.90 ± 0.01
4	$(7.8 \pm 1.1) \times 10^{-4}$	99.97 ± 0.004

(a) Indicates the standard error.

Propylparaben should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

The antimicrobial activity of propylparaben is considerably reduced in the presence of nonionic surfactants as a result of micellization.[6] Absorption of propylparaben by plastics has been reported, with the amount absorbed dependent upon the type of plastic and the vehicle.[7] Magnesium aluminum silicate, magnesium trisilicate, yellow iron oxide, and ultramarine blue have also been reported to absorb propylparaben, thereby reducing preservative efficacy.[8,9]

Propylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13. Method of Manufacture

Propylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with *n*-propanol.

14. Safety

Propylparaben, and other parabens, are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations. Although propylparaben and methylparaben have been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations due to the irritant potential of the parabens.

Systemically, no adverse reactions to parabens have been reported although they have been associated with hypersensitivity reactions. The WHO has set an estimated acceptable total daily intake for methyl, ethyl, and propylparabens at up to 10 mg/kg body-weight.[10]

LD_{50} (dog, oral): 6.0 g/kg[11]
LD_{50} (mouse, IP): 0.2 g/kg
LD_{50} (mouse, SC): 1.65 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylparaben may be irritant to the skin, eyes, and mucous membranes and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16. Regulatory Status

Propylparaben and methylparaben are affirmed GRAS Direct Food Substances in the US at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, inhalations, ophthalmic preparations, oral capsules, solutions, suspensions and tablets, otic, rectal, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Butylparaben; ethylparaben; methylparaben; propylparaben potassium; propylparaben sodium.

Propylparaben potassium: $C_{10}H_{11}KO_3$
Molecular weight: 218.30
CAS number: [84930-16-5]
Synonyms: potassium propyl hydroxybenzoate; propyl 4-hydroxybenzoate potassium salt.

Propylparaben sodium: $C_{10}H_{11}NaO_3$
Molecular weight: 202.20
CAS number: [35285-69-9]
Synonyms: E217; propyl 4-hydroxybenzoate sodium salt; sodium propyl hydroxybenzoate; soluble propyl hydroxybenzoate.
Pharmacopeias: Eur and US.
Appearance: white odorless, or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity: pH = 9.5-10.5 (0.1% w/v aqueous solution)
Solubility: 1 in 50 of ethanol (95%); 1 in 2 ethanol (50%); 1 in 1 of water; practically insoluble in fixed oils.
Comments: propylparaben sodium may be used instead of propylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

19. Comments

See Methylparaben for further information and references.

20. Specific References

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Jian L, Li Wan Po A. Ciliotoxicity of methyl- and propyl-*p* hydroxyhenzoates: a dose-response and surface-response study. *J Pharm Pharmacol* 1993; 45: 925-927.

22. Authors

MM Rieger.

2nd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the~~an~~ active substance ~~chosen among cetirizine,~~ levocetirizine ~~and efletirizine~~, wherein the pharmaceutical composition contains methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.~~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, the preservative being 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.~~

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 preservatives is a mixture of methyl parahydroxybenzoateand propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.~~

~~4. A liquid pharmaceutical composition according to claim 1 or 2, 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.~~

~~5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.~~

~~6. A liquid pharmaceutical composition according to any of the claims 1 to 4, characterized in that the active substance is levocetirizine.~~

37. 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 and ear drops.

2nd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

1st Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, 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.

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 amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) is selected in the range of 0.01 and 1.125 mg/ml of the composition

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

5. A liquid pharmaceutical composition according to any of the claims 1 to 3, characterized in that the active substance is levocetirizine.

6. 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 and ear drops.

1st Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, 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.~~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, the preservative being 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.~~

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 preservatives is a mixture of methyl parahydroxybenzoateand propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.~~

34. A liquid pharmaceutical composition according to claim 1 or 2, characterized in that the amount of p-hydroxybenzoate esters (methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) is selected in the range of 0.01 and 1.125 mg/ml of the composition ~~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.~~

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

56. A liquid pharmaceutical composition according to any of the claims 1 to 34, characterized in that the active substance is levocetirizine.

67. 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 and ear drops.

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Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☒ Letter from the proprietor of the patent of 13.10.10 with literature
- ☐ Letter from the opponent of
- ☐ Copy (copies)

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

☐

For the Opposition Division

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☐ **Registered letter**

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Patent No.: EP-B-1 768 649

Preparation for oral proceedings - Instructions to Support Service

Oral proceedings are to be held in connection with the above patent application

1. The matters to be discussed are set out in the annex (Form 2906)

2. Dispatch the summons using Form 2008/2310 and Form 2906 for the parties to attend on:

Day 29.11.2011 Time 09:00

ROOMS

Room 4330 booked

ORAL 01, 02, 03 and 05 coded

LA 01.08.11
Date Initials

2.1 If no room is available, notify the division on Form 2088

2.2 Parties' submissions in preparation for the oral proceedings, if any, should be made no later than

2 month(s)

before the date of the oral proceedings
(transfer to Form 2008.1 / 2310.1)

2.3 Encode ORAL(04)

coded

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Date Initials

2.4 Dispatch Form 2008.7 / 2310.7 to division

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3. ☐ Arrange for the following special equipment to be provided in the conference room:

..... /
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4. Request language service to provide simultaneous interpretation facilities as necessary

LA 01. 08. 11
Date Initials

5. Return the dossier to primary examiner with Form 2041 (15 days before the oral proceedings)

LA 01. 08. 11
Date Initials

6. Check that summons has been received (Form 2936 / advice of delivery)

7. 15 days before the oral proceedings:
- dispatch the dossier to the primary examiner and
- dispatch Form 2041 with copies for the other members of the examining division.

28.07.11
Date

Sindel, Ulrike	Giró, Annalisa	Giménez Miralles, J	
Chairman	2nd examiner	1st examiner	Legal member
		26.07.11	

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Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
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Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will be public, will take place before the opposition division

on 29.11.11 at 09.00 hrs in Room 4330
at the EPO, Bayerstr. 34, PschorrHöfe, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 1/2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the Special edition No. 3 OJ EPO 2007, 128, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC) is 29.09.11.

You are requested to report in good time beforehand to the porter in the EPO foyer. Room 3473 and 3474 are available as waiting rooms. Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:	2nd Examiner:	Chairman:
Giménez Miralles J	Giró A	Sindel U

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

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1st Examiner:	2nd Examiner:	Chairman:
Giménez Miralles J	Giró A	Sindel U

For the Opposition Division

Annexes:
Confirmation of receipt (Form 2936)
Rule 4 EPC (EPC Form 2043)
Communication (EPO Form 2906)

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Wichtige Hinweise zur mündlichen Verhandlung

Das Europäische Patentamt verfügt über keine eigenen Dolmetscher. Diese müssen im Bedarfsfall von außerhalb, teilweise sogar aus anderen Ländern, beigezogen werden, was mit einem hohen Aufwand an Kosten und organisatorischen Vorbereitungen verbunden ist. Muss ein Verhandlungstermin kurzfristig abberaumt werden, können Kosten für bestellte Dolmetscher nicht mehr vermieden werden.

Es wird daher gebeten, eine Simultanübersetzung nur bei wirklichem Bedarf in Anspruch zu nehmen. Es wäre wünschenswert, wenn sich die Beteiligten (zweckmäßigerweise gleichzeitig mit der Terminabstimmung) auf die Benutzung einer Amtssprache einigen könnten. Bei Verständigungsschwierigkeiten sind die Mitglieder der Einspruchsabteilung bereit zu helfen.

Die von den Verfahrensbeteiligten bevorzugte (abgestimmte) Verhandlungssprache und ggf. eine notwendige Simultanübersetzung sind dem Amt möglichst vor der in Regel 4(1) EPÜ angegebenen Frist mitzuteilen.

☐ Verfahrenssprache ist **Deutsch**

Von der/dem/den Einsprechenden wurde

☐ Englisch

☐ Französisch benutzt.

Es wird um eilige Mitteilung - möglichst per Telefax an den zuständigen Formalprüfer - gebeten,

möglichst bis

Datum **27.09.2011**

1. welche Sprache(n) Sie in der mündlichen Verhandlung verwenden (**Sprechen**)
2. aus welcher Sprache Sie eine Simultanübersetzung benötigen (**Hören**).

Important information concerning oral proceedings

The European Patent Office has no interpreters of its own. When interpreters are needed they have to be brought in from outside, sometimes even from other countries, which is costly and involves considerable organisation. If oral proceedings have to be cancelled at short notice, the cost of interpreters already engaged still has to be borne.

Please therefore make use of simultaneous interpreting facilities only where strictly necessary. If possible the parties should agree on an official language for the proceedings, preferably at the time when they arrange a date. The members of the Opposition Division will be willing to help should any communication problems arise.

The EPO should be told if possible before the period mentioned in Rule 4 (1) EPC which language the parties prefer (agree on) and whether simultaneous interpreting facilities are required.

☒ Language of the proceedings is **English**

The language used by the opponent/s was

☐ German

☐ French.

Please inform us urgently - where possible by fax addressed to the formalities officer concerned -

if possible by

Date **27.09.2011**

1. which language(s) you intend to use during the oral proceedings (**Speaking**)
2. from which language you need simultaneous interpretation (**Listening**).

Très important Procédure orale

L'Office européen des brevets ne dispose pas de son propre service d'interprètes. Aussi faut-il appel le cas échéant à des interprètes de l'extérieur, qui viennent même parfois de l'étranger, ce qui occasionne de frais élevés et demande un grand travail d'organisation. Si la date d'une procédure orale doit être annulée au dernier moment, il n'est plus possible d'éviter les frais d'interprètes.

Les parties à une procédure sont donc priées de ne demander une traduction simultanée qu'en cas de réel besoin. Il serait souhaitable qu'elles puissent se mettre d'accord en même temps qu'elles conviennent de la date sur l'utilisation d'une langue officielle comme langue des débats. Si les parties éprouvent des difficultés de compréhension lors des débats, les membres de la division d'opposition sont disposés à leur prêter leur assistance.

L'Office doit être avisé si possible avant le début du délai mentionné dans la règle 4(1) CBE de la langue préférée par les parties pour le déroulement des débat (et sur laquelle elles se sont préalablement mises d'accord) et de la nécessité éventuelle d'une traduction simultanée.

☐ La langue de la procédure est le **français**

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Date **27.09.2011**

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2. à partir de quelle langue vous aurez besoin d'une traduction simultanée (**pour écouter**).

Soliten Sie Ihren Antrag auf mündliche Verhandlung zurückziehen oder zum anberaumten Verhandlungstermin nicht erscheinen wollen bzw. aus wichtigem Grund daran gehindert sein, werden Sie gebeten,

- **unverzüglich das Amt - möglichst per Telefax - davon zu benachrichtigen, wobei das Schriftstück mit einem deutlichen Vermerk "Dringend, mündliche Verhandlung am ..." oder sinngemäß gekennzeichnet sein sollte;**
- **in dringenden Fällen** (weniger als 1 Monat vor dem Verhandlungstermin) zusätzlich **auch dem/die anderen Verfahrensbeteiligten** bzw. ihre(n) Vertreter auf schnellstem Weg **direkt zu unterrichten.**

In jedem solchen Fall obliegt der Einspruchsabteilung die Entscheidung, ob die Verhandlung durchgeführt oder abberaumt wird. Es wird jedoch darauf hingewiesen, dass einem Verfahrensbeteiligten, der eine nicht rechtzeitige oder unterbliebene Benachrichtigung zu verantworten hat, die dadurch den anderen Beteiligten verursachten Kosten auferlegt werden können (Art. 104 EPÜ).

Hinweis auf Regel 4 EPÜ

Regel 4
Sprache im mündlichen Verfahren

(1) Jeder an einem mündlichen Verfahren vor dem Europäischen Patentamt Beteiligte kann sich anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen, sofern er dies dem Europäischen Patentamt spätestens einen Monat vor dem angesetzten Termin mitgeteilt hat oder selbst für die Übersetzung in die Verfahrenssprache sorgt. Jeder Beteiligte kann sich einer Amtssprache eines Vertragsstaats bedienen, sofern er selbst für die Übersetzung in die Verfahrenssprache sorgt. Von diesen Vorschriften kann das Europäische Patentamt Ausnahmen zulassen.

Should you decide to withdraw your request for oral proceedings or not wish to attend on the date set, or if for some special reason you are unable to do so, you are requested

- **to notify the EPO immediately, where possible by fax, marking the document clearly with the words "Urgent, oral proceedings on ..." or similar;**
- **in urgent cases** (less than one month before the date set for the proceedings), additionally to **notify the other party/parties** and/or their representative(s) **direct as rapidly as possible.**

In all such cases the Opposition Division will decide whether the proceedings are to go ahead or be cancelled. You should however note that costs incurred by the other parties may be charged to a party who either fails to notify them or does not do so in good time (Article 104 EPC).

Attention is drawn to Rule 4 EPC

Rule 4
Language in oral proceedings

(1) Any party to oral proceedings before the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings, if such party gives notice to the European Patent Office at least one month before the date of such oral proceedings or provides for interpretation into the language of the proceedings. Any party may use an official language of a Contracting State, if he provides for interpretation into the language of the proceedings. The European Patent Office may permit derogations from these provisions.

Si vous retirez votre requête tendant à recourir à la procédure orale ou si vous ne souhaitez pas vous présenter à la date fixée pour la procédure orale ou ne pouvez vous y présenter pour une raison sérieuse, veuillez

- **en faire avis sans retard à l'Office, si possible par téléfax, en partant sur votre communication clairement la mention "Urgent, procédure orale le ..." ou une indication similaire;**
- **dans les cas urgents** (moins d'un mois avant la date fixée pour la procédure orale) **en faire avis également directement** pas la voie la plus rapide à **l'autre/aux autres partie(s)** ou bien à son/leurs mandataire(s).

Il appartient alors à la division d'opposition de décider si la procédure orale aura lieu ou non. Il est néanmoins souligné que les frais causés aux autres parties par une partie qui est responsable de l'omission d'un tel avis ou de ce que cet avis n'a pas été fait en temps utile peuvent être mis à la charge de cette partie (art. 104 CBE).

Rappel de la Règle 4 CBE

Règle 4
Langues admissibles lors de la procédure orale

(1) Toute partie à une procédure orale devant l'Office européen des brevets peut utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure, à condition soit d'en aviser l'Office européen des brevets un mois au moins avant la date de la procédure orale, soit d'assurer l'interprétation dans la langue de la procédure. Toute partie peut utiliser une langue officielle de l'un des Etats contractants à condition d'assurer l'interprétation dans la langue de la procédure. L'Office européen des brevets peut autoriser des dérogations aux présentes dispositions.

(2) Die Bediensteten des Europäischen Patentamts können sich im mündlichen Verfahren anstelle der Verfahrenssprache einer anderen Amtssprache des Europäischen Patentamts bedienen.

(2) In the course of oral proceedings, employees of the European Patent Office may use an official language of the European Patent Office other than the language of the proceedings.

(2) Au cours de la procédure orale, les agents de l'Office européen des brevets peuvent utiliser une langue officielle de l'Office européen des brevets autre que la langue de la procédure.

(3) In der Beweisaufnahme können sich die zu vernehmenden Beteiligten, Zeugen oder Sachverständigen, die sich in einer Amtssprache des Europäischen Patentamts oder eines Vertragsstaats nicht hinlänglich ausdrücken können, einer anderen Sprache bedienen. Erfolgt die Beweisaufnahme auf Antrag eines Beteiligten, so werden die Beteiligten, Zeugen oder Sachverständigen mit Erklärungen, die sie in einer anderen Sprache als in einer Amtssprache des Europäischen Patentamts abgeben, nur gehört, sofern dieser Beteiligte selbst für die Übersetzung in die Verfahrenssprache sorgt. Das Europäische Patentamt kann jedoch die Übersetzung in eine seiner anderen Amtssprachen zulassen.

(3) Where evidence is taken, any party, witness or expert to be heard who is unable to express himself adequately in an official language of the European Patent Office or of a Contracting State may use another language. Where evidence is taken upon request of a party, parties, witnesses or experts expressing themselves in a language other than an official language of the European Patent Office shall be heard only if that party provides for interpretation into the language of the proceedings. The European Patent Office may, however, permit interpretation into one of its other official languages.

(3) Lors de l'instruction, les parties, témoins ou experts appelés à être entendus, qui ne possèdent pas une maîtrise suffisante d'une langue officielle de l'Office européen des brevets ou d'un Etat contractant, peuvent utiliser une autre langue. Si la mesure d'instruction est ordonnée sur requête d'une partie, les parties, témoins ou experts qui s'expriment dans une langue autre qu'une langue officielle de l'Office européen des brevets ne sont entendus que si cette partie assure l'interprétation dans la langue de la procédure. L'Office européen des brevets peut toutefois autoriser l'interprétation dans l'une de ses autres langues officielles.

(4) Mit Einverständnis aller Beteiligten und des Europäischen Patentamts kann jede Sprache verwendet werden.

(4) If the parties and the European Patent Office agree, any language may be used.

(4) Sous réserve de l'accord des parties et de l'Office européen des brevets, toute langue peut être utilisée.

(5) Das Europäische Patentamt übernimmt, soweit erforderlich, auf seine Kosten die Übersetzung in die Verfahrenssprache und gegebenenfalls in seine anderen Amtssprachen, sofern ein Beteiligter nicht selbst für die Übersetzung zu sorgen hat.

(5) The European Patent Office shall, if necessary, provide at its own expense interpretation into the language of the proceedings, or, where appropriate, into its other official languages, unless such interpretation is the responsibility of one of the parties.

(5) L'Office européen des brevets assure à ses frais, en tant que de besoin, l'interprétation dans la langue de la procédure, ou, le cas échéant, dans ses autres langues officielles, à moins que cette interprétation ne doive être assurée par l'une des parties.

(6) Erklärungen von Bediensteten des Europäischen Patentamts, Beteiligten, Zeugen und Sachverständigen, die in einer Amtssprache des Europäischen Patentamts abgegeben werden, werden in dieser Sprache in die Niederschrift aufgenommen. Erklärungen in einer anderen Sprache werden in der Amtssprache aufgenommen, in die sie übersetzt worden sind. Änderungen einer europäischen Patentanmeldung oder eines europäischen Patents werden in der Verfahrenssprache in die Niederschrift aufgenommen.

(6) Statements by employees of the European Patent Office, parties, witnesses or experts, made in an official language of the European Patent Office, shall be entered in the minutes in that language. Statements made in any other language shall be entered in the official language into which they are translated. Amendments to a European patent application or European patent shall be entered in the minutes in the language of the proceedings.

(6) Les interventions des agents de l'Office européen des brevets, des parties, témoins et experts faites dans une langue officielle de l'Office européen des brevets sont consignées au procès-verbal dans cette langue. Les interventions faites dans une autre langue sont consignées dans la langue officielle dans laquelle elles sont traduites. Les modifications apportées à une demande de brevet européen ou à un brevet européen sont consignées au procès verbal dans la langue de la procédure.

1. The European patent EP 1 768 649 B1; based upon European patent application 05758582.0; date of filing: 07.07.2005; priority: 14.07.2004 (EP04016519); date of publication and mention of the grant of the patent: 23.09.2009 (Bulletin 2009/39);

Proprietor: UCB Farchim S.A., CH-1630 Bulle, Switzerland

has been opposed by:

Opponent: Zentiva k.s., 102 37 Prague, Czech Republic

2. With notice of opposition filed on 23.06.2010 the Opponent requests revocation of the opposed patent in its entirety based on the grounds of Art. 100(a) EPC for lack of novelty and inventive step (Art. 52(1), 54 and 56 EPC). Alternatively, oral proceedings pursuant to Art. 116 EPC are requested.

3. With letter of observations dated 13.10.2010 filed on 19.10.2010 the patent Proprietor requests rejection of the opposition and maintenance of the patent as granted (Main request), or amended in the form of Auxiliary request 1 or Auxiliary request 2 filed on same date. Alternatively, oral proceedings pursuant to Art. 116 EPC are requested.

4. In the course of the proceedings, the following documents have been submitted as evidence by the parties (the numbering will be adhered to in the rest of the procedure):

D1= EP0605203A2

D2= US5891913

D3= Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), pages 340-343 and 450-453

D4= Wang et al. (2001), Allergy 56, 339-343

D5= Marketing authorization for ZODAC GTT oral drops in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D6= Marketing authorization for ZODAC SIR syrup in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D7= Marketing authorization for ZODAC GTT drops in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D8= Marketing authorization for ZODAC SIR syrup in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D9= ZODAC GTT, Summary of Product Characteristics, date of last text revision 21.10.2009

D10= ZODAC SIR, Summary of Product Characteristics, date of last text revision 21.10.2009

D11= Thomson Reuters Newport Premium, Launched Drug Forms Detail (2010)

5. The opposition, filed in due time, in proper form, and supported by reasoned statements, is formally admissible (Art. 99(1) and 100 EPC, and Rules 3(1) and 76 EPC).

6. According to the parties' requests, oral proceedings will be held. The summons are attached to this communication.

7. The Opposition Division is of the following preliminary non-binding opinion:

7.1 Public prior use

D5, D6, D7, D8 together with D11 demonstrate that the products ZODAC GTT oral drops and ZODAC SIR syrup were launched to the market in the Czech Republic on 31.10.2001, and in Slovakia on 30.09.2002. The Summary of Product Characteristics and Patient Information Leaflet attached to each of D5, D6, D7, D8 demonstrate that ZODAC GTT and ZODAC SIR comprise cetirizine dihydrochloride in aqueous solution containing methylparaben and propylparaben as preservatives. However, the concentration of methylparaben and propylparaben in the solution is not disclosed in D5 to D8.

On the other hand, D9 and D10 are the last revision of the Summary of Product Characteristics (dated 21.10.2009) for ZODAC GTT and ZODAC SIR in the Czech Republic. The Opponent's contention that D9 and D10 were published when the

marketing authorisations were granted is not true. D9 and D10 have been last revised on 21.10.2009, and therefore their publication could not occur before that date. Further, D9 and D10 demonstrate that the first authorisation of ZODAC GTT and ZODAC SIR in the Czech Republic has been renewed once on 28.01.2009, and that the text of the Summary of Product Characteristics has been revised four times, once coinciding with the renewal of the authorisation (28.01.2009). The evidence provided in form of D5, D6, D7, D8, D9 and D10 cannot exclude the possibility that a variation of the excipient composition could have been introduced coinciding with one of those revisions after the product was first launched. It has not been proven beyond any reasonable doubt that the products launched in 2001 and 2002 in the Czech Republic and Slovakia and commercially available before the date of priority of the contested patent had exactly the same concentration of parabens as the products available in 2009 in the Czech Republic as described in D9 and D10. The burden was with the Opponent to prove up to the hilt that the products ZODAC GTT oral drops and ZODAC SIR syrup commercially available in the Czech Republic and Slovakia in 2001 and 2002 had a concentration of parabens of less than 1.5 mg/ml as defined in claim 1 of the opposed patent. The requirement of adequate substantiation by means of extensive evidence regarding this point (what was made available) within the opposition period for the proof of a public prior use has not been met. The actual concentration of parabens in the products ZODAC GTT oral drops and ZODAC SIR syrup launched in the Czech Republic and Slovakia in 2001 and 2002 and commercially available before the priority date of the contested patent remains unknown.

7.2 Inventive step

D1, example 5, is seen as the closest prior art. Difference of claim 1 of the opposed patent is the definition of the paraben concentration of "more than 0 and less than 1.5 mg/ml", whereas D1 discloses 3 mg/ml. The technical effect associated with this difference is the lowering of well-known adverse effects in case of hipersensitivity to parabens whilst maintaining the recommended efficacy for antimicrobial preservation (minimum inhibitory activity). The technical problem was therefore to provide an improved formulation where the health drawbacks associated with use of parabens in case of hipersensitivity and the antimicrobial efficiency (opposing effects) are balanced and optimized. The solution according to the opposed patent is the use of parabens in concentrations of "more than 0 and less than 1.5 mg/ml".

First aspect for discussion during the oral proceedings will be whether or not the problem as formulated above is shown in the patent to be actually solved over the range of paraben concentrations "more than 0 and less than 1.5 mg/ml" defined in claim 1. It is apparent that concentrations of parabens only slightly higher than 0 mg/

ml (say concentrations as low as e.g. 0.0001 mg/ml as described in parag. 20 of the contested patent) can hardly solve the problem of providing formulations meeting the required antimicrobial activity (stability against microbial contamination). It is also apparent from the results of the examples of the contested patent that concentrations lower than 0.15 mg/ml have simply not been tested.

If, in view of this, the technical problem has to be reformulated as to the provision of an alternative formulation to that of D1 (example 5) wherein the risks due to hipersensitivity to parabens in some patients are reduced, then the choice of any possible concentrations of parabens lower than those disclosed in D1 would be equally obvious. Any reduction of the concentration of parabens solves the problem of reducing the risk of adverse reaction in sensitive patients. In this context, it is stressed that the contested patent contains no evidence whatsoever about a reduction of the risk of allergic reactions; however, the achievement of this effect in the contested patent is considered to be plausible in view of the general knowledge of the person skilled in the art. Yet, for the same token, in view of that general knowledge, it would be obvious for the skilled person to reduce the concentration of parabens in order to lower the risk of allergic reactions. The motivation to do so is given by the well-known safety and toxicology concerns about the use of parabens as preservatives.

The eventual recognition of an inventive step will be, therefore, dependent on whether or not the concomitant effect of simultaneously maintaining an acceptable antimicrobial stability can be taken into account, i.e. whether or not it is shown by evidence that the range of paraben concentrations defined in the claims actually represents a critical range of values where the opposing effects of lowering the risk of an adverse hipersensitivity reaction, on the one hand, and achieving minimum antimicrobial efficacy, on the other hand, are balanced and result in a range of values representing a true compromise and an improvement over the prior art. In this regard, the general knowledge of the skilled person represented by handbooks such as D3 must be taken into account. The skilled person is well aware that concentrations of 0.15-2 mg/ml methylparabens and/or 0.05-0.1 mg/ml propylparabens in ophthalmic drops or 0.1-0.2 mg/ml propylparabens in oral solutions are the usual amounts to be employed (see D3, pages 340 and 450). These values almost completely overlap with the range of concentrations defined in claim 1 of the contested patent.

It appears, therefore, that claim 1 as granted does not involve an inventive step.

The foregoing line of reasoning is also valid as regards the ranges of paraben concentrations defined in the auxiliary requests 1 and 2. Further, if the choice of a combination of methylparaben and propylparaben in a particular weight ratio (Auxiliary request 1) and/or the choice of levocetirizine (levorotatory enantiomer of cetirizine) specifically (Auxiliary request 2) can be associated with some particular effect(s) which should be taken into account for the definition of the technical problem, this

should be demonstrated by evidence. In absence of such substantiation, the further limitations introduced in auxiliary requests 1 and 2 represent just trivial variations obvious for a skilled person. General handbooks such as D3 disclose the use of methylparaben and propylparaben in combination (see D3 page 341, section 10), and in particular in a weight ratio 9:1 in several pharmaceutical formulations for parenteral use (see D3 page 340, section 7). Taking the concentration ranges for methylparaben and propylparaben and the weight ratio 9:1 disclosed in D3, one arrives at combined concentration values for total parabens falling within the ranges defined in auxiliary requests 1 and 2. As regards the limitation to levocetirizine, the effect of paraben preservatives is the same on both optical isomers of cetirizine. Accordingly, no inventive contribution can be seen in these limitations.

In preparation for the inventive step discussion, the parties are again reminded that any technical effect is expected to be demonstrated by way of evidence and comparative tests, and that any technical effect must be credibly shown over the whole area covered by the claims. Unreasonably broad generalisations will not be accepted. The parties should be prepared for this discussion.

8. Further remarks:

Claim 1 of Auxiliary request 1 seems to comply with A.123(2) and (3) EPC. However, the introduction of a new claim 3 based on page 4 lines 28-29 of the original patent application does not comply with Rule 80 EPC, because this amendment is not occasioned by a ground for opposition in that claim 3 is only a dependent claim dependent on claim 1; the introduction of a new claim 3 based only on the description and not having a basis in the claims as granted is neither appropriate nor necessary to overcome a ground for opposition, as the relevant independent claim 1 has already been amended for that purpose. The right to amendment of a patent in opposition is not an occasion to improve the patent (T127/85). The introduction of a new dependent claim additionally to the amendment of the relevant independent claim upon which the former depends is clearly an improvement of the patent by incorporation of a possible fallback position. Such an improvement of the patent and of the patentee's position is not allowable under Rule 80 EPC.

9. The parties are informed that further comments, evidence, information, submissions and/or requests in preparation of the oral proceedings, if any, are to be filed in agreement with the requirements of Rule 116(1) EPC, i.e. not later than the final date indicated on the EPO form 2310 (cf. Guidelines E-III, 5 and D-VI, 3.2).

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03. 08. 11 OPPOSITION

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Apotex, Inc. (IPR2019-00400), Ex. 1015, p. 337

Lechien, Monique
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Date: 03-08-2011

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649

Applicant/Proprietor: UCB FARCHIM S.A.

EPA/EPO/OEB Formblatt/Form/Formulaire : 2310

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Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately**:

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

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Monique LECHIEN
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22. Aug. 2011

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Date: 03-08-2011

Reference		Application No./Patent No.
B0199PI-EP	OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor		
UCB FARCHIM S.A.		

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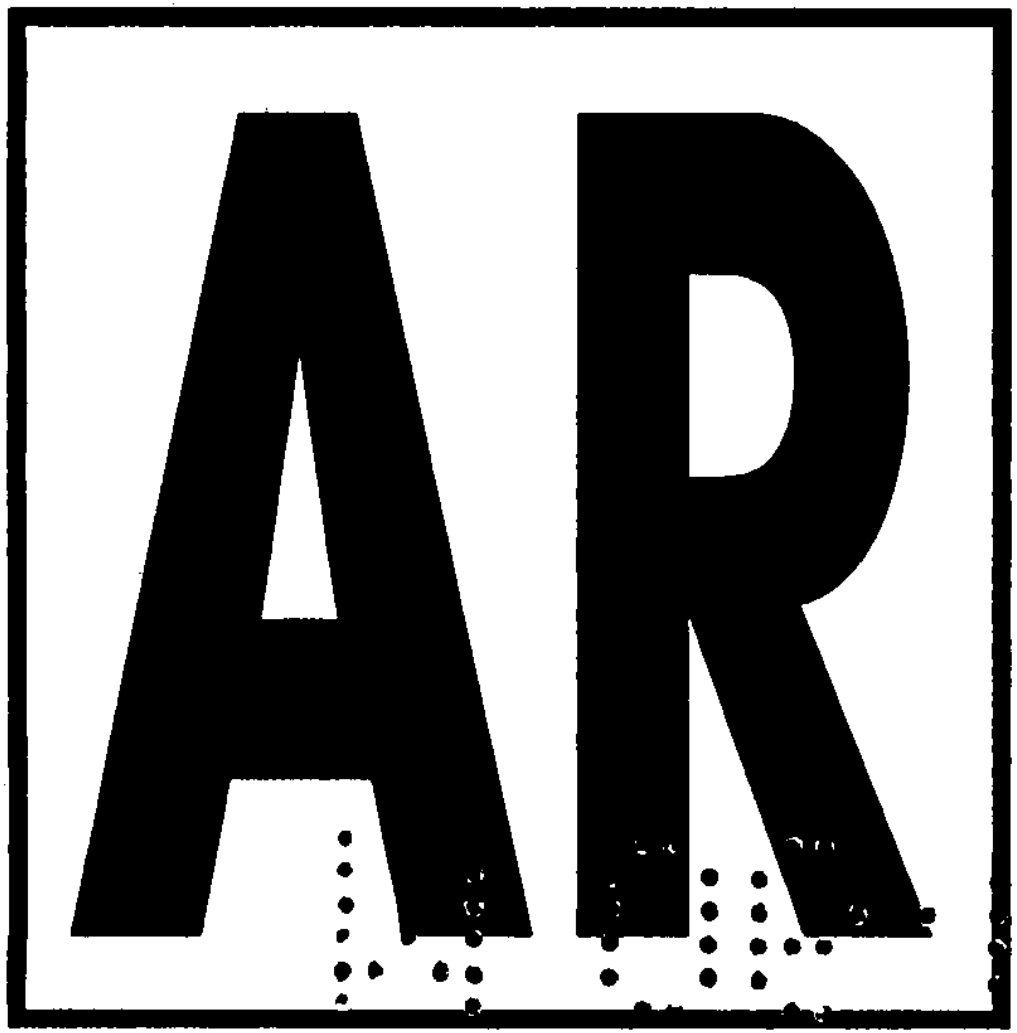

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*3 European Design Attorney

27 September 2011

Re.: **European Patent No.** **1768649**
Owner: **UCB Farchim S.A**
Opponent: **Zentiva k.s.**

Dear Sirs,

With reference to your Summons to attend oral proceedings pursuant to Rule 115(1)EPC, dated 3 August 2011, please be informed that we will use the English language during the proceedings and wish to get interpretation if the Opponent uses French or German.

Yours faithfully,
BORENIUS & Co Oy Ab

Jonna Sahlin
European Patent Attorney (09231490)

BORENIUS & Co Est 1928

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27 September 2011

Re.: **European Patent No. 1768649**
Owner: UCB Farchim S.A
Opponent: Zentiva k.s.

Dear Sirs,

I request you to record a change in the Representative in the above case. Please send all future correspondence to:

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Yours faithfully,
BORENIUS & Co Oy Ab

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Registration No. 09231490

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P30048-EPOP WB/SAN/lvo September 29, 2011

Opposition against Patent No. 1 768 649
(Application No: 05 758 582.0)
Proprietor: UCB Farchim S.A.
Opponent: Zentiva k.s.

This is in response to the summons to attend oral proceedings pursuant to Rule 115(1) EPC dated August 3, 2011:

I. REPRESENTATION

It is indicated herewith that we will represent patentee in the further course of the proceedings, and will attend the oral proceedings dated November 29, 2011 on his behalf.

II. LANGUAGE USED DURING THE ORAL PROCEEDINGS

We intend to use the English language during the oral proceedings.

No simultaneous interpretation is needed.

III. WRITTEN SUBMISSION IN PREPARATION OF THE ORAL PROCEEDINGS ON NOVEMBER 29, 2011

Since no further submission was filed by the opponent subsequent to the letter filed by patentee on October 13, 2010, we would like to note that, formally, the arguments submitted therein are fully maintained.

III.1 Auxiliary Requests/Amendments

The Opposition Division outlined that, although claim 1 of auxiliary request 1 seems to comply with Article 123(2) and (3) EPC, new claim 3 of auxiliary request 1 contravenes Rule 80 EPC. The amendment accordingly is not occasioned by a ground for opposition since claim 3 is a dependent claim. In order to overcome this objection, claim 3 of auxiliary request 1 has been deleted. Therefore, new auxiliary request 1 comprises 5 claims (attached to this letter).

The claims according to the second auxiliary request have not been objected to. Therefore, we assume that the claims according to the first and second auxiliary request are admissible and fulfil the requirements of Article 123(2) EPC.

Further, a third auxiliary request is submitted comprising minor amendments in relation to the second auxiliary request as previously submitted. Claim 1 of the third auxiliary request is directed to a liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are defined as being selected from methyl/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

The fact that the liquid pharmaceutical composition comprises levocetirizine and preservatives is self-explanatory and can be found throughout the patent text. Furthermore, [0019] clearly defines that

> *"best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight".*

From this passage, it becomes clear that the exclusive use of methyl parahydroxybenzoate and propyl parahydroxybenzoate as preservatives is disclosed in the application as filed. The amount selected in the range of 0.01 and 1.125 mg/ml, as disclosed in [0020], is directly related to the above sentence, therefore, giving a direct and unambiguous teaching for a pharmaceutical composition exclusively comprising methyl p-hydroxybenuoate / propyl p-hydroxybenzoate as preservatives in the amounts indicated in claim 1 of the third auxiliary request.

Further, a fourth auxiliary request is submitted based on the third auxiliary request but directed to a range of 0.1 and 1.125 mg/ml of methyl / propyl p-hydroxybenzoate. This amendment is based on [0019] and [0020] of the description as well. It is referred to T925/98 indicating that according to the established Case Law, in the case of a disclosure of both a general and a preferred range, a combination of the preferred disclosed narrower range and one of the part-ranges lying within the disclosed overall range on either side of the narrower range is unequivocally derivable from the original disclosure of the patent-in-suit and, thus supported by it (see further T02/81; T201/83 and many others). Therefore, the broader range of 0.01 and 1.125 mg/ml and the narrower range of 0.1 and 1 mg/ml for the parabenes inherently discloses also a range of from 0.1 to 1.125 mg/ml.

Therefore, the amendments meet the requirements of Article 123(2) EPC.

III.2 Novelty

The only novelty attack submitted by the opponent was based on the alleged prior use of products Zodac® GTT Oral Drops and Zodac® SIR Syrup which were launched in the Czech Republic on October 31, 2001 and on September 30, 2002 in Slovakia.

The product characteristics and patient information leaflet was attached as D5, D6, D7 and D8 whereas documents D9 and D10 showed the last revision of the summary of product characteristics.

As outlined in the submission of October 13, 2010, we would again like to point out that important details are missing in the line of arguments submitted along with the Notice of

Opposition as regards the alleged prior use. According to T6/86, T329/86 and T78/90, if an opponent wishes to rely upon the prior use as being part of the state of the art for the purpose of Article 54(2) EPC and as part of the legal and factual framework within the substantive examination of the opposition, the Notice of Opposition must indicate within the opposition period all the facts which make it possible to determine the date of prior use, what has been used and the circumstances relating to the prior use. According to T538/89, the main points of what was made available to the public, where, when, how and by whom have to be submitted during the opposition period. At least one point, i.e. what was made available, was not substantiated by the opponent during the opposition period.

As the Opposition Division correctly outlined, the actual concentration of parabenes in the product Zodac® GTT Oral Drops and Zodac® SIR Syrup launched in the Czech Republic and Slovakia in 2001 and 2002 which were commercially available before the priority date of the contested patent remains unknown.

Zodac® GTT and Zodac® SIR contained 1.35 mg/ml of methylparaben and 0.15 mg/ml of propylparaben each in the form of the renewed marketing authorization of January 2009. Opponent did not indicate which amount of both substances were provided in the Zodac® GTT and Zodac® SIR products launched in the Czech Republic and in Slovakia in October 2001 and September 2002. Therefore, the required facts were not submitted during the opposition period. As a precautional remark, even if the opponent now would submit further evidence regarding the precise composition of the Zodac® GTT and Zodac® SIR products launched in October 2001 and September 2002, this will not remedy the deficiencies of the argumentation provided in the Notice of Opposition since it was not filed during the opposition period.

Therefore, it is submitted that public prior use has not been shown by the opponent and, thus, the subject matter of claim 1 according to the main request as well as according to the first, second, third and fourth auxiliary request is clearly novel according to Article 54(1) and (2) EPC.

III.3 Lack of Inventive Step

The opponent has based the inventive step attack on documents D1 and D3.

The Opposition Division confirmed that D1, example 5, has to be seen as the closest prior art. Example 5 discloses an ophthalmic composition comprising 0.2 g methylparaben and 0.1 g propylparaben, i.e. an overall amount of para-hydroxybenzoates of 0.3 g.

As outlined by the Opposition Division, this is clearly more than "less than 1.5 mg/ml" as in the liquid pharmaceutical composition of claim 1 according to the main request.

However, the Opposition Division indicated that the broad range of "more than 0 and less than 1.5 mg/ml" does not seem to be supported by experimental evidence in the Examples (and will not result in a plausible effect). In more detail, the Examining Division outlined that, from the results of the examples, it is apparent that concentrations lower than 0.15 mg/ml have simply not been tested.

As a result of the alleged breadth of the claims, the Examining Division came to the conclusion that the technical problem has to be re-formulated as the provision of an alternative formulation to that of D1. The Opposition Division further outlined that lowering the concentrations of parabens in view of those disclosed in D1 would be straightforward for a skilled person since the negative effects of parabens (allergic reactions) are well-known and, thus, there would have been a motivation of the skilled person to simply reduce the concentration of parabens in order to avoid these negative side effects. However, we respectfully disagree.

Considering the tailored scope of the claims according to the auxiliary requests (in particular 4th auxiliary request) it is noted that the amounts of parabens disclosed therein are well covered by the experimental evidence given in the patent-in-suit. See e.g. examples 3 and 4 disclosing the use of a mixture of parabens (methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight) starting form 0.15 mg/ml to 0.375

mg/ml, 0.45 mg/ml, 0.75 mg/ml, and 0.125 mg/ml. This, for example, covers the range indicated in claim 1 according to the 4th auxiliary request well.

In view of the alleged motivation of the skilled person to *simply lower* the amounts of preservatives in order to avoid the toxicity, we would like to refer to the letter submitted on October 13, 2010. Special care has to be taken in the field of the production of pharmaceutical products in terms of product safety. Although potential side effects of preservatives are, of course, an issue for a skilled person, product safety usually will be the main topic which has to be addressed, in particular regarding microbial contaminations in liquid pharmaceutical preparations (such as ophthalmic formulations). For a skilled person, it is not a straightforward way to simply lower the amounts of preservatives in such a composition, since he/she has to expect that product safety is considerably affected, thus not leading to a safe, reliable and tradable product.

The Opposition Division's attention is again drawn to D3, table I, indicating that the minimum inhibitory concentration of methylparaben has to be more than 4 mg/ml since a well known and harmful pathogen (*Pseudomonas aeruginosa*) leading to harmful infections of the eye and even to blindness, requires a minimum inhibitory concentration of 4,000 µg/ml.

In the absence of any information which is related to the "self-preserving" effect of cetirizine/levocetirizine and efletirizine, a skilled person would not have any motivation to simply lower the amounts of preservatives indicated in D3.

Therefore, there is no reason to assume that a skilled person would have a motivation based on D1 and D3 to simply lower the amount of parabens in the pharmaceutical formulation and to arrive at the subject matter presently claimed.

Thus, the subject matter according to the main request and the first, second, third and fourth auxiliary request is based on an inventive step in the meaning of Article 56 EPC.

IV. REQUESTS

Therefore, it is still requested to reject the opposition and to maintain the present patent as granted or, as auxiliary requests, in the scope of the first, second, third or fourth auxiliary request.

Respectfully submitted,

Wolfgang Sandmann
European Patent Attorney

Enclosures:

Amended Auxiliary Request 1
Auxiliary Requests 3 and 4

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Deutschland

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Page 1 of 18

Our ref: B0199PI-EP

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*3 European Design Attorney

29 September 2011

Re.: **European Patent No. 1768649**
Owner: UCB Farchim S.A
Opponent: Zentiva k.s.

Dear Sirs,

With reference to your Summons to attend oral proceedings dated 3 August 2011 we hereby file our written submissions.

Procedual matters

During the oral proceedings the opponent will be represented by European Patent Attorneys Jonna Sahlin and Annika Hakkila.

Cited documents

D12 Johnston C.S. et al., "Vinegar: Medicinal Uses and Antiglycemic Effect", MedGenMed. 2006; 8(2): 61
D13 Ryssel H. et al., "The antimicrobial effect of acetic acid – An alternative to common local antiseptics?", Burns 35, (2009), pages 695-700
D14 Frech G. et al., "Sodium acetate as a preservative in protein hydrosylate solutions.", Am J Hosp Pharm. 36(12), (1979), abstract
D15 Juslin M. et al., farmasian teknologia, 6. edition 2001, FOY Fortis ry., page 450.

Novelty of the main and the auxiliary requests

The applicant disagrees with the preliminary opinion of the Opposition Division regarding the novelty of the claims over prior use.

Independently of whether the information on the amounts of parabens of ZODAC®GTT and ZODAC®SIR was published at the priority date of B1 or not, the compositions of the products were part of the state of the art after the launch of the products since the composition of the products could be analyzed without undue burden. This is confirmed by T406/86 and G1/92.

Inventive step of the main and the auxiliary requests

The patent proprietor agrees with the preliminary decision of the Opposition Division regarding lack of inventive step of the claims over the cited prior art publications.

The Opposition Division presents two references in view of which the invention lacks inventive step:

D1 EP 0 605 203 A2 (publ. 6 July 1994)
D3 KIBBE A.H., "Handbook of Pharmaceutical Excipients", 3. edition 2000, American Pharmaceutical Association, pages 340, 450.

The Opposition Division expresses that the problem to be solved by the opposed patent was to provide an improved formulation where the health drawbacks associated with use of parabens in case of hypersensitivity and the antimicrobial efficiency are balanced and optimized (page 3, point 7.2 of the communication accompanying the summons).

As stated by the Division (page 4, 2.paragraph) and in the Notice of Opposition (on page 6, 4. paragraph) it was general knowledge of the person skilled in the art to reduce the concentration of parabens in order to lower the risk of allergic reactions. The skilled person was therefore well motivated to take into account general knowledge represented by a handbook such as D3.

Contrary to the statement of the patent proprietor (page 5, 6. paragraph of their letter of 13 October 2010) D3 states that methylparaben can be used alone **or** in combination with other parabens. In D3 it is only said that mixtures of parabens are frequently used, but not that this is preferred or obligatory in any way. Therefore neither the statement of the proprietor regarding it being unclear how the table of section 7 of the chapter "Methylparaben" should be interpreted nor the reference to section 10 regarding the activity of methylparaben bring any new relevant information the skilled person would take into account when checking D3 for usual amounts of methylparabens (or propylparabens) employed in ophthalmic drops or oral solutions. The same applies to section 14 indicating the irritant potential of the parabens and which on the contrary discusses the widespread use of parabens, defines that parabens have been used also in ophthalmic preparations and states that reactions to parabens are relatively uncommon.

Moreover, based on these sections the use of combinations of methylparaben and propylparaben and also the certain ratio of methylparaben/propylparaben 9/1 expressed by weight of claim 1 of Auxiliary requests 1 and 2 is certainly obvious for the skilled person based on D3.

Therefore, since the concentration values of D3 overlap the range of concentrations defined in claim 1 of the Main request and also the ranges defined in claim 1 of Auxiliary requests 1 and 2 it is clear that these claims do not involve an inventive step.

Moreover, we completely agree with the first aspect brought forward by the Division for discussion during the oral proceedings, i.e. whether or not the problem as formulated above is in fact shown in the patent to be actually solved over the range of paraben concentrations "more than 0 and less than 1.5 mg/ml" defined in claim 1. Thereto in our opinion there is a serious doubt whether the problem as defined above can at all be solved with the invention according to claim 1.

In the examples 1 and 2 two traditional preservatives/antimicrobial agents, acetic acid and sodium acetate are used in the compositions without parabens. Examples 3 and 4 relate to the use of acetic acid and sodium acetate together with parabens. None of the examples actually support the claimed improved antimicrobial efficiency of only parabens alone combined with the active ingredients cetirizine, levocetirizine and efletirizine. Especially there is no support that cetirizine, levocetirizine and efletirizine alone have any antimicrobial effect (for example at the lowest concentration of parabens of claim 1). Thus it remains unclear whether the desired effect actually originates from the use of one or more of the antimicrobial agents not being parabens or from any of the other components of the compositions, especially taking into account the disclosures presented in D12 to D15.

D12 relates to vinegar, i.e. acetic acid and its use already by Hippocrates (c. 420 BC) medicinally to manage wounds. D13 also describes the use of acetic acid in medicine for more than 6000 years for disinfection of wounds and especially as an antiseptic agent in the treatment and prophylaxis of the plague. These clearly show that the antimicrobial effect of acetic acid was well known already many thousand years ago. D14 relates to the preservative use of sodium acetate. D15 is a text book relating to pharmaceutical technology, where chapter 26 relates to stability of drugs. Section 6 of this chapter relates to microbiological stability and in part 6.1 the decrease of microbe concentrations in medicinal products is discussed. According to the second paragraph of the right column on page 450 (translation from Finnish);

> *The efficiency of preservatives can be increased by choosing a suitable combination of agents. The most well-known is probably the simultaneous use of methyl parahydroxybenzoate and propyl parahydroxybenzoate. 0.01 % addition of EDTA made benzalconium chloride effective against Pyozyanus-strains resistant to quaternary ammonium compounds. The addition of propylene glycol, glycerol and sorbitol to aqueous solutions of drug substances enhances the effect of the preservative. Heat has been shown to fasten the spore killing effect of benzyl alcohol (Lingnau 1977).*

Based on the above extract many of the compounds, for example propylene glycol, glycerol and sorbitol, which are used in the compositions of the Examples of the patent, influence on the antimicrobial stability. The patentee has provided no information or explanations of these additional compounds. Thereto as explained above none of the examples actually show unambiguously that the active ingredients cetirizine, levocetirizine and efletirizine have any antimicrobial action.

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Conclusion

In our opinion the set of claims of the Main request as well as Auxiliary requests 1 and 2 do not fulfill the requirements of the European Patent Convention. We refer to our arguments presented above and further to our argumentation presented in the "Notice of Opposition" dated 23 June 2010.

Yours faithfully,
BORENIUS & Co Oy Ab

Jonna Sahlin
European Patent Attorney (09231490)

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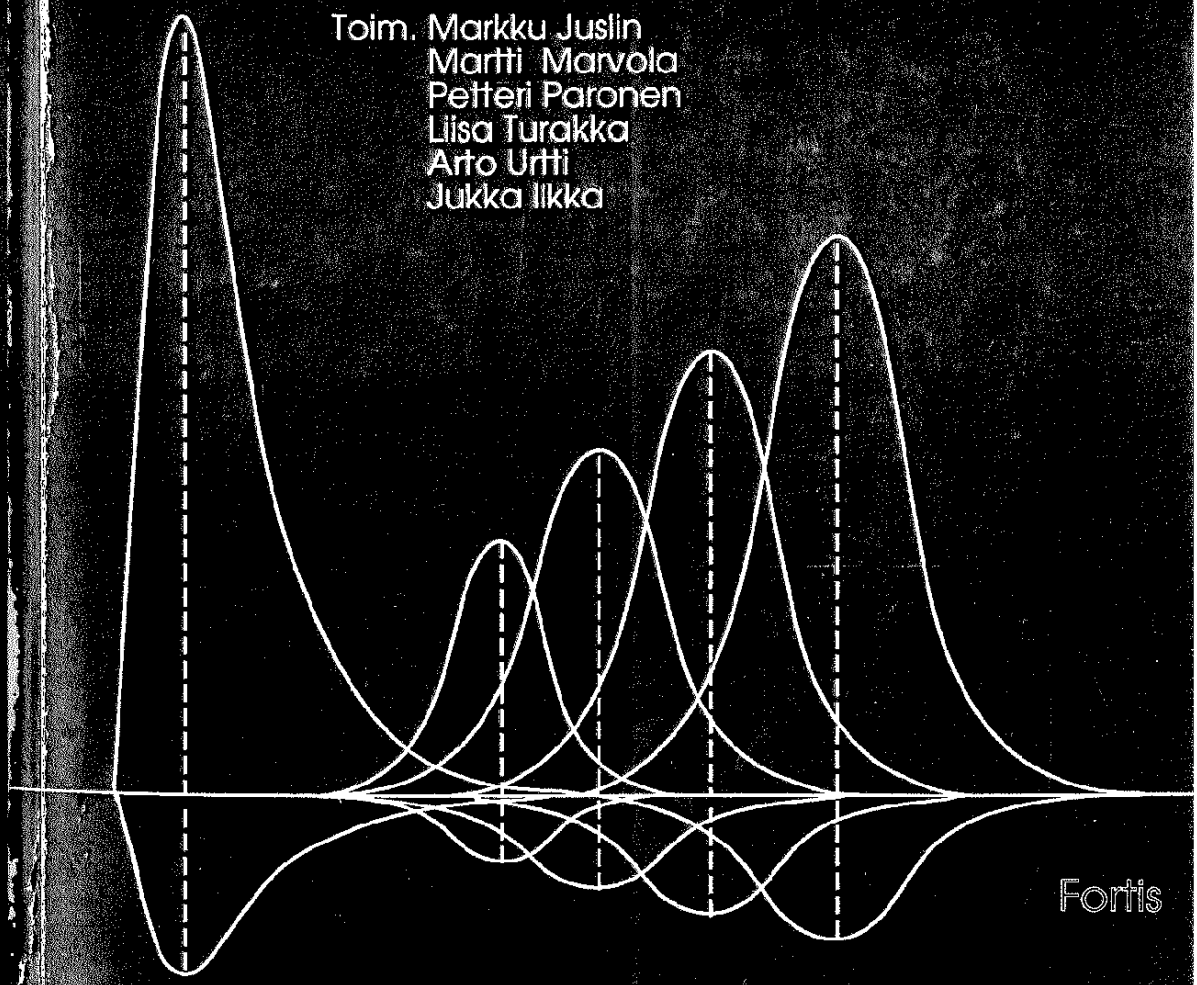

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antimikrobinen teho voi jäädä odotettua pienemmäksi. Reaktiot ovat riippuvaisia säilytysaineiden sähköisestä varauksesta ja lääkkeiden pH-arvosta. Ullmann (1977) on ryhmitellyt reaktiot lääke- ja apuaineiden kanssa sekä pakkausmateriaalien kanssa:

1) Kemialliset reaktiot, jotka perustuvat lääkeaineen ja säilytysaineen vastakkaisiin varauksiin, aineiden väkevyyksiin ja ionisoitumisasteeseen. Mm. kationiaktiiviset säilytysaineet bentsalkoniumkloridi ja klorheksidiini voivat reagoida anioniaktiivisten lääkeaineiden, tensidien ja makromolekyylien kanssa muodostaen suoloja. Säilytysaine saattaa saostua ja muuttua tehottomaksi.
2) Pinta-aktiivisten aineiden vaikutuksesta ja säilytysaineen lipofiilisen luonteen voimakkuudesta riippuen voi syntyä "vääriä misellejä", joissa säilytysaine on sidottu. Esim. polyetyleeniglykoli-400-stearaatti kerrostuu pieninä pitoisuuksina vesiliuoksessa rajapinnalle ilma/vesi. Kun kriittinen pitoisuus ylittyy, muodostuu lipofiilinen misellifaasi, johon huonosti veteen liukeneva säilytysaine voi solubilisoitua. Samalla aineen pitoisuus vedessä pienenee ja teho laskee. Ilmiön seurauksena on välttämätöntä nostaa säilytysaineen määrää. Myös kvaternääriset ammoniumyhdisteet menettävät osan tehostaan ionisoitumattomien tensidien vaikutuksesta. p-Hydroksibentsoaattien ja fenolien reaktioita pinta-aktiivisten aineiden kanssa on tutkittu (Kostenbauer 1962).
3) Ionisoituvat säilytysaineet, joilla on voimakas rajapinta-aktiviteetti, reagoivat liuenneiden ja liukenemattomien makromolekyylien rajapinnoilla lietteissä, emulsioissa ja hydrogeeleissä. Makromolekyylien kyky muodostaa komplekseja säilytysaineen kanssa saattaa pienentää säilytysaineen vesifaasipitoisuutta odotetun tehon kustannuksella. Makromolekyyleistä mainitaan karboksimetyyliselluloosa, metyyliselluloosa ja epäorgaaniset silikaatit. Näiden ja säilytysaineiden välisiä reaktioita on selitetty yksityiskohtaisesti (Ullmann 1971, Ullmann 1977).
4) Säilytysaineen vesi/öljy -jakautumiskerroin vaikuttaa emulsioissa, jos säilytysaine on lipofiilinen. Jakautuminen vesi- ja öljyfaasiin vähentää säilytysaineen pitoisuutta vedessä ja riittävän pitoisuuden saavuttamiseksi säilytysaineen määrää on tällaisessakin tapauksessa lisättävä.
5) Säilytysaineiden sorptio muoveihin on tunnettua. Mm. elohopeayhdisteet absorboituvat kumitulppiin. Sitoutumista polyeteeniin, polypropeeniin, polyvinyylikloridiin, polyamidiin ja selluloosa-asetaattiin pitkän varastointiajan kuluessa on tutkittu (Autian 1963). Reaktiomekanismit ovat monenlaisia. Säilytysaineiden ja muovin välillä on hydrofiilista ja hydrofobista vuorovaikutusta. Pinta-aktiivisten inverttisaippuoiden sorptio selluloosa-asetaattiin ja polyamidiin johtuu näiden kemiallisesta rakenteesta, hydrofiilisista funktioista ja näitä säilytysaineita aggregoivasta kyvystä. Esimerkkinä mainitaan setyylipyridiniumkloridi. Huomattavaa on, että säilytysaineet sitoutuvat useimpiin steriilisuodatuksessa käytettyihin suodatinmateriaaleihin (Ullmann 1971, Ullmann 1977).

Säilytysaineiden tehokkuutta voidaan nostaa valitsemalla sopiva ainekombinaatio. Tunnetuin lienee metyyli- ja propyyliparahydroksibentsoaatin samanaikainen käyttö. Bentsalkoniumkloridi saatiin tehoamaan kvaternaarisille ammoniumyhdisteille resistentteihin Pyozyanus-kantoihin 0,01 % EDTA-lisäyksen ansiosta. Propyleeniglykolin, glyserolin ja sorbitolin lisäys lääkeaineiden vesiliuoksiin tehostaa säilytysaineen vaikutustaa. Lämmön on havaittu nopeuttavan bentsyylialkoholin itiöitä tappavaa tehoa (Lingnau 1977).

Monissa yhteyksissä on korostettu säilytysaineiden olevan tehokkaita vain biologisesti aktiivisessa muodossa. Ne eivät saa olla pakkausmateriaaleihin tai apuaineisiin sitoutuneita. Siksi säilytysaineiden antimikrobinen teho erilaisissa lääke- ja apuaineyhdistelmissä on testattava tuotteita kehiteltäessä (Lingnau 1977). Koska myös säilytysaineet muuttuvat ulkoisten tekijöiden vaikutuksesta mm. hydrolyyttisesti ja hapettumalla, on mikrobisidisen tehon säilyminen varmistettava uusintatesteillä (Nürnberg 1977).

7 Toksikologinen säilyvyys

Sekä lääkeaineissa että apuaineissa voi olla epäpuhtauksia, jotka ovat peräisin synteesiin käytetyistä kemikaaleista tai säilytyk-

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Vinegar: Medicinal Uses and Antiglycemic Effect

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Abstract

Vinegar folklore is as colorful as it is practical. Legend states that a courtier in Babylonia (c. 5000 BC) "discovered" wine, formed from unattended grape juice, leading to the eventual discovery of vinegar and its use as a food preservative. Hippocrates (c. 420 BC) used vinegar medicinally to manage wounds. Hannibal of Carthage (c. 200 BC), the great military leader and strategist, used vinegar to dissolve boulders that blocked his army's path. Cleopatra (c. 50 BC) dissolved precious pearls in vinegar and offered her love potion to Anthony. Sung Tse, the 10th century creator of forensic medicine, advocated hand washing with sulfur and vinegar to avoid infection during autopsies. Based on the writings of US medical practitioners dating to the late 18th century, many ailments, from dropsy to poison ivy, croup, and stomachache, were treated with vinegar,[1] and, before the production and marketing of hypoglycemic agents, vinegar "teas" were commonly consumed by diabetics to help manage their chronic ailment. This review examines the scientific evidence for medicinal uses of vinegar, focusing particularly on the recent investigations supporting vinegar's role as an antiglycemic agent. Epidemiologic studies and clinical trials were identified by a MEDLINE title/abstract search with the following search terms: vinegar, glucose; vinegar, cancer; or vinegar, infection. All relevant randomized or case-control trials were included in this review.

Readers are encouraged to respond to George Lundberg, MD, Editor of *MedGenMed*, for the editor's eye only or for possible publication via email: glundberg@medscape.net

Vinegar Production

Vinegar, from the French *vin aigre*, meaning "sour wine," can be made from almost any fermentable carbohydrate source, including wine, molasses, dates, sorghum, apples, pears, grapes, berries, melons, coconut, honey, beer, maple syrup, potatoes, beets, malt, grains, and whey. Initially, yeasts ferment the natural food sugars to alcohol. Next, acetic acid bacteria (*Acetobacter*) convert the alcohol to acetic acid. Commercial vinegar is produced by either fast or slow fermentation processes. For the quick methods, the liquid is oxygenated by agitation and the bacteria culture is submerged permitting rapid fermentation. The slow methods are generally used for the production of the traditional wine vinegars, and the culture of acetic acid bacteria grows on the surface of the liquid and fermentation proceeds slowly over the course of weeks or months. The longer fermentation period allows for the accumulation of a nontoxic slime composed of yeast and acetic acid bacteria, known as the *mother* of vinegar. Vinegar eels (nematoda*Turbatrix aceti*) feed on these organisms and occur in naturally fermenting vinegar.[2] Most manufacturers filter and pasteurize their product before bottling to prevent these organisms from forming. After opening, *mother* may develop in stored vinegar; it is considered harmless and can be removed by filtering. Many people advocate retaining the *mother* for numerous, but unsubstantiated, health effects.

The chemical and organoleptic properties of vinegars are a function of the starting material and the fermentation method. Acetic acid, the volatile organic acid that identifies the product as vinegar, is responsible for the tart flavor and pungent, biting odor of vinegars. However, acetic acid should not be considered synonymous with vinegar. The US Food and Drug Administration (FDA) states that diluted acetic acid is not vinegar and should not be added to food products customarily expected to contain vinegar.[3] Other constituents of vinegar include vitamins, mineral salts, amino acids, polyphenolic compounds (eg, galic acid, catechin, caffeic acid, ferulic acid), and nonvolatile organic acids (eg, tartaric, citric, malic, lactic).[4,5]

In the United States, vinegar products must contain a minimum of 4% acidity.[6] European countries have regional standards for vinegar produced or sold in the area. White distilled vinegars are generally 4% to 7% acetic acid whereas cider and wine vinegars are 5% to 6% acetic acid. Specialty vinegars are grouped as herbal or fruit vinegars. Herbal vinegars consist of wine vinegars or white distilled vinegars, which may be seasoned with garlic, basil, tarragon, cinnamon, clove, or nutmeg. Fruit vinegars are wine and white vinegars sweetened with fruit or fruit juice to produce a characteristic sweet-sour taste. Traditional vinegars are produced from regional foods according to well-established customs. The balsamic vinegar of Modena, Italy, is made from the local white Trebbiano grapes, which are harvested as late as possible, fermented slowly, and concentrated by aging in casks of various woods. Traditional rice wine vinegars are produced in Asia, coconut and cane vinegars are common in India and the Philippines, and date vinegars are popular in the Middle East.

Medicinal Uses of Vinegar

Anti-infective Properties

The use of vinegar to fight infections and other acute conditions dates back to Hippocrates (460-377 BC; the father of modern medicine), who recommended a vinegar preparation for cleaning ulcerations and for the treatment of sores. Oxymel, a popular ancient medicine composed of honey and vinegar, was prescribed for persistent coughs by Hippocrates and his contemporaries, and by physicians up to modern day.[7] The formulation of oxymel was detailed in the *British Pharmacopoeia* (1898) and the *German Pharmacopoeia* (1872), and, according to the *French Codex* (1898), the medicine was prepared by mixing virgin honey, 4 parts, with white wine vinegar, 1 part, concentrating and clarifying with paper pulp.[8]

Recent scientific investigations clearly demonstrate the antimicrobial properties of vinegar, but mainly in the context of food preparation.[9–12] Experts advise against using vinegar preparations for treating wounds.[13] At concentrations nontoxic to fibroblasts and keratinocytes (≤ 0.0025%), acetic acid solutions were ineffective at inhibiting the growth of *Escherichia coli*, group D *Enterococcus*, or *Bacteroides fragilis* bacteria, and only slightly effective at inhibiting the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria.[13] Similarly, experts caution against using vinegar as a household disinfectant against human pathogens because chemical disinfectants are more effective.[14,15] However, undiluted vinegar may be used effectively for cleaning dentures, and, unlike bleach solutions, vinegar residues left on dentures were not associated with mucosal damage.[16]

Although investigations have demonstrated the effectiveness of diluted vinegar (2% acetic acid solution at pH 2) for the treatment of ear infections (otitis externa, otitis media, and granular myringitis),[17,18] the low pH of these solutions may irritate inflamed skin and damage cochlear outer hair cells.[19] Immediate vinegar application at the site of jellyfish stings is practiced at various coastal locations around the world[20,21] because vinegar deactivates the nematocysts. However, hot-water immersion is considered the most efficacious initial treatment for jellyfish envenomation because the venom is deactivated by heat.[22,23]

In the popular media, vinegar is commonly recommended for treating nail fungus, head lice, and warts, yet scientific support for these treatment strategies is lacking. Takano-Lee and colleagues[24] demonstrated that, of 7 home remedies tested, vinegar was the least effective for eliminating lice or inhibiting the hatching of eggs. Scattered reports suggest that the successive topical application of highly concentrated acetic acid solutions (up to 99%) alleviated warts,[25,26] presumably due to the mechanical destruction of wart tissue. One treatment protocol, however, required local anesthesia, excision, and rapid neutralization at the site of application, thus limiting its use by the lay public.

Although not a treatment modality, vinegar washes are used by midwives in remote, poorly resourced locations (eg, Zimbabwe and the Amazon jungle) to screen women for the human papilloma virus infection.[27,28] Contact with acetic acid causes visual alterations of the viral lesions permitting rapid detection of infection with 77% sensitivity[29] and the option of immediate treatment with cryotherapy.

Cardiovascular Effects

Kondo and colleagues[30] reported a significant reduction in systolic blood pressure (approximately 20 mm Hg) in spontaneously hypertensive (SHR) rats fed a standard laboratory diet mixed with either vinegar or an acetic acid solution (approximately 0.86 mmol acetic acid/day for 6 weeks) as compared with SHR rats fed the same diet mixed with deionized water. These observed reductions in systolic blood pressure were associated with reductions in both plasma renin activity and plasma aldosterone concentrations (35% to 40% and 15% to 25% reductions in renin activity and aldosterone concentrations, respectively, in the experimental vs control SHR rats). Others have reported that vinegar administration (approximately 0.57 mmol acetic acid, orally) inhibited the renin-angiotensin system in nonhypertensive Sprague-Dawley rats.[31]

Trials investigating the effects of vinegar ingestion on the renin-angiotensin system have not been conducted in humans, and there is no scientific evidence that vinegar ingestion alters blood pressure in humans. In their report, Kondo and colleagues[30] speculated that dietary acetic acid promoted calcium absorption and thereby downregulated the renin-angiotensin system.[32] In the rat model, acetic acid administration enhanced calcium absorption and retention[33]; moreover, in humans, calcium absorption in the distal colon was enhanced by acetate.[34] Clearly, much work is needed to establish whether vinegar ingestion alters calcium absorption and/or blood pressure regulation in humans.

Whether chronic vinegar ingestion affects other risk factors for cardiovascular disease in humans is not known. Hu and colleagues[35] reported a significantly lower risk for fatal ischemic heart disease among participants in the Nurses' Health Study who consumed oil-and-vinegar salad dressings frequently (5-6 times or more per week) compared with those who rarely consumed them (multivariate RR: 0.46; CI: 0.27-0.76, *P* for trend = .001). Frequent consumption of mayonnaise or other creamy salad dressings was not significantly associated with risk for ischemic heart disease in this population (multivariate RR: 0.84; CI: 0.50-1.44, *P* for trend = .44). The study authors contend that because oil and vinegar dressings are a major dietary source of dietary alpha-linolenic acid, an antiarrhythmic agent, alpha-linolenic acid may potentially be the beneficial ingredient of this food.[35] Yet, creamy, mayonnaise-based salad dressings are also rich in alpha-linolenic acid and did not show the same risk benefit as the oil and vinegar dressings.

Antitumor Activity

In vitro, sugar cane vinegar (Kibizu) induced apoptosis in human leukemia cells,[36] and a traditional Japanese rice vinegar (Kurosu) inhibited the proliferation of human cancer cells in a dose-dependent manner.[37] An ethyl acetate extract of Kurosu added to drinking water (0.05% to 0.1% w/v) significantly inhibited the incidence (−60%) and multiplicity (−50%) of azoxymethane-induced colon carcinogenesis in male F344 rats when compared with the same markers in control animals.[38] In a separate trial, mice fed a rice-shochu vinegar-fortified feed (0.3% to 1.5% w/w) or control diet were inoculated with sarcoma 180 (group 1) or colon 38 (group 2) tumor cells (2×10^6 cells subcutaneously).[39] At 40 days post-inoculation, vinegar-fed mice in both experimental groups had significantly smaller tumor volumes when compared with their control counterparts. A prolonged life span due to tumor regression was also noted in the mice ingesting rice-shochu vinegar as compared with controls, and in vitro, the rice-shochu vinegar stimulated natural killer cell cytotoxic activity.[39]

The antitumor factors in vinegar have not been identified. In the human colonic adenocarcinoma cell line Caco-2, acetate treatment, as well as treatment with the other short-chain fatty acids (SCFA) n-butyrate and propionate, significantly prolonged cell doubling time, promoted cell differentiation, and inhibited cell motility.[40] Because bacterial fermentation of dietary fiber in the colon yields the SCFA, the investigators concluded that the antineoplastic effects of dietary fiber may relate in part to the formation of SCFA. Others have also documented

the antineoplastic effects of the SCFA in the colon, particularly n-butyrate.[41] Thus, because acetic acid in vinegar deprotonates in the stomach to form acetate ions, it may possess antitumor effects.

Vinegars are also a dietary source of polyphenols,[6] compounds synthesized by plants to defend against oxidative stress. Ingestion of polyphenols in humans enhances in vivo antioxidant protection and reduces cancer risk.[42] Kurosu vinegar is particularly rich in phenolic compounds, and the in-vitro antioxidant activity of an ethyl acetate extract of Kurosu vinegar was similar to the antioxidant activity of alpha-tocopherol (vitamin E) and significantly greater than the antioxidant activities of other vinegar extracts, including wine and apple vinegars.[43] Kurosu vinegar extracts also suppressed lipid peroxidation in mice treated topically with H_2O_2-generating chemicals.[43] Currently, much interest surrounds the role of dietary polyphenols, particularly from fruits, vegetables, wine, coffee, and chocolate, in the prevention of cancers as well as other conditions including cardiovascular disease[44]; perhaps vinegar can be added to this list of foods and its consumption evaluated for disease risk.

Epidemiologic data, however, is scarce and unequivocal. A case-control study conducted in Linzhou, China, demonstrated that vinegar ingestion was associated with a decreased risk for esophageal cancer (OR: 0.37).[45] However, vinegar ingestion was associated with a 4.4-fold greater risk for bladder cancer in a case-control investigation in Serbia.[46]

Blood Glucose Control

The antiglycemic effect of vinegar was first reported by Ebihara and Nakajima[47] in 1988. In rats, the blood glucose response to a 10% corn starch load was significantly reduced when coadministered with a 2% acetic acid solution.[45] In healthy human subjects, although the glucose response curve was not significantly altered, the area under the insulin response curve following the ingestion of 50 g sucrose was reduced 20% when coadministered with 60 mL strawberry vinegar.[47] Several years later, Brighenti and colleagues[48] demonstrated in normoglycemic subjects that 20 mL white vinegar (5% acetic acid) as a salad dressing ingredient reduced the glycemic response to a mixed meal (lettuce salad and white bread containing 50 g carbohydrate) by over 30% ($P < .05$). Salad dressings made from neutralized vinegar, formulated by adding 1.5 g sodium bicarbonate to 20 mL white vinegar, or a salt solution (1.5 g sodium chloride in 20 mL water) did not significantly affect the glycemic response to the mixed meal.[48] Separate placebo-controlled trials have corroborated the meal-time, antiglycemic effects of 20 g vinegar in healthy adults.[49–51]

While compiling a glycemic index (GI) table for 32 common Japanese foods, Sugiyama and colleagues[52] documented that the addition of vinegar or pickled foods to rice (eg, sushi) decreased the GI of rice by 20% to 35%. In these trials, healthy fasted subjects ingested the reference and test foods, each containing 50 g carbohydrate, on random days, and the food GI was calculated using the areas under the 2-hour blood glucose response curves. In the vinegar-containing foods, the amount of acetic acid was estimated to be 0.3-2.3 g, an amount similar to that found in 20 g vinegar (approximately 1 g). Ostman and colleagues[53] reported that substitution of a pickled cucumber (1.6 g acetic acid) for a fresh cucumber (0 g acetic acid) in a test meal (bread, butter, and yogurt) reduced meal GI by over 30%[53] in healthy subjects.

Recently, the antiglycemic property of vinegar was demonstrated to extend to individuals with marked insulin resistance or type 2 diabetes.[54] In this crossover trial, individuals with insulin resistance (n = 11, fasting insulin concentrations greater than 20 mU/mL) or with diagnosed type 2 diabetes (n = 10) consumed a vinegar test drink (20 g vinegar, 40 g water, 1 tsp saccharine) or placebo immediately before the consumption of a mixed meal (87 g total carbohydrate). In the insulin-resistant subjects, vinegar ingestion reduced postprandial glycemia 64% as compared with placebo values ($P = .014$) and improved postprandial insulin sensitivity by 34% ($P = .01$). In individuals with type 2 diabetes, vinegar ingestion was less effective at reducing mealtime glycemia (−17%, $P = .149$); however, vinegar ingestion was associated with a slight improvement in postprandial insulin sensitivity in these subjects (+19%, $P = .07$).[54] The lack of a significant effect of vinegar on mealtime glycemia in the type 2 diabetics may be related to the use of venous blood sampling in this trial. Greater within-subject variation in glucose concentrations are noted for venous blood as compared with capillary blood; moreover, the concentration

of glucose in venous blood is lower than that in capillary blood. Thus, capillary blood sampling is preferred for determining the glycemic response to food.[55]

The marked antiglycemic effect of vinegar in insulin-resistant subjects is noteworthy and may have important implications. Multicenter trials have demonstrated that treatment with antiglycemic pharmaceuticals (metformin or acarbose) slowed the progression to diabetes in high-risk individuals[56,57]; moreover, because these drugs improved insulin sensitivity, the probability that individuals with impaired glucose tolerance would revert to a normal, glucose-tolerant state over time was increased.[57]

In healthy subjects, Ostman and colleagues[58] demonstrated that acetic acid had a dose-response effect on postprandial glycemia and insulinemia. Subjects consumed white bread (50 g carbohydrate) alone or with 3 portions of vinegar containing 1.1, 1.4, or 1.7 g acetic acid. At 30 minutes post-meal, blood glucose concentrations were significantly reduced by all concentrations of acetic acid as compared with the control value, and a negative linear relationship was calculated between blood glucose concentrations and the acetic acid content of the meal ($r = -0.47$, $P = .001$). Subjects were also asked to rate feelings of hunger/satiety on a scale ranging from extreme hunger (−10) to extreme satiety (+10) before meal consumption and at 15-minute intervals after the meal. Bread consumption alone scored the lowest rating of satiety (calculated as area under the curve from time 0-120 minutes). Feelings of satiety increased when vinegar was ingested with the bread, and a linear relationship was observed between satiety and the acetic acid content of the test meals ($r = 0.41$, $P = .004$).[58]

In a separate trial, healthy adult women consumed fewer total calories on days that vinegar was ingested at the morning meal.[50] In this trial, which used a blinded, randomized, placebo-controlled, crossover design, fasting participants consumed a test drink (placebo or vinegar) followed by the test meal composed of a buttered bagel and orange juice (87 g carbohydrate). Blood samples were collected for 1 hour after the meal. At the end of testing, participants were allowed to follow their normal activities and eating patterns the remainder of the day, but they were instructed to record food and beverage consumption until bedtime. Vinegar ingestion, as compared with placebo, reduced the 60-minute glucose response to the test meal (−54%, $P < .05$) and weakly affected later energy consumption (−200 kilocalories, $P = .111$). Regression analyses indicated that 60-minute glucose responses to test meals explained 11% to 16% of the variance in later energy consumption ($P < .05$).[50] Thus, vinegar may affect satiety by reducing the meal-time glycemic load. Of 20 studies published between 1977 and 1999, 16 demonstrated that low-glycemic index foods promoted postmeal satiety and/or reduced subsequent hunger.[59]

It is not known how vinegar alters meal-induced glycemia, but several mechanisms have been proposed. Ogawa and colleagues examined the effects of acetic acid and other organic acids on disaccharidase activity in Caco-2 cells.[60] Acetic acid (5 mmol/L) suppressed sucrase, lactase, and maltase activities in concentration- and time-dependent manners as compared with control values, but the other organic acids (eg, citric, succinic, L-maric, and L-lactic acids) did not suppress enzyme activities. Because acetic acid treatment did not affect the de-novo synthesis of the sucrase-isomaltase complex at either the transcriptional or translational levels, the investigators concluded that the suppressive effect of acetic acid likely occurs during the posttranslational processing of the enzyme complex.[60] Of note, the lay literature has long proclaimed that vinegar interferes with starch digestion and should be avoided at meal times.[61]

Several investigations examined whether delayed gastric emptying contributed to the antiglycemic effect of vinegar. Using noninvasive ultrasonography, Brighenti and colleagues[50] did not observe a difference in gastric emptying rates in healthy subjects consuming bread (50 g carbohydrate) in association with acetic acid (ie, vinegar) vs sodium acetate (ie, vinegar neutralized by the addition of sodium bicarbonate); however, a significant difference in post-meal glycemia was noted between treatments with the acetic acid treatment lowering glycemia by 31.4%. In a later study, Liljeberg and Bjorck[62] added paracetamol to the bread test meal to permit indirect measurement of the gastric emptying rate. Compared with reference values, postmeal serum glucose and paracetamol concentrations were reduced significantly when the test meal was consumed with vinegar. The results of this study should be carefully considered, however, because paracetamol levels in blood may be affected by food factors and other gastrointestinal events. In rats fed experimental diets containing the indigestible

marker polyethylenglycol and varying concentrations of acetic acid (0, 4, 8, 16 g acetic acid/100 g diet), dietary acetic acid did not alter gastric emptying, the rate of food intake, or glucose absorption.[63]

Safety of Vinegar

Vinegar's use as a condiment and food ingredient spans thousands of years, and perhaps its use can be labeled safe by default. Yet there are rare reports in the literature regarding adverse reactions to vinegar ingestion. Inflammation of the oropharynx and second-degree caustic injury of the esophagus and cardia were observed in a 39-year-old woman who drank 1 tablespoon of rice vinegar in the belief it would dislodge a piece of crab shell from her throat.[64] (The use of vinegar in these situations is a popular Chinese folk remedy.) Her symptoms resolved spontaneously after several days. Esophageal injury by vinegar is likely very rare but deserves notice. Chronic inflammation of the esophagus is a cancer risk; but, as reported previously,[45] vinegar use was inversely related to risk for cancer of the esophagus.

The unintentional aspiration of vinegar has been associated with laryngospasm and subsequent vasovagal syncope that resolved spontaneously.[65] Hypokalemia was observed in a 28-year-old woman who had reportedly consumed approximately 250 mL apple cider vinegar daily for 6 years.[66] Although speculative, the hypokalemia was attributed to elevated potassium excretion related to the bicarbonate load from acetate metabolism.

These complications attributed to vinegar ingestion are isolated occurrences, but with the increased interest in vinegar as adjunct therapy in diabetes, carefully controlled trials to examine potential adverse effects of regular vinegar ingestion are warranted.

Summary

For more than 2000 years, vinegar has been used to flavor and preserve foods, heal wounds, fight infections, clean surfaces, and manage diabetes. Although vinegar is highly valued as a culinary agent, some varieties costing $100 per bottle, much scrutiny surrounds its medicinal use. Scientific investigations do not support the use of vinegar as an anti-infective agent, either topically or orally. Evidence linking vinegar use to reduced risk for hypertension and cancer is equivocal. However, many recent scientific investigations have documented that vinegar ingestion reduces the glucose response to a carbohydrate load in healthy adults and in individuals with diabetes. There is also some evidence that vinegar ingestion increases short-term satiety. Future investigations are needed to delineate the mechanism by which vinegar alters postprandial glycemia and to determine whether regular vinegar ingestion favorably influences glycemic control as indicated by reductions in hemoglobin A1c. Vinegar is widely available; it is affordable; and, as a remedy, it is appealing. But whether vinegar is a useful adjunct therapy for individuals with diabetes or prediabetes has yet to be determined.

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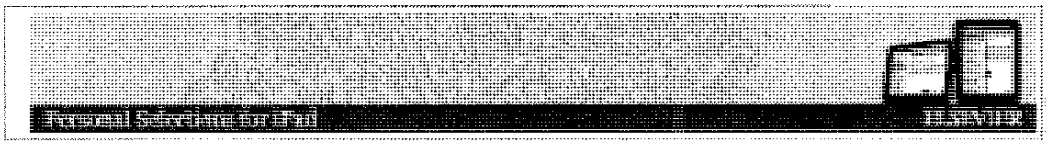

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The antimicrobial effect of acetic acid—An alternative to common local antiseptics?

H. Ryssel, O. Kloeters, G. Germann, Th. Schäfer, G. Wedemann, M. Oehlbauer

Accepted 17 November 2008.

Abstract Full Text PDF Images References

Abstract

Acetic acid has been commonly used in medicine for more than 6000 years for the disinfection of wounds and especially as an antiseptic agent in the treatment and prophylaxis of the plague. The main goal of this study was to prove the suitability of acetic acid, in low concentration of 3%, as a local antiseptic agent, especially for use in salvage procedures in problematic infections caused by organisms such as *Proteus vulgaris*, *Acinetobacter baumannii* or *Pseudomonas aeruginosa*.

This study was designed to compare the *in vitro* antimicrobial effect of acetic acid with those of common local antiseptics such as povidone–iodine 11% (Betaisodona®), polyhexanide 0.04% (Lavasept®), mafenide 5% and chlorhexidine gluconate 1.5% cetrimide 15% (Hibicet®). Former studies suggest the bactericidal effect of acetic acid, but these data are very heterogeneous; therefore, a standardised *in vitro* study was conducted.

To cover the typical bacterial spectrum of a burn unit, the following Gram-negative and Gram-positive bacterial strains were tested: *Escherichia coli*, *P. vulgaris*, *P. aeruginosa*, *A. baumannii*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *methicillin-resistant Staphylococcus aureus* (MRSA) and β-haemolytic *Streptococcus* group A and B.

The tests showed excellent bactericidal effect of acetic acid, particularly with problematic Gram-negative bacteria such as *P. vulgaris*, *P. aeruginosa* and *A. baumannii*. The microbiological spectrum of acetic acid is wide, even when tested at a low concentration of 3%. In comparison to our currently used antiseptic solutions, it showed similar – in some bacteria, even better – bactericidal properties. An evaluation of the clinical value of topical application of acetic acid is currently underway. It can be concluded that acetic acid in a concentration of 3% has excellent bactericidal effect and, therefore, seems to be suitable as a local antiseptic agent, but further clinical studies are necessary.

Keywords: Acetic acid, Antimicrobial power, Bacteria, Burns, Topical antiseptics

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Sodium acetate as a preservative in protein hydrolysate solutions.

Frech G, Allen LV Jr, Stiles ML, Levinson RS.

Abstract

The inhibitory effect of sodium acetate on microorganism growth in protein hydrolysate solutions was studied. Solutions of 5% protein hydrolysate and 5% dextrose in water (seven parts) and 50% dextose in water (three parts) containing 0, 30, 50 and 90 mEq/liter of sodium acetate were inoculated with Staphylococcus aureus, Escherichia coli, Candida albicans and Pseudomonas aeruginosa. The number of colony-forming units in the solutions after inoculation was compared with that after incubation for 24 hours at 37 C. Sodium acetate inhibited growth of S aureus and E coli. Growth of P aeruginosa was inhibited in protein hydrolysate solutions with and without sodium acetate; inhibition could not be attributed solely to sodium acetate and may have been releated to pH of the solutions (4.7 to 5.4). Growth of C albicans was not inhibited by sodium acetate. Sodium acetate reduced growth of some common contaminants of protein hydrolysates. Sodium acetate is known to reduce metabolic acidosis, a reported complication of parenteral nutrient therapy and a possible predisposing factor in C albicans sepsis. Addition of sodium acetate to protein hydrolysate solutions should be considered seriously.

PMID:118672[PubMed - indexed for MEDLINE]

MeSH Terms, Substances

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Submission in opposition proceedings

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- representing the proprietor(s):	UCB FARCHIM S.A.
Proprietor/representative's reference	P30048-EPOP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1768649
Application No.	EP05758582.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	23 September 2009
Title of the invention	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES
Proprietor of the patent	UCB FARCHIM S.A.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Reply of the patent proprietor to the notice(s) of opposition	P30048-EPOP Wrtten Submission.pdf	OBSO3.pdf
2	Auxiliary request in opposition	P30048-EPOP 1st Auxiliary Request clean.pdf	AUXREQ-1.pdf
3	Auxiliary request in opposition	P30048-EPOP 1st Auxiliary Request marked-up.pdf	AUXREQ-2.pdf
4	Auxiliary request in opposition	P30048-EPOP 3rd Auxiliary Request clean.pdf	AUXREQ-3.pdf

5	Auxiliary request in opposition	P30048-EPOP 3rd Auxiliary Request marked-up.pdf	AUXREQ-4.pdf
6	Auxiliary request in opposition	P30048-EPOP 4th Auxiliary Request clean.pdf	AUXREQ-5.pdf
7	Auxiliary request in opposition	P30048-EPOP 4th Auxiliary Request marked-up.pdf	AUXREQ-6.pdf

Signatures

Place:	**Munich**
Date:	**29 September 2011**
Signed by:	**DE, Reinhard Skuhra Weise & Partner GbR, W. Sandmann 12098**
Capacity:	**(Representative)**

3rd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

1st Auxiliary Request **27.9.2011**

CLAIMS:

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, 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.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

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

4. A liquid pharmaceutical composition according to any of the claims 1 or 2, characterized in that the active substance is levocetirizine.

5. 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 and ear drops.

4th Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.1 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

1st Auxiliary Request **27.9.2011**

CLAIMS:

1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, 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.~~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, the preservative being 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.~~

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 preservatives is a mixture of methyl parahydroxybenzoateand propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.~~

~~3~~4. ~~A liquid pharmaceutical composition according to claim 1 or 2, characterized in that the amount of p hydroxybenzoate esters (methyl p hydroxybenzoate / propyl p hydroxybenzoate in a ratio of 9/1 expressed in weight) is selected in the range of 0.01 and 1.125 mg/ml of the composition~~ ~~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.~~

3~~4~~5. A liquid pharmaceutical composition according to any of the preceding claims, characterized in that the active substance is cetirizine.

456. A liquid pharmaceutical composition according to any of the claims 1 ~~or~~to 2~~3~~4, characterized in that the active substance is levocetirizine.

567. 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 and ear drops.

4th Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from~~the pharmaceutical composition contains~~ methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.~~0~~1 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

3rd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from~~the pharmaceutical composition contains~~ methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

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Acknowledgement of receipt

We hereby acknowledge receipt of the following submission by the proprietor:

Submission number	1347564
Application number	EP05758582.0
Patent number	EP1768649
Date of receipt	29 September 2011
Your reference	P30048-EPOP
Proprietor	UCB FARCHIM S.A.
Title	PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Documents submitted	
package-data.xml	ep-opposition-data.xml
ep-oppo.pdf (2 p.)	OBSO3.pdf\P30048-EPOP Wrtten Submission.pdf (7 p.)
AUXREQ-1.pdf\P30048-EPOP 1st Auxiliary Request clean.pdf (1 p.)	AUXREQ-2.pdf\P30048-EPOP 1st Auxiliary Request marked-up.pdf (2 p.)
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Submitted by	CN=W. Sandmann 12098,O=Reinhard Skuhra Weise & Partner GbR,C=DE
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Correction by the EPO of errors in debit instructions filed by eOLF

Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

Communication of amended entries in the Register of European Patents

It is confirmed that, according to the request dated 27.09.11

1. ☐ the name
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   ☐ of the (co-)applicant / patentee,
   ☐ of the opponent

   as from , has/have been amended as follows:

2. ☒ the appointment of a representative
   ☐ the authorisation
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17.80.EP (WO)	05758582.0 - 2112 / 1768649
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BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☒ ORAL PROCEEDINGS on 29.11.11

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent 01 of 27.09.11 (telecopy)
- ☒ Copy (copies) EPO Form 2575 dated 30.09.11

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

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Date
05-10-2011

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☒ ORAL PROCEEDINGS on 29.11.11

Enclosure(s):
- ☒ Letter from the proprietor of the patent of 29.09.11
- ☐ Letter from the opponent of
- ☐ Copy (copies)

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

☐

For the Opposition Division

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☐ **Registered letter**

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Fax +49 (0)89 2399 - 4465

Reinhard - Skuhra - Weise & Partner GbR
Patent- und Rechtsanwälte
Friedrichstrasse 31
80801 München
ALLEMAGNE

For any questions about this communication:
Tel.:+31 (0)70 340 45 00

Date
06.10.11

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 2112 / 1768649

Applicant/Proprietor
UCB FARCHIM S.A.

Communication of amended entries concerning the representative (R. 143(1)(h) EPC)

As requested, for the above-mentioned European patent application / European patent the entries concerning the representative have been amended as follows:

Reinhard - Skuhra - Weise & Partner GbR
Patent- und Rechtsanwälte
Friedrichstrasse 31
80801 München
DE

The amendment will be recorded in the Register of European Patents.

For the Opposition Division

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Client Data Registration
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European Patent Office
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Lechien, Monique
UCB, S.A.,
Intellectual Property Department
Allée de la Recherche 60
1070 Brussel
BELGIQUE

Formalities Officer
Name: Kiendl, Werner
Tel.: 8777
or call:
+31 (0)70 340 45 00

Date: 06-10-2011

Reference	Application No./Patent No.
17.80.EP (WO)	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

Communication pursuant to Article 1(2) of the decision of the President of the EPO dated 12.07.2007 concerning the filing of authorisations (Special edition No. 3, OJ EPO 2007, L.1.)

Concerning the above-mentioned European patent application/patent the EPO has been notified of the appointment of a new representative for the

☒ applicant.

☐ proprietor of the patent.

☐ opponent

☒ A copy of the authorisation/the letter of the new representative is enclosed.

☐ The new representative

has referred to his general authorisation No. .

Subsequent proceedings will be conducted with the new representative

Important note to the users of the automatic debiting procedure (AAD)

Attention is drawn to points 14(d) and (13) AAD.
In case of withdrawal from representation, the automatic debiting procedure does not automatically ceases to be effective. It only ceases to be effective on the day on which notification is received of the representative's withdrawal and of his revocation of the automatic debit order. Thus, should you wish to also revoke automatic debit orders being made from your deposit account in relation to the present patent application, you are required to inform the EPO accordingly.

For the Opposition Division

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Sahlin, Jonna Elisabeth
BORENIUS & Co Oy Ab
Itämerenkatu 5
00180 Helsinki
FINLANDE

Formalities Officer
Name: Kiendl, Werner
Tel.: 8777
or call:
+31 (0)70 340 45 00

Date: 06-10-2011

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy (copies) EPO Form 2548

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

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Reinhard - Skuhra - Weise & Partner GbR
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ALLEMAGNE

For any questions about this communication:
Tel.:+31 (0)70 340 45 00

Date
06.10.11

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 2112 / 1768649

Applicant/Proprietor
UCB FARCHIM S.A.

Communication of amended entries concerning the representative (R. 143(1)(h) EPC)

As requested, for the above-mentioned European patent application / European patent the entries concerning the representative have been amended as follows:

Reinhard - Skuhra - Weise & Partner GbR
Patent- und Rechtsanwälte
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DE

The amendment will be recorded in the Register of European Patents.

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Date: 07-10-2011

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 2112 / 1768649

Applicant/Proprietor: UCB FARCHIM S.A.

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☒ ORAL PROCEEDINGS on 29.11.11

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☒ Letter from the opponent 01 of 29.09.11 (telecopy with literature)
- ☐ Copy (copies)

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are now available via the Register Plus online service under **http://www.epoline.org** (see Special edition No. 3, OJ EPO 2007, J.2). Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

☐

For the Opposition Division

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European Patent Office
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Anmeldenummer	Application No.	Numéro de la demande:
	05758582.0	

INFORMATION

Die mündliche Verhandlung am:	The oral proceedings of:	La procédure orale du:
	29.11.11	
hat ergeben:	resulted in:	fut conclue comme suit:
☐ Das europäische Patent wird widerrufen da wenigstens ein Einspruchsgrund der Aufrechterhaltung des europäischen Patents entgegensteht (Art. 101(2) EPÜ).	The European patent is revoked because at least one ground for opposition prejudices the maintenance of the European patent (Art. 101(2) EPC)	Le brevet européen est révoqué car au moins un motif d'opposition s'oppose au maintien du brevet européen (art. 101(2) CBE).
☒ Das europäische Patent wird widerrufen, da unter Berücksichtigung der vom Patentinhaber im Einspruchsverfahren vorgenommenen Änderungen das europäische Patent und die Erfindung, die es zum Gegenstand hat, den Erfordernissen des EPÜ nicht genügen (Art. 101 (3) b) EPÜ).	The European patent is revoked because, account being taken of the amendments made by the patent proprietor during opposition proceedings, the patent and the invention to which it relates were found not to meet the requirements of the EPC (Art. 101(3)(b) EPC).	Le brevet européen est révoqué car il a été établi que, compte tenu des modifications apportées par le titulaire du brevet au cours de la procédure d'opposition, le brevet et l'invention qui en fait l'objet ne satisfont pas aux exigences de la Convention sur le brevet européen (art. 101(3)(b) CBE).
☐ Der Einspruch wird/Die Einsprüche werden zurückgewiesen (Art. 101(2) EPÜ).	The opposition(s) is/are rejected (Art. 101(2) EPC).	L'opposition est/Les oppositions sont rejetée(s) (art. 101(2) CBE).
☐ Es wird festgestellt, dass unter Berücksichtigung der vom Patentinhaber im Einspruchsverfahren vorgenommenen Änderungen das Patent und die Erfindung, die es zum Gegenstand hat, den Erfordernissen des Europäischen Patentübereinkommens genügen (Art. 101(3)(a) EPÜ).	Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of European Patent Convention (Art. 101(3)(a) EPC).	Il est établi que, compte tenu des modifications apportées par le titulaire du brevet au cours de la procédure d'opposition, le brevet et l'invention qui en fait l'objet satisfont aux exigences de la Convention sur le brevet européen (art. 101(3)(a) CBE).
☐ Die während der mündlichen Verhandlung eingereichten Änderungen sind beigefügt.	Amendments filed during oral proceedings are annexed.	Les modifications soumises pendant la procédure orale sont annexées.

29-11-2011
Datum / Date / Date

Unterschrift / Signature / Signature

NB: Dieses Formblatt ist nur als Information zu sehen. Die schriftliche Entscheidung hat Vorrang.
This form is provided for the sake of information only. The written decision prevails.
Le présent formulaire n'a qu'une valeur informative. La décision écrite prévaut.

Scanned to Phoenix
LA 29.11.11

isarpatent

REINHARD · SKUHRA · WEISE & PARTNER GbR

PATENT- UND RECHTSANWÄLTE
| PATENT ATTORNEYS LAWYERS AND CERTIFIED IP-LAWYERS

Dipl.-Biol. Dr. Werner Behnisch [1,2]
Dipl.-Phys. Dr. Stephan Barth [1,2]
Dipl.-Ing. Glyndwr Charles [1,2]
Dipl.-Ing. Oliver Hasse [1,2]
Dipl.-Phys. Ralf Peckmann [1,2]
M.P.H. Wolfgang Sandmann [1,2]
Vera Delichau [1,4]
Dipl.-Phys. Dr. Pamela Kalb [1,2]
Franz Stangl [1]
Dipl.-Biol. Dr. Alexander von Harmeyer [1]
Dipl.-Phys. Dr. Christoph Hecht [1]
Laura Kocs [3], Ph.D. in Physics
Dipl.-Ing. Daniel Papst [1,4]

[1] PATENTANWALT
[2] EUROPEAN PATENT ATTORNEY
[3] U.S. PATENT AGENT
[4] RECHTSANWALT (MÜNCHEN)
[5] FACHANWALT FÜR GEWERBLICHEN RECHTSSCHUTZ

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Nur per FAX: 089 2399 4465
Europäisches Patentamt
Erhardtstraße 27
80298 München

Unser Zeichen: A02208 WB/lvo | 14. Dezember 2011

Namensänderung – Zusammenschlussnummer: 73

Sehr geehrte Damen und Herren,

im Nachgang zu unserem nochmals in Kopie beiliegenden Schreiben vom 18. Oktober 2011 dürfen wir folgendes klarstellen. Die Mitglieder des Zusammenschlusses Nr. 73, welcher nunmehr auf den Namen „isarpatent" lautet, sind alle im Briefkopf genannten Anwälte, die damit unterschrifts- und vertretungsberechtigt sind.

Es wird weiterhin gebeten, die vorhandenen Smart-Cards für Online-Services auf „isarpatent" abzuändern und uns, falls notwendig, neue Smart-Cards zu übersenden.

Für Rückfragen steht Ihnen der Unterzeichner gerne zur Verfügung.

Mit freundlichen Grüßen

Dr. Werner Behnisch
Patentanwalt

Anlage:
Kopie unseres Schreibens vom 18. Oktober 2011

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Dipl.-Biol. Dr. Werner Behnisch [1,2]
Dipl.-Phys. Dr. Stephan Barth [1,2]
Dipl.-Ing. Glyndwr Charles [1,2]
Dipl.-Ing. Oliver Hassa [1,2]
Dipl.-Phys. Ralf Peckmann [1,2]
M.P.H. Wolfgang Sandmann [1,3]
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Dipl.-Phys. Dr. Pamela Kolb [1,2]
Franz Stangl [4]
Dipl.-Biol. Dr. Alexander von Hornmayer [1]
Dipl.-Phys. Dr. Christoph Hecht [1]
Laura Kocs [3], Ph.D. in Physics
Dipl.-Ing. Daniel Pépuz [1,2]

[1] PATENTANWALT
[2] EUROPEAN PATENT ATTORNEY
[3] U.S. PATENT AGENT
[4] RECHTSANWALT (MÜNCHEN)
[5] FACHANWALT FÜR GEWERBLICHEN RECHTSSCHUTZ

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Europäisches Patentamt

Erhardtstraße 27
80298 München

Ihr Zeichen: | Unser Zeichen: A0027 WB/lvo | 18. Oktober 2011

Namensänderung – Zusammenschlussnummer: 73

Sehr geehrte Damen und Herren,

wir dürfen Ihnen hiermit mitteilen, dass wir ab sofort die Kanzleibezeichnung „Reinhard Skuhra Weise & Partner GbR in „Isarpatent" ändern. Die Rechtsform „GbR" bleibt unverändert. Die Mitglieder der Sozietät bleiben ebenfalls unverändert und sind wie folgt:

Dr. Werner Behnisch, Dr. Stephan Barth, Glyndwr Charles, Oliver Hassa, Ralf Peckmann.

Wir dürfen höflich um Eintragung der Änderung bitten. Für Rückfragen steht Ihnen Herr Dr. Werner Behnisch gerne zur Verfügung.

Mit freundlichen Grüßen

Dr. Werner Behnisch
Patentanwalt

Dr. Stephan Barth
Patentanwalt

Glyndwr Charles
Patentanwalt

Oliver Hassa
Patentanwalt

Ralf Peckmann
Patentanwalt

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Reinhard - Skuhra - Weise & Partner GbR
Patent- und Rechtsanwälte
Friedrichstrasse 31
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Formalities Officer
Name: Ullrich, Chantal
Tel: +49 89 2399 - 2322
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Application No. / Patent No.	Ref.	Date
05 758 582.0 - 2112 / 1 768 649 /	P30048-EPOP WB	22.12.2011
Proprietor UCB FARCHIM S.A.		

Provision of a copy of the minutes in accordance with Rule 124(4) EPC

The attached copy of the minutes of the oral proceedings is sent to you in accordance with Rule 124(4) EPC.

Ullrich, Chantal
Formalities Officer
Tel. No.: +49 89 2399 - 2322

Enclosure(s): Copy of the minutes (Form 2309)

Registered Letter
EPO Form 2042 12.07TRI

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European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Application No.: 05 758 582.0

Patent No.: EP-B-1 768 649

Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

Proceedings opened on 29.11.2011 at 09:01 hours

Present as members of the opposition division:

Chairman:	Sindel, Ulrike
1st member:	Giménez Miralles, J
2nd member:	Giró, Annalisa
Minute writer:	Giró, Annalisa

Present as or for the party or parties:

- For the Proprietor(s): UCB FARCHIM S.A.

  Sandmann, Wolfgang (Authorized Representative)
  accompanied by Lechien, Monique (UCB Farchim S.A.)

- For the Opponent 1: Zentiva k.s.

  Sahlin, Jonna (Authorized Representative)
  Hakkila, Annika (Authorized Representative)

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the discussion and possible relevant statements of the parties:

After deliberation of the opposition division,

- the chairman announced the following **decision**:

"The European patent is revoked."

Regarding the reasons for the decision, the chairman referred to:

Article 101(2) EPC, first sentence: the following ground(s) for opposition mentioned in Article 100 EPC prejudice(s) the maintenance of the patent as granted.

The division's opinion is that, even taking into consideration the amendments made by the proprietor of the patent during the opposition proceedings, the patent does **not** meet the requirements of the Convention (Article 101(3)(b)EPC)

The Main Request (patent as granted) and the 1st and 2nd Auxiliary Requests do not meet the requirements of Article 56 EPC.

The chairman **closed the oral proceedings** on 29.11.2011 at 14:35 hours.

signed:

Sindel, Ulrike
. . . . . .
Chairman

signed:

Giró, Annalisa
. . . . . .
Minute Writer

Enclosure(s):

After deliberation of the opposition division,

- the chairman announced the following **decision**:

"The European patent is revoked."

Regarding the reasons for the decision, the chairman referred to:

Article 101(2) EPC, first sentence: the following ground(s) for opposition mentioned in Article 100 EPC prejudice(s) the maintenance of the patent as granted.

Article 101(3)(b)EPC: Taking into consideration the amendments made by the proprietor of the patent during the opposition proceedings, the patent and the invention to which it relates do **not** meet the requirements of the Convention

The Main Request (patent as granted) and the 1st and 2nd Auxiliary Requests do not meet the requirements of Article 56 EPC.

The chairman **closed the oral proceedings** on 29.11.2011 at 14:35 hours.

Sindel, Ulrike
Chairman

Giró, Annalisa
Minute Writer

Annex(es):

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Application No.: 05 758 582.0

Patent No.: EP-B- 1 768 649

A copy of the communication (communication, decision, minutes) was printed for and notified to each of the following representatives/parties:

Reinhard - Skuhra - Weise Partner GbR
Patent- und Rechtsanwälte
Friedrichstrasse 31
80801 München
ALLEMAGNE

01
Sahlin, Jonna Elisabeth
BORENIUS & Co Oy Ab
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Application No.: 05 758 582.0

Patent No.: EP-B- 1 768 649

A copy of the communication (communication, decision, minutes) was printed for and notified to each of the following representatives/parties:

Reinhard - Skuhra - Weise Partner GbR
Patent- und Rechtsanwälte
Friedrichstrasse 31
80801 München
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01
Sahlin, Jonna Elisabeth
BORENIUS & Co Oy Ab
Itämerenkatu 5
00180 Helsinki
FINLANDE

Facts and submissions

I. The European patent EP 1 768 649 B1; based upon European patent application 05758582.0; date of filing: 07.07.2005; priority: 14.07.2004 (EP04016519); date of publication and mention of the grant of the patent: 23.09.2009 (Bulletin 2009/39);

Proprietor: UCB Farchim S.A., CH-1630 Bulle, Switzerland

has been opposed by:

Opponent: Zentiva k.s., 102 37 Prague, Czech Republic

II. With notice of opposition filed on 23.06.2010 the Opponent requested revocation of the opposed patent in its entirety based on the grounds of Art. 100(a) EPC for lack of novelty and inventive step (Art. 52(1), 54 and 56 EPC). Alternatively, oral proceedings pursuant to Art. 116 EPC were requested.

III. With letter of observations dated 13.10.2010 filed on 19.10.2010 the patent Proprietor requested rejection of the opposition and maintenance of the patent as granted (Main request), or amended in the form of Auxiliary request 1 or Auxiliary request 2 filed on same date. Alternatively, oral proceedings pursuant to Art. 116 EPC were requested.

IV. With official communication dated 03.08.2011 the Opposition Division gave a preliminary opinion and summoned to oral proceedings. In particular, Auxiliary request 1 (claim 3) was objected to under Rule 80 EPC.

V. With letter dated 29.09.2011 the patent Proprietor filed an amended Auxiliary request 1 replacing former Auxiliary request 1, and filed new Auxiliary requests 3 and 4, together with further arguments regarding inventive step.

VI. With letter dated 29.09.2011 the Opponent filed documents D12 to D15 and put forward further arguments regarding inventive step based on these new documents.

VII. Oral proceedings took place on 29.11.2011.

At the beginning of the oral proceedings the patent Proprietor confirmed his requests of maintenance of the contested patent as granted (Main request; see Annex I), or amended in form of Auxiliary request 1 (29.09.2011), Auxiliary request 2 (19.10.2010), Auxiliary request 3 (29.09.2011), or Auxiliary request 4 (29.09.2011). In the course of the proceedings, the Patentee withdrew Auxiliary requests 1 and 3. Auxiliary requests 2 and 4 were renumbered as Auxiliary requests 1 and 2 (see Annexes II and III), respectively. Further, the Patentee requested not to admit documents D12-D15 into the proceedings as being late filed and not prima facie more relevant than documents already on file.

The Opponent maintained the request to revoke the patent in its entirety based on the grounds mentioned in paragraph II above. Further, regarding Auxiliary request 1 (former Auxiliary request 2) the Opponent additionally raised the objection of lack of clarity (Art. 84 EPC). With regard to Auxiliary request 2 (former Auxiliary request 4), the Opponent raised objections under Art. 123(2) and 84 EPC.

The text of the claims under consideration in the form of the Main request and the Auxiliary requests 1 and 2 is appended to this decision (Annexes I to III).

For the essentials of the discussion during the oral proceedings, reference is made to the minutes.

VIII. In the course of the proceedings, the following documents have been submitted as evidence by the parties:

D1= EP0605203A2

D2= US5891913

D3= Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), pages 340-343 and 450-453

D4= Wang et al. (2001), Allergy 56, 339-343

D5= Marketing authorization for ZODAC GTT oral drops in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D6= Marketing authorization for ZODAC SIR syrup in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D7= Marketing authorization for ZODAC GTT drops in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D8= Marketing authorization for ZODAC SIR syrup in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D9= ZODAC GTT, Summary of Product Characteristics, date of last text revision 21.10.2009

D10= ZODAC SIR, Summary of Product Characteristics, date of last text revision 21.10.2009

D11= Thomson Reuters Newport Premium, Launched Drug Forms Detail (2010)

D12= Johnston et al. (2006), MedGenMed 8(2): 61

D13= Abstract of Ryssel et al. (2009), Burns 35(5), 695-700

D14= Abstract of Frech et al. (1979), Am. J. Hosp. Pharm. 36(12), 1672-1675

D15= Juslin et al. (2001) "Farmasian teknologia", 6th ed., Foy Fortis ry., page 450

IX. The arguments put forward by the parties can be summarised as follows:

IX.1 Novelty

The Opponent essentially alleges that novelty of claim 1 as granted is prejudiced by the public prior use of two pharmaceutical products named Zodac GTT and Zodac SIR which were launched in the Czech Republic and in Slovakia in 2001 and 2002, respectively, as demonstrated by the Launched Drug Forms Detail list D11. According to the Opponent, when the marketing authorisations were granted (D5 to D8), the patient information leaflets D9 and D10 (Summary of Product Characteristics) were published. The information contained in D9 and D10 was therefore available to the public before the date of priority of the contested patent. In D9 and D10 it is explained that the products Zodac GTT and Zodac SIR comprise 1.35 mg methylparaben and 0.15 mg propylparaben per 1 ml solution, this making a total amount of parabens of 1.5 mg/ml. The Opponent further alleges that, regardless of whether or not the information about the amounts of parabens in the products Zodac GTT and Zodac SIR was published before the priority date of the opposed patent, the compositions of these two products were part of the state of the art as soon as they were launched, since they could be analyzed by standard methods without undue burden. The Opponent argues that the products Zodac GTT and Zodac SIR publicly used before

the date of priority of the contested patent comprise a total amount of methylparaben and propylparaben of 1.5 mg/ml (as demonstrated by D9, D10 and D11), and the upper limit "lower than 1.5 mg/ml" for the concentration of preservatives defined in claim 1 of the contested patent is not novel over the prior use value 1.5 mg/ml, because under consideration of the margin of error inherent to any experimental measurement (tolerance area around an experimental value), as held in T594/01, the upper end point of the claimed range "lower than 1.5 mg/ml" cannot be distinguished from the experimental value 1.5 mg/ml of the public prior use.

The patent Proprietor essentially argues that the substantiation of the public prior use (in particular as to what was made available to the public) in the Notice of Opposition (i.e. within the opposition period) is insufficient. The Patentee holds that it is at least doubtful what was made available to the public through the use of the products Zodac GTT and Zodac SIR. According to the Patentee, D9 and D10 cannot be taken as evidence of the precise composition of Zodac GTT and Zodac SIR before the priority date of the opposed patent (14.07.2004), since it is evident from D9 and D10 themselves (chapters 9 and 10) that the publication date of these information sheets is later than 14.07.2004, and the text has been revised several times. Furthermore, D9 and D10 prove that there was a renewal of the authorisation in January 2009. It is therefore doubtful whether the Summary of Product Characteristics D9 and D10 truly and identically reflect the composition characteristics of the products Zodac GTT and Zodac SIR launched in 2001 and 2002, as the evidence provided is insufficient. For these reasons, the alleged public prior use has not been convincingly demonstrated beyond any remaining doubt. The Patentee further argues that, even if D9 and D10 could be taken as a proof of the composition of Zodac GTT and Zodac SIR as launched in 2001 and 2002, the amount of methylparaben and propylparaben of 1.5 mg/ml is outside the limit "less than 1.5 mg/ml" defined in claim 1 of the contested patent. According to the patent Proprietor, T594/01 is of no general applicability and is not relevant for the present case, in particular because in the pharmaceutical field the contents of any ingredients are determined very precisely due to regulatory requirements. Claim 1 as granted is therefore novel in view of the alleged prior use of Zodac GTT and Zodac SIR, and this even more applies to the subject-matter of the auxiliary requests where the amounts of parabens have been restricted.

IX.2 Inventive step

The Opponent argues that D1 (example 5) disclosing a liquid ophthalmic composition comprising cetirizine hydrochloride, and methylparaben (2 mg/ml) and propylparaben (1 mg/ml) as preservatives (page 3 line 52) represents the closest prior art. D1 does

not disclose the amount of parahydroxybenzoate esters (parabens) being "less than 1.5 mg/ml" as defined in claim 1 of the opposed patent. The technical effect of this feature, so the Opponent, is achieving the recommended efficacy criteria of antimicrobial preservation for different uses of the composition. According to the Opponent, the problem was therefore to provide a useful liquid composition of cetirizine, levocetirizine or efletirizine having the recommended efficacy of antimicrobial preservation. According to the Opponent, D1 itself indicates that the amount of additives (including preservatives) to be used can be determined by those skilled in the art within the ranges adopted for ordinary ophthalmic or nasal solutions (page 3 lines 56-57). Furthermore, the skilled person is well aware of the need to keep the concentration of parabens in liquid pharmaceutical compositions on the lowest possible levels due to the controversial discussions ongoing before and at the time of the priority of the opposed patent about the safety and toxicology concerns regarding the use of parabens as preservatives in pharmaceuticals. This provides a clear incentive to the skilled person to carefully consider the concentration of parabens. The skilled person would therefore turn to a handbook of pharmaceutical excipients such as D3. In D3 the skilled person finds information regarding the concentration of methylparaben and propylparaben suitable for ophthalmic and nasal solutions. D3 discloses using 0.15 to 2 mg/ml methylparaben and/or 0.05 to 0.1 mg/ml propylparaben in ophthalmic preparations; 0.15 to 2 mg/ml methylparabens and/or 0.1 to 0.2 mg/ml propylparaben in oral solutions/suspensions; and 0.33 mg/ml methylparaben and/or 0.17 mg/ml propylparaben in nasal solutions (see table in Section 7). This provides the indication for the skilled person to modify the ophthalmic formulation of D1 (example 5) to comprise 0.15-2 mg/ml methylparaben and/or 0.05-0.1 mg/ml propylparaben, thus ending up with combined amounts of parabens falling within the range "more than 0 and less than 1.5 mg/ml" defined in claim 1 of the contested patent, since three of the amounts explicitly disclosed in D3 fall within this range. With regard to the limitation to levocetirizine and/or specific combinations of parabens in the auxiliary requests, the Opponent argues that no particular technical effect is demonstrated in the patent in suit for these features, and hence this subject-matter merely represents obvious alternatives. Further, the use of levocetirizine instead of racemic cetirizine would be obvious from D4, as this enantiomer has enhanced activity. As for the use of methylparaben and propylparaben in combination in ratio 9/1 of methylparaben/propylparaben, the Opponent argues that this feature is also disclosed in D3 for parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7), and the skilled person would also apply this ratio to ophthalmic preparations. Using the lowest (0.05 mg/ml) and highest (0.1 mg/ml) amounts of propylparaben indicated in D3 for ophthalmic formulations and the ratio 9/1 of methylparaben to propylparaben also disclosed in D3, one ends up with total amounts of combined methylparaben + propylparaben of 0.5 mg/ml or 1.0 mg/ml

suitable for antimicrobial preservation of ophthalmic solutions, both concentrations falling within the range defined in the claims of the opposed patent (main request and auxiliary requests). The Opponent further argues that the examples of the patent in suit relate to the use of parabens together with other traditional preservatives/ antimicrobial agents such as acetic acid and sodium acetate, and none of the examples actually supports the claimed improved antimicrobial efficiency of only parabens alone combined with cetirizine/levocetirizine or efletirizine. Thus, it remains unclear whether the desired effect actually originates from one or more of the antimicrobial agents used not being parabens. The Opponent also contends that a "self-preserving" effect of cetirizine/levocetirizine or efletirizine has not been demonstrated in the opposed patent.

The patent Proprietor essentially argues that starting from D1 (example 5) the objective problem is that stated in the contested patent, paragraph [0008], namely providing a liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine with a reduced amount of preservatives (selected from parabens). He argues that the amounts of methylparaben indicated in the table of Section 7 of D3 are only amounts intended for use in combination with other preservatives, not for use as the only preservative. D3, so the Patentee, does not indicate that the amounts given in the table of Section 7 are sufficient for effective preservative effect when used as the only preservative. D3 in Section 11 (table I) provides information about the MICs (minimum inhibitory concentrations) of methylparaben in aqueous solutions. From table I in D3 one can derive that the minimum inhibitory concentration of methylparaben in ophthalmic solutions has to be more than 4 mg/ml (4000 microgram/ml) which is the minimum concentration required for inhibition of Pseudomonas aeruginosa, a pathogen involved in harmful eye infections. By comparing Sections 7 and 11 (table I) of D3 one easily understands that the amounts indicated in Section 7 (lower limits) are only theoretical and not suitable for providing sufficient preservative effect when methylparaben is used as the only preservative. Same considerations apply to propylparaben. Hence, D3 would teach that not even the concentration of parabens used in D1 (3 mg/ml) is sufficient to defeat well known pathogens which may occur in ophthalmic formulations. Furthermore, the skilled person, so the Patentee, would not have any motivation for combining D1 with D3, because D3 (Section 14) indicates that "although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for this type of formulations...". Hence, D3 would suggest that parabens should not be used in ophthalmic preparations. D1 and D3, so the Patentee, can be combined only with the use of hindsight. Indeed, in view of D3 the skilled person would be deterred from using parabens in liquid pharmaceutical formulations. Further, the Patentee contends that in the absence of any information which is related to the "self-preserving" effect of

cetirizine/levocetirizine and efletirizine, a skilled person would not have any motivation to simply lower the amounts of parabens based on D1 and D3, in particular in consideration of the fact that he has to expect that product safety would be considerably affected.

Reasons for the decision

1. The opposition, filed in due time, in proper form, and supported by reasoned statements, is formally admissible (Art. 99(1) and 100 EPC, and Rules 3(1) and 76 EPC).

2. Admissibility of D14

Whereas D12, D13 and D15 (D12 and D13 being post-published documents) merely represent the common general knowledge of any person skilled in the art, and there is no need to resort to them as a proof of said accepted common knowledge, this is not the case of D14. D14 is a document in the area of hospital parenteral nutrition, and hence in the field of pharmaceuticals, and reports on analogous problem of microbial contamination risk/preservation of aqueous solutions for pharmaceutical use. Indeed, during the oral proceedings D14 turned out to be useful for the discussion of the role of sodium acetate in the microbial growth inhibitory activity of the formulations of the patent in suit comprising sodium acetate (in particular examples 1-4), as D14 reports on antimicrobial activity of sodium acetate on same microorganisms (Staphylococcus, Escherichia, Pseudomonas, Candida) tested in the patent in suit. D14 is hence pertinent for understanding the role of the various ingredients of the compositions according to the opposed patent in the preservative effect(s) allegedly demonstrated in the patent. Although the patent Proprietor initially claimed that D14 is not relevant (at least not more relevant than other documents already on file), he himself used this document later on in favour of his argumentation of inventive step. For all these reasons, D14 late filed by the Opponent after expiry of the opposition period is considered as prima facie relevant for the present discussion, and the Opposition Division has decided to admit it into the proceedings.

Main request

3. Novelty - Alleged public prior use

D5, D6, D7, D8 together with D11 demonstrate that the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) were indeed launched to the market in the Czech Republic on 31.10.2001, and in Slovakia on 30.09.2002. The Summary of Product Characteristics and Patient Information Leaflet attached to each of D5, D6, D7 and D8 demonstrate that ZODAC GTT and ZODAC SIR comprise cetirizine dihydrochloride in aqueous solution containing methylparaben and propylparaben as preservatives. However, the concentration of methylparaben and propylparaben in the solution is not disclosed in D5 to D8.

On the other hand, D9 and D10 are the last revision of the Summary of Product Characteristics (dated 21.10.2009) for ZODAC GTT and ZODAC SIR in the Czech Republic. The Opponent's contention that D9 and D10 were published when the marketing authorisations were granted is not true. D9 and D10 have been last revised on 21.10.2009, and therefore their publication could not have occurred before that date. Further, D9 and D10 demonstrate that the first authorisation of ZODAC GTT and ZODAC SIR in the Czech Republic has been renewed once on 28.01.2009, and that the text of the Summary of Product Characteristics has been revised four times, once coinciding with the renewal of the authorisation (28.01.2009). The contents of D9 and D10 are different from those of the Summary of Product Characteristics and Patient Information Leaflet attached to D5, D6, D7 and D8. The evidence produced in form of D5, D6, D7, D8, D9 and D10 cannot exclude beyond any reasonable doubt the possibility that a variation of the excipient composition could have been introduced coinciding with one of those revisions or renewal after the products were first launched.

It has not been proven without any remaining doubt that the products launched in 2001 and 2002 in the Czech Republic and Slovakia and commercially available before the date of priority of the contested patent (14.07.2004) had exactly the same concentration of parabens as the products available in 2009 in the Czech Republic as described in D9 and D10.

D9 and D10 do not demonstrate the composition of the products publicly available before 14.07.2004, and the Opponent has not provided any further piece of evidence in this respect. The actual concentration of parabens in the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) publicly available in the Czech Republic and Slovakia before the priority date of the contested patent remains unknown.

The fact that, as alleged by the Opponent, the compositions of Zodac GTT and Zodac SIR publicly available from 2001 and 2002 and before 14.07.2004 could be or could have been analyzed by standard methods without any undue burden (which is not denied) does not change anything to this situation: It remains unknown what (which concentration of parabens) would have been found, had this analysis been carried out, and the Opponent has not provided sufficient evidence in this respect.

For the full substantiation of a public prior use, the burden was with the Opponent to prove up to the hilt that the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) publicly available before 14.07.2004 actually had a concentration of parabens of less than 1.5 mg/ml as defined in claim 1 of the opposed patent, so that this concentration was actually available to any member of the public who would have carried out a chemical analysis of the product composition. Yet, the actual concentration of parabens in the Zodac GTT and Zodac SIR products of the state of the art before 14.07.2004, and in particular before the revisions and authorisation renewal documented in D9 and D10, is not known. The paraben concentration is only known from D9 and D10 after said revisions and authorisation renewal after the priority date. The requirement of adequate substantiation within the opposition period for the proof of a public prior use by means of extensive evidence regarding this point (what was effectively made available, or what would have been actually available to the public through the analysis of the composition) before the priority date has not been fulfilled.

Under these circumstances, it is irrelevant to the question of novelty whether or not the upper limit for the concentration of preservative defined in claim 1 of the opposed patent as "less than 1.5 mg/ml" can be distinguished from the experimental concentration value 1.5 mg/ml within the unavoidable margin of error or tolerance associated with the experimental measurement of said amount in a pharmaceutical composition, since said experimental value 1.5 mg/ml does not form part of the prior art within the meaning of Art. 54(1) and (2) EPC for the reasons explained above.

4. Inventive step

4.1 Technical effect(s) and problem to be solved

4.1.1 D1 can be considered as the closest prior art. This has been acknowledged by both parties during the proceedings. D1, in example 5, discloses a liquid ophthalmic composition comprising cetirizine hydrochloride (3 mg/ml), and methylparaben (2 mg/

ml) and propylparaben (1 mg/ml) as preservatives (see page 3 line 52). The composition further comprises other excipients and additives such as sodium acetate (1 mg/ml) and propyleneglycol (20 mg/ml).

The difference of claim 1 of the opposed patent as granted with respect to D1 (example 5) is the definition of the concentration of parahydroxybenzoate esters (parabens) selected from methylparaben, ethylparaben, propylparaben, or mixtures thereof of "more than 0 and less than 1.5 mg/ml", whereas D1 discloses a total concentration of methylparaben and propylparaben of 3 mg/ml. It is noted that the wording of claim 1, however, does not exclude the presence of other additives, in particular other preservatives, in the composition.

4.1.2 The Opposition Division already expressed in the annex to the summons the view that the technical effect(s) which may be taken into account in view of this technical difference appear to relate to: i) the reduction of safety and toxicology concerns regarding the use of parabens in pharmaceuticals (lowering of well-known adverse effects in case of hipersensitivity to parabens), whilst ii) providing a sufficient efficacy for antimicrobial preservation (fulfilling the recommended efficacy criteria).

The advantage of reducing the concentration of preservatives leading to a reduction of the risk of an allergic reaction in sensitive patients is invoked in paragraph [0030] of the opposed patent. However, this passage does not relate specifically to parabens, but the patent describes the use of a number of different preservatives (see paragraphs [0011], [0018] and [0019], and the examples). Furthermore, the patent in suit does not contain any experimental details at all concerning this alleged effect or advantage. In particular, there is no demonstration in the patent of any effect of the parabens concentration values defined in claim 1 on an actual reduction of the risk of allergic reactions of the claimed compositions. The patent contains no information and no details whatsoever in this respect. Whereas the reduction of the risk of allergic reactions by reducing the concentration of preservatives may be considered as feasible in general in view of the common knowledge of the person skilled in the art, it is stressed that the contested patent is not concerned with this aspect (except for the assertion in paragraph [0030]), and it contains no evidence whatsoever making the achievement of this alleged effect in the present case at least plausible.

During the oral proceedings the patent Proprietor stated that there is a linear correlation between the reduction of preservative concentration and the lowering of risk/occurrence of adverse allergic reactions. However, no evidence has been provided in support of this allegation. It remains a matter of speculation whether this correlation is linear, or whether a statistically significant effect can be observed at all for the reduction of risk/occurrence of adverse effects when lowering the amount of

parabens to less than 1.5 mg/ml (as claimed in the opposed patent) when compared to parabens concentration of e.g. 3 mg/ml as described in the closest prior art D1 (example 5). Accordingly, in the absence of evidence supporting the comparison with the prior art this merely speculative advantage cannot be taken into consideration in determining the technical problem underlying the invention (Case Law of the BoA, 6th Ed., I.D.4.2).

The effect of providing/maintaining a sufficient antimicrobial efficacy in terms of fulfilling the recommended efficacy criteria is, however, sufficiently substantiated in the patent in suit. The examples in the patent specification describe a number of aqueous formulations of cetirizine, levocetirizine or efletirizine in form of oral solution or drops comprising different excipients and preservatives. The testing of the antimicrobial preservative effectiveness is carried out in terms of fulfilment of the recommended efficacy criteria according to the Eur. Pharmacopoeia (Chap. 5.1.3) by determining the number of viable microorganisms per ml 28 days after inoculation with bacterial (Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus) and yeast (Candida albicans, Aspergillus niger) suspensions. All the compositions described, except those of examples 1 and 2 in form of oral solution (see tables 2 and 5), show compliance with the recommended efficacy criteria (see example 1: table 3; example 2: table 6; example 3: tables 7-14; example 4: tables 15-20; example 5: paragraph [0047]; example 6: paragraph [0049]; example 7: paragraph [0051]; example 8: paragraph [0053]; example 9: paragraph [0055]).

In examples 1, 2, 5 and 7 the compositions do not comprise parabens, whereas the formulations of examples 3, 4, 6, 8 and 9 do. It is also apparent that all the compositions comprising parabens further comprise other additives and excipients which may exert a concomitant antimicrobial effect, and hence fulfil the functional definition "preservative". Thus, formulations of examples 3, 4 and 8 comprise sodium acetate and acetic acid; composition of example 6 comprises sodium phosphates and disodium edetate; composition of example 9 comprises boric acid. All of these additives are also preservatives within the meaning of the present patent (see paragraph [0019]). Other additives present in the compositions of the patent in suit such as propyleneglycol (examples 1-4 and 8) are known to have an enhancing effect on antimicrobial preservative efficacy of parabens (see D3, Section 7). Furthermore, it is stated in the patent in suit that the active ingredients (substituted benzhydryl piperazines such as cetirizine, levocetirizine or efletirizine) possess themselves a preservative effect in aqueous solution (see paragraphs [0007] and [0009]).

A great deal of discussion was devoted during the oral proceedings to the latter question of whether or not a "self-preserving" effect of the active agent itself is actually demonstrated in the patent. In the Opposition Division's opinion, the examples of the patent in suit do not allow to draw any conclusion in this respect, because all the

formulations comprise a combination of substances which may have an antimicrobial stabilising effect, and/or an antimicrobial enhancing effect, alone or in combination. In this context, the Patentee stated during the oral proceedings that sodium acetate used in examples 1-4, 7 and 8 in concentrations of up to 10 mg/ml has no preservative effect at all, and hence the preservative effect observed for compositions of examples 1 and 2 must be attributed to the self-preserving effect of the active agent. However, the Patentee has not provided any further evidence in support of this contention. Contrary to the Patentee's allegation, D14 discloses the growth inhibitory effect of sodium acetate on Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa in aqueous solution for parenteral nutrient therapy. The Patentee has further argued that D14, however, indicates that growth of Candida albicans is not inhibited by sodium acetate. Since examples 1 and 2 (tables 2, 3 and 6) do demonstrate an antimicrobial effect for Candida albicans, this effect must be attributed to the active agent.

Irrespective of the above controversy, the consideration of this effect –if it actually exists– is irrelevant for the formulation of the technical problem, as it does not derive from the technical difference of the subject-matter of claim 1 of the opposed patent over D1 (example 5), namely the lower concentration of parabens, but allegedly from the presence of the active agent, and hence this effect would have been also present, even if unrecognized, in the composition of D1 (example 5). The only decisive consequence of the above discussion in the present analysis, is that it remains doubtful to which component or combination of components the antimicrobial stabilisation effect shown in the compositions of the patent in suit is to be attributed.

Now, turning to the effect of the concentration of parabens, comparison of results in table 3 of the opposed patent (cetirizine drop formulation without parabens) and results in tables 11-14 (cetirizine drop formulation with various amounts of parabens) reveals no technical effect in terms of microbial preservation which could be attributed to the presence or absence of parabens. Same is true for levocetirizine formulations from the comparison of table 6 (no parabens) and tables 18-20 (with parabens). On the other hand, comparison of results in table 2 (oral solution formulation of cetirizine without parabens) and results in tables 7-10 (oral solution formulation of cetirizine with various amounts of parabens); and table 5 (oral solution formulation of levocetirizine without parabens) and results in tables 15-17 (oral solution formulation of levocetirizine with various amounts of parabens) reveals an effect of the presence of parabens in the stabilisation against yeast contamination (Candida albicans and in particular Aspergillus niger) which can be observed for concentration of parabens as low as 0.15 mg/ml (see table 7).

In view of the above analysis, it appears that the presence or absence of a technical effect in terms of microbial preservation which could be attributed to the presence or absence of parabens depends on the composition (concentration of active agent, amount of other additives such as propyleneglycol) of the pharmaceutical formulation, as it is not the same for oral solutions as for drops (see tables 1 and 4). It is stressed in this context, that claim 1 of the contested patent is not limited to drop formulations, and it does not exclude the presence of other additives.

4.1.3 Finally, the specification of the patent invokes an additional advantage, namely the ability of making the manufacturing process easier by avoiding the need of solubilising important amounts of preservatives not freely soluble in water (paragraph [0031]). However, no further details are provided in the specification in support of this speculative statement, and the Opposition Division concludes that in absence of supporting evidence this merely alleged advantage cannot be taken into consideration in determining the technical problem underlying the invention.

4.1.4 The Opposition Division stresses in particular that, in view of the evidence available, the correct formulation of the technical problem cannot be that of providing compositions having the lowest possible concentration of parabens still compatible with an effective antimicrobial activity fulfilling the recommended efficacy criteria. Compositions according to claim 1 of the opposed patent can comprise as much as "less than 1.5 mg/ml" of parabens. Neither the limit of the paraben concentration range "less than 1.5 mg/ml" defined in claim 1 of the opposed patent nor even the lowest paraben concentration value of 0.15 mg/ml used in various examples of the patent in suit have been shown to be critical in this respect, i.e. the lowest possible concentration of parabens still compatible with an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of cetirizine, levocetirizine and efletirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens. On the other hand, no significant difference is observed in tables 7 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.15, 0.375, 0.45, 0.75, 1.05 or 1.125 mg/ml of parabens. In this sense, the upper limit of less than 1.5 mg/ml of parabens defined in claim 1 of the opposed patent appears to be fully arbitrary.

It is also particularly stressed that the technical problem cannot be that as formulated by the patent Proprietor, namely providing a liquid pharmaceutical composition of cetirizine with a reduced amount of preservatives selected from parabens, as this

formulation merely amounts to a repetition of the technical difference vis-à-vis the closest prior art (D1, example 5), and includes a part of the solution in the statement of the problem, which necessarily results in an ex post facto view.

In summary, the Opposition Division comes to the conclusion that the objective technical problem can only be reasonably formulated in terms of **providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens having the recommended efficacy of antimicrobial preservation**. The Opposition Division therefore agrees with the Opponent's formulation of the technical problem.

4.1.5 Following the problem-solution analysis, it has to be first decided whether or not the problem as formulated above is shown in the patent to be actually solved across the whole area covered by claim 1 of the contested patent, in particular for any liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine comprising parabens in concentrations of "more than 0 and less than 1.5 mg/ml".

It is apparent from the evaluation of the disclosure of the patent in suit that this question has to be answered in the negative. Concentrations of parabens lower than 0.15 mg/ml have simply not been tested. However, it is apparent from tables 2, 5 and 7 that concentrations of parabens lower than 0.15 mg/ml, e.g. only slightly higher than 0 mg/ml (say concentrations as low as e.g. 0.0001 mg/ml as described in paragraph [0020] of the contested patent) may result, in particular in the case of oral solutions, in insufficient antimicrobial effectiveness against yeast contamination (Aspergillus and Candida), as the recommended efficacy criteria are not fulfilled. This is however not the case for drops formulations (see tables 3, 6 and 11), i.e. the achievement of the recommended efficacy criteria depends on the particular composition of the pharmaceutical formulation (concentration of active agent, amount of other additives/ excipients which may have a concomitant or enhancing effect). This demonstrates that the technical problem as formulated above is not effectively solved across the range of concentrations of parabens and across the variety of liquid pharmaceutical compositions covered by claim 1 of the opposed patent.

In view of this, the technical problem has to be reformulated less ambitiously, namely in terms of **providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens showing (some degree of) antimicrobial preservative effectiveness**.

4.2 Obviousness

The technical problem as formulated in paragraph 4.1.5 above is solved in the patent in suit by providing compositions comprising parahydroxybenzoate esters (parabens) in concentrations of more than 0 and less than 1.5 mg/ml. Examples 1-9 of the opposed patent demonstrate that this problem is actually solved across the whole area covered by claim 1.

It only remains to be ascertained whether this solution (use of parabens concentrations of more than 0 and less than 1.5 mg/ml) would have been obvious for the skilled person.

The Opposition Division agrees with the Opponent in that, confronted with the problem as formulated above, the skilled person would immediately resort to his general knowledge and to handbooks of pharmaceutical excipients such as D3 (chapters dealing with methyl- and propylparaben).

The motivation to resort to D3 is given first of all by the formulation of the problem itself, namely to find out suitable concentrations of parabens providing effective antimicrobial preservation in liquid pharmaceutical compositions. Secondly, the skilled person is well aware that keeping the concentration of parabens in liquid pharmaceutical compositions at low levels is generally desired due to the controversial discussions ongoing at the time of priority of the opposed patent about the safety and toxicology concerns regarding the use of parabens as preservatives in pharmaceuticals. This safety concern is even recognized and discussed in D3 (Section 14). Both facts provide a clear incentive for the skilled person to carefully consider the typical concentrations of parabens for various liquid pharmaceutical formulations disclosed in D3.

In D3 (tables under Section 7 on pages 340 and 450) the skilled person finds a clear indication regarding the usual concentrations of methylparaben and propylparaben to be employed for antimicrobial preservation of ophthalmic, nasal and oral solutions. D3 indicates using 0.15 to 2 mg/ml methylparaben and/or 0.05 to 0.1 mg/ml propylparaben in ophthalmic preparations; 0.15 to 2 mg/ml methylparabens and/or 0.1 to 0.2 mg/ml propylparaben in oral solutions/suspensions; and 0.33 mg/ml methylparaben and/or 0.17 mg/ml propylparaben in nasal solutions. The ranges of concentrations indicated in D3 almost completely overlap with the range of concentrations defined in claim 1 of the contested patent. The skilled person, in order to solve the technical problem as formulated in paragraph 4.1.5 above, would with every expectation of success, directly follow the indications provided in D3 (table under Section 7), and he would modify the ophthalmic formulation of D1 (example 5) to comprise 0.15-2 mg/ml methylparaben and/or 0.05-0.1 mg/ml propylparaben. In doing so, the skilled person would end up necessarily with combined amounts of parabens falling within the range "more than 0 and less than 1.5 mg/ml" defined in claim 1 of the contested patent in a straightforward manner.

The patent Proprietor has alleged that the skilled person would not use the concentrations of parabens indicated in Section 7 of D3 for three reasons:

i) Fisrtly, the amounts of methylparaben and propylparaben indicated in the tables under Section 7 of D3 (pages 340 and 450) are only amounts intended for use in combination with other preservatives, not for use of methylparaben, propylparaben or their combination as the only preservative(s).

However, this contention is of no merit, because, as explained above, claim 1 of the opposed patent does not require that parabens are the only preservatives present in the composition. The technical problem is not that of finding effective antimicrobial concentrations for use of parabens alone. In this sense, the Opponent's allegation that the patent in suit does not provide any demonstration of an effect for the combination of the active ingredient with parabens alone is irrelevant for the present analysis. It is apparent that the patent in suit does not disclose such antimicrobial use of parabens alone, but, to the contrary, it relates to the use of parabens always in combination with various other antimicrobial preservatives or preservative-enhancing agents. It is true that D3 teaches that parabens are generally used in combination with other antimicrobial and/or preservative-enhancing agents, and that additive and synergistic effects may occur (see Section 10). Precisely this, and nothing else, is what is disclosed also in the patent in suit. Furthermore, D3 in Section 10 also teaches that parabens are specially active against yeast and molds (such as Aspergillus and Candida). Thus, in order to achieve a broad-spectrum antimicrobial effect, the skilled person would indeed use the parabens concentrations indicated in D3 in combination with other antimicrobials and/or preservative-enhancing agents, thereby arriving at the subject-matter of the opposed patent. For these reasons, the Patentee's argument must fail.

ii) Secondly, according to the Patentee D3 does not indicate that the amounts of parabens given in the tables under Section 7 are sufficient for achieving an effective preservative effect when used as the only preservative. D3 in Section 11 (table I) provides information about the MICs (minimum inhibitory concentrations) of methylparaben and propylparaben in aqueous solutions. From table I on page 341 of D3 one can derive that the minimum inhibitory concentration of methylparaben in ophthalmic solutions has to be more than 4 mg/ml (4000 microgram/ml) which is the minimum concentration required for inhibition of Pseudomonas aeruginosa, a pathogen involved in harmful eye infections. By comparing Sections 7 and 11 (table I) of D3 one easily understands that the amounts indicated in Section 7 (lower limits) are only theoretical and not suitable for providing sufficient preservative effect when methylparaben is used as the only preservative. Same considerations apply to

propylparaben. Hence, D3 would teach that not even the concentration of parabens used in D1 (3 mg/ml) is sufficient to defeat well known pathogens which may occur in ophthalmic formulations.

This argumentation is also devoid of merit. Firstly, it is stressed again that claim 1 of the opposed patent does not require that parabens are the only preservatives present in the composition. Secondly, claim 1 does not require that the parabens include necessarily methylparaben; the parahydroxybenzoate ester can be e.g. propylparaben; in the case of propylparaben, the MIC value required for inhibition of Pseudomonas aeruginosa indicated in D3 (table I on page 451) is >1 mg/ml, which is, by the way, the concentration of propylparaben used in D1 (example 5), and fully overlaps with the range of less than 1.5 mg/ml defined in present claim 1. More importantly, the argumentation of the patent Proprietor appears to be only a deliberate attempt to create confusion. The MIC values of an antimicrobial agent is a property thereof defined as the lowest concentration of the antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation, which allows for comparison of the activity of antimicrobial agents. The MIC values reported in table I of D3 are not the minimum concentrations actually needed for providing sufficient or effective preservation in an aqueous solution. In the patent in suit, compliance with the recommended efficacy criteria according to the Eur. Pharmacopoeia requires the number of viable spores to be less than 1000 per ml after 28 days from the inoculation, which is a different criterion than that used in determining the MIC values. In D3, suitable/typical concentration values needed for providing effective antimicrobial preservation in various liquid pharmaceutical formulations are given in the tables under Section 7, not in tables I under Section 11; otherwise, the information provided in the tables under Section 7 would be simply superfluous and useless. It is apparent from D3 (Sections 7 and 10) that typical concentration values of parabens suitable for providing effective antimicrobial preservation in various liquid pharmaceutical formulations may be much lower than the MIC values reported on table I, as parabens are usually employed in combination and additive and synergistic effects occur (see Section 10). In summary, the information provided in table I of D3 would by no means deter the skilled person from using the typical values for paraben concentrations indicated under Section 7.

iii) Thirdly, the skilled person, so the Patentee, would not have any motivation for combining D1 with D3, because D3 (Section 14) indicates that "although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for this type of formulations". Hence, D3 would suggest that parabens should not be used in ophthalmic preparations.

The Opposition Division also dismisses this contention. First of all, it is apparent that claim 1 of the contested patent is not limited to ophthalmic preparations. On the contrary, the patent in suit covers also e.g. oral solutions (see claim 7). D3 in the tables under Section 7 reflects the concerns existing before the date of priority of the contested patent regarding the use of parabens in injection and ophthalmic preparations in particular. These concerns are further explained in Section 14 of D3, as the Patentee correctly notes. However, under Section 14 it is also explained that parabens are widely used in e.g. oral pharmaceutical compositions, and in that application methylparaben is typically used in amounts as high as 2 mg/ml (see table under Section 7). In any event, it is true that D3 reflects the existing safety concerns at the date of priority of the patent in suit, and it reports that the WHO has set an estimated total acceptable daily intake for methyl-, ethyl- and propylparabens at up to 10 mg/kg body-weight (see Section 14). Following this explicit indication of D3, the skilled person would be by no means deterred from using the typical paraben concentration values for oral solutions of 0.15 to 2 mg/ml for methylparaben and/or 0.1 to 0.2 mg/ml for propylparaben indicated in the tables under Section 7, but would be inclined to use the lower values in the aforementioned ranges, thereby unavoidably ending up with concentration values falling within the area covered by claim 1 of the opposed patent.

For all these reasons, the Opposition Division comes to the conclusion that the subject-matter of claim 1 of the patent in suit as granted is obvious.

Finally, the following remarks are added: The line of reasoning underlying the patent Proprietor's argumentation of inventive step stresses the point that the discovery or realisation of a self-preserving effect of the active agents cetirizine, levocetirizine and efletirizine in liquid preparations for all strains except for Aspergillus is the decisive fact allowing the reduction of the amounts of parabens as claimed in the patent in suit. The Opposition Division underlines again that this line of reasoning is, however, based on an incorrect formulation of the objective technical problem following the problem-solution approach. Furthermore, irrespective of whether or not the alleged self-preserving effect of the active agent actually exists, the above analysis demonstrates that the discovery or realisation of this alleged effect is not the only motivation or incitation that the skilled person, starting from D1 (example 5), would have for carefully considering and looking at the concentration of parabens in liquid pharmaceutical compositions of cetirizine.

Auxiliary request 1

Claim 1 of Auxiliary request 1 is limited to liquid pharmaceutical compositions comprising levocetirizine and methylparaben/propylparaben in weight ratio 9/1 in concentrations of 0.01 to 1.125 mg/ml.

During the oral proceedings, the Opponent raised objections of lack of clarity and lack of inventive step.

Regarding clarity, the Opponent argues that it is unclear whether the amounts referred to in claim 1 relate to each of methylparaben and propylparaben independently, or to their combination; and/or whether the compositions as defined in claim 1 may comprise other preservatives, in particular other parabens.

The Opposition Division cannot agree with the Opponent's view. It is clear that claim 1 defines a fixed combination of methylparaben and propylparaben in fixed weight ratio methylparaben/propylparaben of 9/1, and hence the concentrations 0.01 to 1.125 mg/ml defined in claim 1 are the concentrations of the fixed combination. On the other hand, a composition comprising levocetirizine and the fixed combination methylparaben/propylparaben does not exclude the presence of any other additives or excipients, in particular those which may exert an antimicrobial and/or preservative-enhancing function, as already explained above for the Main request. Any other interpretation is only meaningless in view of the disclosure of the patent and/or an attempt to create confusion. Hence, claim 1 of Auxiliary request 1 meets the requirements of Art. 84 EPC.

Regarding inventive step, the additional features introduced in claim 1 of Auxiliary request 1 do not change anything to the problem-solution analysis as carried out above in respect of the Main request.

With regard to the limitation to levocetirizine, no particular technical effect in terms of antimicrobial preservation/stabilisation of the liquid composition is demonstrated in the patent in suit for the levorotatory enantiomer of cetirizine as compared to the racemic form (cetirizine). Furthermore, the use of levocetirizine instead of racemic cetirizine would be obvious from D4, as the levorotatory enantiomer has more therapeutic activity than racemic cetirizine, and hence less amounts of the pure enantiomer than of the racemic mixture are required in the formulation.

As for the use of methylparaben/propylparaben in fixed combination in weight ratio 9/1, this feature merely represents an obvious alternative, as it is not shown to be associated with any particular technical effect. The compositions of examples 3 and 4 of the patent in suit all comprise methylparaben/propylparaben in fixed combination in ratio 9/1; hence the analysis carried out above for the Main request applies mutatis mutandis to Auxiliary request 1.

As for the limits of the concentration range 0.01 to 1.125 mg/ml, both end point values are not shown to be linked to any technical effect in particular. Analogous considerations apply as for the range more than 0 and less than 1.5 mg/ml of the Main request.

It is stressed once more that the technical problem is not that of determining the lowest possible concentration of parabens having effective antimicrobial activity for the reasons explained above, and hence a limitation of the concentration range cannot change anything in the problem-solution analysis unless some further technical effect can be demonstrated within the limited range. The compositions according to claim 1 of Auxiliary request 1 may comprise as much as 1.125 mg/ml of parabens (methylparaben/propylparaben 9/1). However, the limit of the concentration range 1.125 mg/ml has not been shown to be critical in terms of achieving an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of levocetirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens (see table 6). On the other hand, no significant difference is observed in tables 15 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.375, 0.75 or 1.125 mg/ml of methylparaben/propylparaben 9/1. In this sense, the upper limit 1.125 mg/ml defined in claim 1 of Auxiliary request 1 appears to be a completely arbitrary choice.

In the absence of any further technical effect being demonstrated for these technical features, any possible ratios of methylparaben to propylparaben and any concentration values taken from those indicated in D3 (Section 7, tables) would equally solve the technical problem as formulated in paragraph 4.1.5 above with every expectation of success, and hence merely represent trivial alternatives. In this sense, the arbitrary choice of any possible limit values for the range of paraben concentrations in any weight ratios of methylparaben/propylparaben among those explicitly indicated in D3 (Section 7, tables) is equally obvious for the skilled person.

Furthermore, the fixed combination of methylparaben/propylparaben in weight ratio 9/1 defined in claim 1 of Auxiliary request 1 is also indicated in D3 in the context of parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7). Claim 1 of Auxiliary request 1 also covers parenteral formulations. The skilled person would therefore apply the ratio 9/1 in a straightforward manner to any typical/suitable concentrations of parabens as disclosed in D3 (Section 7, tables) for various liquid pharmaceutical compositions. Thus, e.g. taking the typical concentration values 0.05 mg/ml and 0.1 mg/ml of propylparaben indicated in D3 (Section 7, table), one ends up with total amounts of combined methylparaben/propylparaben in ratio 9/1 of (9x0.05 + 0.05 =) 0.5 mg/ml, or (9x0.1 + 0.1 =) 1.0 mg/ml, both concentration values falling within the range defined in claim 1 of Auxiliary request 1.

Accordingly, Auxiliary request 1 lacks an inventive step.

Auxiliary request 2

Claim 1 of Auxiliary request 2 is limited to liquid pharmaceutical compositions comprising levocetirizine and preservatives selected from methylparaben/ propylparaben in weight ratio 9/1 in concentrations of 0.1 to 1.125 mg/ml.

During the oral proceedings, the Opponent expressed objections of added matter (Art. 123(2) EPC), lack of clarity and lack of inventive step.

Regarding clarity, the Opponent argues in same way as with respect to the Auxiliary request 1.

Regarding Art. 123(2) EPC, the Opponent essentially alleges that the limitation to compositions comprising methylparaben/propylparaben as the only preservatives in the formulation is not disclosed in the originally filed patent application.

The patent Proprietor argues that support for this feature can be found in the patent application as originally filed (page 4 lines 22-24, corresponding to paragraph [0019] last sentence of the specification).

The Opposition Division, again, does not agree with the Opponent's contentions in this respect.

As for clarity, same reasons apply as for Auxiliary request 1. A technically sensible interpretation of the wording of claim 1 of Auxiliary request 2, in particular in the context of the actual disclosure of the specification, does not exclude that the liquid composition may comprise any other additives or excipients, in particular those which may exert an antimicrobial and/or preservative-enhancing function. Claim 1 is clear in this respect, and the requirements of Art. 84 EPC are met.

Precisely because the only technically sensible reading of claim 1 of Auxiliary request 2 is that as explained above, it follows that the requirements of Art. 123(2) EPC are also met. Basis for the claimed ratio 9/1 is found in the sentence "Best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight" on page 4 lines 22-24 of the original patent application. Claim 1 of Auxiliary request 2 does not limit in any manner the subject-matter to liquid compositions of levocetirizine containing methylparaben/propylparaben as the only preservatives exclusively. If an

interpretation of claim 1 with this intentional meaning were to be done, then claim 1 would find no basis in the aforementioned passage on page 4 lines 22-24, and it would indeed add subject-matter in contravention of Art. 123(2) EPC.

Regarding inventive step, the further limitation of claim 1 of Auxiliary request 2 to compositions comprising the fixed combination of methylparaben/propylparaben in weight ratio 9/1 in concentration values starting with 0.1 mg/ml does not change anything to the problem-solution analysis carried out in respect of Auxiliary request 1. Again, the end point values of the concentration range 0.1 to 1.125 mg/ml represent only a trivial variation and an arbitrary choice among the concentration values of parabens indicated in D3 (Section 7, tables) which the skilled person would equally use with every expectation of success to solve the technical problem as formulated in paragraph 4.1.5 above.

It is stressed again that the technical problem is not that of determining the lowest possible concentration of parabens having effective antimicrobial activity. Hence, a limitation of the concentration range cannot change anything in the problem-solution analysis unless some further technical effect can be demonstrated within the limited range. The compositions according to claim 1 of Auxiliary request 2 may comprise, again, as much as 1.125 mg/ml of methylparaben/propylparaben 9/1. Neither the upper limit of the concentration range 1.125 mg/ml nor the lower limit 0.1 mg/ml have been shown to be critical in terms of achieving an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of levocetirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens (see table 6). On the other hand, no significant difference is observed in tables 15 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.375, 0.75 or 1.125 mg/ml of methylparaben/propylparaben 9/1. In this sense, the upper limit 1.125 mg/ml defined in claim 1 of Auxiliary request 2 appears to be a completely arbitrary choice.

In the absence of any further technical effect being demonstrated for these technical features, any possible ratios of methylparaben to propylparaben and any concentration values taken from those indicated in D3 (Section 7, tables) would equally solve the technical problem as formulated in paragraph 4.1.5 above with every expectation of success, and hence merely represent trivial alternatives. In this sense, the arbitrary choice of any possible limit values for the range of paraben concentrations in any weight ratios of methylparaben/propylparaben among those explicitly indicated in D3 (Section 7, tables) is equally obvious for the skilled person.

Furthermore, the fixed combination of methylparaben/propylparaben in weight ratio 9/1 defined in claim 1 of Auxiliary request 2 is also indicated in D3 in the context of parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7). Claim 1 of Auxiliary request 2 also covers parenteral formulations. The

skilled person would apply the ratio 9/1 in a straightforward manner to any typical/ suitable concentrations of parabens as disclosed in D3 (Section 7, table) for various liquid pharmaceutical compositions. Thus, e.g. taking the concentration values 0.05 mg/ml and 0.1 mg/ml of propylparaben disclosed in D3 (Section 7, table), one ends up with total amounts of combined methylparaben/propylparaben in ratio 9/1 of (9x0.05 + 0.05 =) 0.5 mg/ml, or (9x0.1 + 0.1 =) 1.0 mg/ml, both concentrations falling within the range defined in claim 1 of Auxiliary request 2. Thus, the skilled person arrives at the subject-matter of claim 1 of Auxiliary request 2 in a straightforward manner.

Final remarks regarding Auxiliary requests 1 and 2

Finally, it is particularly stressed that a more ambitious formulation of the technical problem (as in point 4.1.4 above) in view of the limitation of Auxiliary request 2 to concentrations of methylparaben/propylparaben 9/1 starting with 0.1 mg/ml cannot be accepted.

D3 teaches the use of parabens, in particular in combination, to defeat specifically yeast/mold contamination, as it indicates that parabens are more active against yeast/ mold than against bacteria (see Sections 7 and 10). D3 clearly indicates minimum concentrations of methylparaben in oral solutions and ophthalmic preparations of 0.15 mg/ml, and minimum concentrations of 0.05 mg/ml for propylparaben (Section 7, tables). Hence, an expectation of success in meeting the recommended efficacy criteria (preservative effectiveness) on yeast/mold strains such as Aspergillus and Candida requires the use of the minimum concentrations disclosed in D3. Contrary to this, the concentration 0.1 mg/ml of methylparaben/propylparaben 9/1 defined in present claim 1 means concentration values of 0.09 mg/ml methylparaben and 0.01 mg/ml propylparaben; in particular the latter value is 5 times lower than the minimum concentration of propylparaben indicated in D3 (Section 7, table). It is therefore not credible that the concentration of 0.1 mg/ml of methylparaben/propylparaben 9/1 defined in claim 1 of Auxiliary request 2 would be sufficient for solving the problem of fulfilling the recommended efficacy criteria, in particular in terms of providing preservative effectiveness against yeast/molds such as in particular Aspergillus, and the patent specification does not provide any demonstration in this respect either. Rather to the contrary, it shows in table 7 that a concentration of 0.15 mg/ml of methylparaben/propylparaben 9/1 is on the borderline as to the fulfilment of the recommended efficacy criteria for Aspergillus in liquid compositions of cetirizine. For levocetirizine specifically, the lowest concentrations of methylparaben/propylparaben 9/1 tested in the patent in suit are even much higher than 0.15 mg/ml (0.375 mg/ml,

see tables 15-20). Comparison of results in tables 7 and 15 of the patent in suit demonstrates that in oral solutions of levocetirizine comprising 0.375 mg/ml of methylparaben/propylparaben 9/1 (table 15) the number of viable Aspergillus spores after 14 days from inoculation is even higher than in corresponding oral solutions of racemic cetirizine comprising only 0.15 mg/ml of methylparaben/propylparaben 9/1 (table 7). Hence, it is not plausible that a concentration of 0.1 mg/ml of methylparaben/propylparaben 9/1 would be sufficient to meet the recommended efficacy criteria for Aspergillus.

These reasons even more apply to claim 1 of Auxiliary request 1 defining the lower limit of the concentration range 0.01 mg/ml.

Accordingly, the Opposition Division comes to the conclusion that the objective technical problem must remain as formulated in point 4.1.5 above. It follows that Auxiliary requests 1 and 2 do not involve an inventive step.

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Application No. / Patent No.	Ref.	Date
05 758 582.0 - 2112 / 1 768 649 /	P30048-EPOP WB	22.12.2011
Proprietor UCB FARCHIM S.A.		

Decision revoking the European Patent (Art. 101(2) and 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 29.11.2011 - has decided:

European Patent No. EP-B- 1 768 649 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

Registered letter with advice of delivery
EPO Form 2331 12.07TRI

Chairman: Sindel, Ulrike
2nd Examiner: Giró, Annalisa
1st Examiner: Giménez Miralles, J

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Enclosure(s): 24 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97-98 EPC (Form 2019)
Minutes of oral proceedings
Main request, Aux. request 1, and Aux. request 2

to EPO postal service: 19.12.11

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Application No.: 05 758 582.0

Patent No.: EP-B-1 768 649

Direct Decision:

☐ **yes** ☒ **no**

Revocation of the European Patent (Art. 101(2) and 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 29.11.2011 - has decided:

European Patent No. EP-B- 1 768 649 is revoked.

The Grounds for the decision (Form 2916) are enclosed.

7.12.11
Date

Chairman	1st Examiner	2nd Examiner	Legally qualified member
Sindel, Ulrike	Giménez Miralles, J	Giró, Annalisa	

02/12/11

1. After opening the oral proceedings at 9:01h, the Chairwoman summarized the requests on file as being, for the Opponent, the revocation of the patent in its entirety, on the grounds of Article 100(a) EPC in combination with Articles 54 and 56 EPC and, for the Patent Proprietor, the rejection of the opposition and the maintenance of the patent as granted (Main Request), or in the amended form of Auxiliary Requests 1, 3 or 4 filed on 29.09.2011 or of Auxiliary Request 2 filed on 19.10.2010. The parties confirmed their requests.

2. The novelty of the Main Request was discussed. The Opponent referred to her written submissions and pointed out that claim 1 lacked novelty over the public prior use of the products ZODAC GTT and ZODAC SIR, which comprised 1.5 mg/ml of parabens. This was shown by the marketing authorizations of said products in Slovakia and Czech Republic (documents D5-D8) in combination with their information leaflets (D9 and D10) and the dates of their launch on market (D11). In particular, the Opponent stressed that a content of 1.5 mg/ml of parabens was novelty destroying to the claimed upper limit of "less than 1.5 mg/ml", as, due to a certain margin of error during the manufacturing procedure, the products would comprise parabens in an amount of about 1.5 mg/ml, i.e. also in a lower amount. The Opponent further referred to the decision T1022/99.

The Patentee objected that the value of 1.5 mg/ml falled outside the range of "less than 1.5 mg/ml". Further, in the pharmaceutical field the exactness of amounts in a composition was of outmost importance and, however, variations in manufacturing procedures were irrelevant while assessing novelty over the disclosure of a particular document. The Patentee stressed also that D9 and D10 did not provide evidence of the actual parabens concentration in ZODAC GTT and ZODAC SIR which were commercially available before the priority date.

3. After a break for deliberation (9.18h-9.31h), the Chairwoman announced that the Opposition Division was of the opinion that the Main Request was novel and invited the parties to discuss inventive step.

3.1 The Opponent indicated D1, example 5, as the closest prior art. This document disclosed a composition comprising cetirizine and parabens in an amount of 0.3 g/ 100ml, corresponding to 3.0 mg/ml. An amount of "more than 0 and less than 1.5 mg/ ml" was not disclosed, nor the presence of levocetirizine or efletirizine. The technical effect deriving from the reduced amount of parabens was the fulfilment of antimicrobial efficacy criteria while lowering the adverse effects related to hypersensitivity to parabens. The technical problem was therefore formulated as the provision of a composition wherein antimicrobial efficacy of parabens and their toxicity

are balanced and optimized. The Opponent argued that in the patent no convincing evidence was provided to make credible that the problem was actually solved over the claimed range of parabens concentrations “more that 0 and less than 1.5 mg/ml”. Indeed, no compositions comprising less than 0.15 mg/ml had been tested and it appeared that very low concentrations hardly could provide an antimicrobial activity, i.e. could solve the problem. Further, while no evidence for the achievement of reduced allergic reactions was provided in the patent, it was general knowledge for the skilled person to reduce parabens amount as much as possible in order to reduce their toxicity. Said general knowledge was represented by a handbook such as D3, which explicitly suggested the use of methylparaben and propylparaben in ophthalmic drops, oral and nasal solutions in concentrations falling within the range claimed in the Main Request. The Opponent also added that no particular effect appeared to arise from the choice of levocetirizine or efletirizine, as well as from the selection of the claimed parabens, which are very well known in the art.

Finally, referring to her written submissions dated 29.09.2011, the Opponent doubted whether the problem as defined above could at all be solved by the subject-matter of claim 1. In fact, the compositions tested in the patent always comprised other substances having a preservative effect, such as acetic acid, sodium acetate (as from D12-D15) or boric acid (as from [0019] of the patent), or substances having an enhancing effect on parabens preservation efficiency, such as sorbitol, glycerin and propyleneglycol (as from D3 and D15). Therefore, as it was not clear which impact these substances had on the antimicrobial effect shown in the examples, no evidence could be found to support that said effect was only due to parabens alone combined with the active ingredients. In particular, none of the examples showed unambiguously that cetirizine, levocetirizine or efletirizine alone possessed any antimicrobial effect.

3.2. The Patentee pointed out that D12-D15 were belated, not prima facie relevant and therefore not admissible documents. In addition, two of them were published after the priority date and did not relate to the field of pharmaceuticals. The Opposition Division postponed the decision concerning the admissibility of D12-D15 to a later stage of the discussion.

The Patentee stressed the difference between a disinfectant and a preservative and explained that acetic acid, sodium acetate, sorbitol, glycerin and propyleneglycol were usual excipients in pharmaceutical preparations, but they did not possess any preservative or preservative enhancing effect, in particular at the low concentrations used in the compositions reported in the examples. In addition, glycerin and sorbitol were usually employed in growth media for microbial cultures as supplement for bacterial growth. Further, the Patentee explained that the field of pharmaceutical is highly regulated in terms of safety and that for a product to be marketed specific criteria, such as those required by the European Pharmacopoeia, must be met.

Therefore, simply lowering the amount of preservatives in a composition in order to reduce their toxicity would not be a straightforward way for the skilled person, as safety of the composition could be affected. In addition, the Patentee noted that the antimicrobial activity tested in the examples of the patent corresponded to the Preservative Efficacy Test (PET) according to the European Pharmacopoeia (Chap. 5.1.3.). By comparing the results obtained for Examples 1 and 2 with those for Examples 3 and 4 it was clear that, while cetirizine possesses a self-preserving effect (see Examples 1 and 2) against *P. aeruginosa*, *E. coli*, *S. aureus* and *C. albicans*, only after the addition of very low amounts of methylparaben and propylparaben (e.g. 0.15 mg/ml) also *A. niger* could be inhibited, thereby fulfilling the PET recommended efficacy criteria. At the request of the Chairwoman for evidence showing that the PET requirements would be met also by the addition of lower amounts of parabens (such as 0.0001 mg/ml), the Patentee answered that no data were available.

4. After a break for deliberation (10.34h-11.06h), the Chairwoman announced that the Opposition Division was of the opinion that the Main Request did not meet the inventive step requirements of Article 56 EPC, as the problem was not proven to be solved over the whole claimed scope.

4.1 The Patentee withdrew the 1st Auxiliary Request and renumbered previous 2nd, 3rd and 4th Auxiliary Requests in new 1st, 2nd and 3rd Auxiliary Requests, respectively.

4.2 The Opponent raised an objection under Article 84 EPC against the 1st Auxiliary Request, specifying that this objection did not apply to the patent as granted. The Opponent considered unclear, according to the wording of claim 1, whether the range of 0.01-1.125 mg/ml referred to the amount of methylparaben alone, of propylparaben alone or of a mixture of the two. Further, it was not clear whether other kind of parabens could additionally be present in the composition, contrary to the whole teaching of the patent. The Patentee agreed in amending claim 1 according to the wording of claim 1 as granted in order to clarify that the only parabens present in the composition are methylparaben and propylparaben. The Opponent accepted this solution. This amendment was postponed to a later point.

4.3 The Opponent had no objections under Articles 123(2) EPC and 54 EPC, but reiterated the inventive step objections based on D1 in combination with D3 mentioned under point 3.1. To these arguments, the Opponent added that D3 suggested the use of methylparaben and propylparaben in combination in a weight ratio 9:1, that no specific effect arised from the selection of levocetirizine as active agent and that, again, the patent provided no evidence that levocetirizine possessed a preservative activity.

The Patentee argued that, as cetirizine was a racemic mixture containing 90% of levocetirizine, it was credible that the self-preservative activity shown in Example 1 for cetirizine also applied to levocetirizine. This was also evident from the comparison of Example 3, Tables 7 and 8, with Example 4, Table 15.

5. After a break for deliberation (11.34h-12.01h), the Chairwoman announced that the Opposition Division was of the opinion that the 1st Auxiliary Request did not meet the inventive step requirements of Article 56 EPC, as the problem was not proven to be solved over the whole claimed scope.

5.1 The Patentee withdrew the 2st Auxiliary Request and renumbered the 3rd Auxiliary Request in new 2nd Auxiliary Request (corresponding to the 4th Auxiliary Request filed on 29.09.2011). The admissibility of D14 was discussed. The Opposition Division admitted D14 as a relevant document.

5.2 The Opponent objected that the wording of claim 1 of the 2nd Auxiliary Request referred to methylparaben and propylparaben in a ratio of 9:1 as being the only preservatives comprised in the composition, a limitation not provided in the granted patent and therefore contrary to Article 123(2) EPC.

5.3 The Patentee replied that basis for the subject-matter of claim 1 was given in [0019]-[0020] of the patent, wherein methylparaben and propylparaben in a ratio of 9:1 were disclosed as a preferred embodiment.

6. After a break for deliberation (12.11-12.25h), the Chairwoman announced that the Opposition Division was of the opinion that the 2nd Auxiliary Request met the requirements of Article 123(2) EPC.

The Opponent objected to the 2nd Auxiliary Request under Article 84 EPC, in relation to the possible presence in the composition of other parabens in addition to methylparaben and propylparaben, as already mentioned under point 4.2. The Patentee proposed again to amend the wording of claim 1.

7. After a break for deliberation (12.31h-13.31h), the Chairwoman announced that the Opposition Division was of the opinion that the 2nd Auxiliary Request met the requirements of Article 84 EPC.

7.1 The Opponent had no objections under Article 54 EPC, but reiterated the inventive step objections based on D1 in combination with D3 mentioned under point 3.1. Further, the Opponent added that in the patent no evidence was provided for the presence of a particular technical effect in relation to the selection of the range

0.1-1.125 mg/ml, which appeared to be arbitrary. The Opponent finally argued that, if it was to assume that also the active agent possessed some preservative effect, its amount was an essential feature for the solution of the problem missing from claim 1.

7.2 The Patentee replied with the same arguments mentioned under point 3.2. In particular, he pointed out that the range of 0.1-1.125 mg/ml was well covered by the examples, which showed that the preservative effect obtained therein was only due to parabens. In this regard, the Patentee stressed that D14 was not relevant, as this document described sodium acetate as having only an inhibitory effect on microorganism growth and not an antimicrobial effect as defined by the patent, i.e. the capability to kill microorganisms (see [0018]). In addition, D14 disclosed that sodium acetate had no effect on *C. albicans*, while in Examples 1 and 2 *C. albicans* was inhibited, thereby confirming that the preservative effect of the compositions was not due to sodium acetate, but only to the self preserving properties of the active agents. Finally, the Patentee underlined that, while on the one hand it was clear that by reducing the parabens amount a linear reduction of adverse effects due to hypersensitivity would be obtained (i.e. no need of evidence for this effect), on the other hand in the field of pharmaceuticals it was not obvious to find a balance between antimicrobial efficacy of parabens and their toxicity whilst still obtaining a composition which fulfilled the PET requirements.

8. After a break for deliberation (14.03h-14.33h), the Chairwoman announced that the Opposition Division was of the opinion that the 2nd Auxiliary Request did not meet the inventive step requirements of Article 56 EPC in view of D1 combined with D3. As no further request had been filed by the Patentee, the Chairwoman announced the decision of the Opposition Division to revoke the patent according to Articles 101(2) and 101(3)(b) EPC.

The proceedings were closed at 14.35h.

[0053] 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 (reference), chlorhexidine acetate (reference) and p-hydroxybenzoate esters.

[0054] 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

[0055] 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, the preservative being 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.

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 preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

4. A liquid pharmaceutical composition according to claim 1 or 2, **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.

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

6. A liquid pharmaceutical composition according to any of the claims 1 to 4, **characterized in that** the active substance is levocetrizine.

7. 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.

Patentansprüche

1. Flüssige pharmazeutische Zusammensetzung, umfassend eine aktive Substanz, ausgewählt aus Cetirizin, Levocetirizin und Efletirizin, und mindestens ein Konservierungsmittel, wobei die Menge an Konservierungsmittel im Falle von Parahydroxybenzoatestern mehr als 0 und weniger als 1,5 mg/ml der Zusammensetzung beträgt, wobei das Konservierungsmittel aus der Gruppe von Methylparahydroxybenzoat, Ethylparahydroxybenzoat, Propylpara-

EP 1 768 649

~~2nd~~ **Auxiliary Request 1**

Kopie für Prüfer

AR 1

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

EP 1 768 649

~~4th~~ **Auxiliary Request** 2

Kopie für Patentakte

AR2

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.1 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

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Date
22-12-2011

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 2112 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

EPA/EPO/OEB Formblatt/Form/Formulaire : 2331 + 2042

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Applicant/Proprietor: UCB FARCHIM S.A.	

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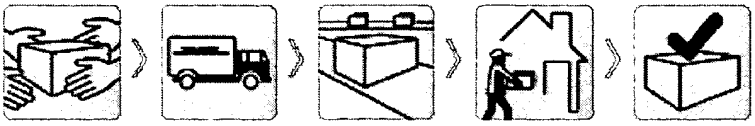

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UCB FARCHIM S.A.	

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European patent application No. 05758582.0

Appeal - for immediate attention

I. Findings

1. ☒ Appeal in which **more than one party** is involved (opposition procedure, except when all oppositions have been withdrawn). Refer the case to the Board of Appeal without delay using EPO Form 2703.

2. ☐ Appeal in which **only one party** is involved (examination procedure and opposition procedure if all oppositions have been withdrawn).

2.1 Requirements of Article 108 EPC

The **notice of appeal** has been filed within the time limit.	yes ☐	no ☐
The **appeal fee** has been paid within the time limit.	yes ☐	no ☐
The **statement of grounds** has been filed within the time limit.	yes ☐	no ☐

If one of the answers set out above is "no", refer the case to the Board of Appeal without delay using EPO Form 2703. The Board of Appeal decides on the admissibility of the appeal.

2.2 Special cases which have to be referred to the Board of Appeal without delay using EPO Form 2703

☐ Request for re-establishment of rights into the appeal period (Art. 122 EPC)
☐ Withdrawal of the appeal
☐ Expiry of the three-month time limit for Interlocutory revision (Art. 109(2) EPC)
☐ Request for correction of the appeal (R. 139 EPC)

.....	.....	.....
Date	Formalities Officer	Director/SCAPE (for information)

II. Appeal against the decision of the Formalities Officer

☐ The appeal is allowable and well-founded. The decision under appeal is rectified (Art. 109(1) EPC). EPO Form 2710 is to be dispatched.
  ☐ No request for reimbursement of the appeal fee has been filed.
  ☐ A request for reimbursement of the appeal fee has been filed.
    ☐ Reimbursement of the appeal fee is ordered (R. 103 EPC).
    ☐ The request for reimbursement of the appeal fee cannot be allowed. **Refer the case to the Board of Appeal without delay using Form 2703 (R. 103(2) EPC).**
☐ The decision under appeal is not rectified. Refer the case to the Board of Appeal without delay using EPO Form 2703 (Art. 109(2) EPC).

.....	.....	.....
Date	Formalities Officer	SCAPE (for information)

III. Appeal against the decision of the Examining/Opposition Division

☐ To the Examining Division ☐ To the Opposition Division
X To the Board of Appeal

20-02-2012	Ullrich, Chantal
Date	Formalities Officer

To the Formalities Officer

☐ The appeal is allowable and well-founded. The decision under appeal is rectified (Art. 109(1) EPC). EPO Form 2710 is to be dispatched.

- ☐ No request for reimbursement of the appeal fee has been filed.
- ☐ A request for reimbursement of the appeal fee has been filed.
  - ☐ Reimbursement of the appeal fee is ordered (R. 103 EPC).
  - ☐ The request for reimbursement of the appeal fee cannot be allowed. **Refer the case to the Board of Appeal without delay using EPO Form 2703 (R. 103(2) EPC).**

☐ The decision under appeal is not rectified. Refer the case to the Board of Appeal without delay using EPO Form 2703 (Art. 109(2) EPC).

☐ Examining Division ☐ Opposition Division

.....
Date

.....	.....	.....	.....
Chairman	2nd Examiner	Primary Examiner	Legal Member

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Dipl.-Phys. Dr. Stephan Barth [1,2]
Dipl.-Ing. Glyndwr Charles [1,2]
Dipl.-Ing. Oliver Hassa [1,2]
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Our Ref.: P30048-EPOP SAN/lvo | February 17, 2012

Opposition against EP 1 768 649 B1 – Decision of the Opposition Division of December 22, 2011
Opponent: Zentiva k.s.
Appellant/Patentee: UCB FARCHIM S.A, Allée de la Recherche 60, 1070 Bruxelles, Belgium

On behalf of the Patentee an

Appeal

is filed against the decision of the Opposition Division according to Art. 106 to 108 EPC.

Requests:

1. It is requested to set aside the decision of the opposition division of *December 22, 2011* in its entirety.

2. Oral proceedings are requested should the Board of Appeal intend not to grant the request according to 1.

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The official fee for the appeal shall be deducted from our current account No. 28 000 484 at the EPO. A written statement setting out the grounds of appeal will be filed in due course.

Respectfully submitted

Wolfgang Sandmann

European Patent Attorney

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	05758582.0
Applicant's or representative's reference	P30048-EPOP

	Description of document	Original file name	Assigned file name
1	Notice of appeal	P30048-EPOP Appeal.pdf	APPEAL.pdf

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	011 Fee for appeal	1	1 180.00	1 180.00
	Total:		**EUR**	**1 180.00**

	Payment	
1	Mode of payment	Debit from deposit account
	Currency:	EUR
	The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.	
	Deposit account number:	28000484
	Account holder:	Isarpatent
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28000484
	Account holder:	Isarpatent

Signatures

Place: **Munich**

Date:	**20 February 2012**
Signed by:	**DE, Isarpatent GbR, W. Sandmann 12098**
Capacity:	**(Representative)**

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	1513169	
Application number	EP05758582.0	
Date of receipt	20 February 2012	
Receiving Office	European Patent Office, The Hague	
Your reference	P30048-EPOP	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (2 p.)	ep-sfd-request.xml APPEAL.pdf\P30048-EPOP Appeal.pdf (2 p.)
Submitted by	CN=W. Sandmann 12098,O=Isarpatent GbR,C=DE	
Method of submission	Online	
Date and time receipt generated	20 February 2012, 11:59 (CET)	
Message Digest	D0:67:6A:E1:84:79:EF:54:B7:93:9D:50:F0:AA:D7:26:1D:6D:5D:15	

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Datum/Date
23.02.12

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

File number: **T0371/12-3.3.02**

Commencement of Proceedings before the Board of Appeal

The letter dated 17.02.12 filed by the patent proprietor against the decision of the European Patent Office of 22.12.11 has been referred to Board of Appeal 3.3.02.

The reference number is mentioned above.

Any further communications should be addressed to Directorate-General 3 of the European Patent Office and should quote this reference number.

The Registrar D. Meyfarth
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Annex: letter dated 17.02.12
Registered letter

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Datum/Date
23.02.12

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO 01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

File number: **T0371/12-3.3.02**

Commencement of Proceedings before the Board of Appeal

The letter dated 17.02.12 filed by the patent proprietor against the decision of the European Patent Office of 22.12.11 has been referred to Board of Appeal 3.3.02.

The reference number is mentioned above.

Any further communications should be addressed to Directorate-General 3 of the European Patent Office and should quote this reference number.

The Registrar D. Meyfarth
Tel.: 089 / 2399 - 3321

Annex: letter dated 17.02.12

Registered letter

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Date: 06.03.12

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

Refund of fees

The following fee(s) was/were paid in respect of the application 05758582.0:

Fee	Reference	Voucher No	Date	Currency	Amount
Appeal fee	011	00574472	20.02.12	EUR	1 180,00
Appeal fee	011	00573526	20.02.12	EUR	1 180,00

According to the present state of the file the refund will be made by:

CREDITING THE DEPOSIT ACCOUNT 28000484 Isarpatent GbR.

Amount refundable:	Reference	Currency	Amount	Voucher No
	011	EUR	1.180,00	00057633

Reason for refund: Fee paid twice

The Authorising Officer
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Appeal number: T0371/12-3.3.02

Order

1. In accordance with the business distribution scheme of the Technical Boards of Appeal, the following shall hear the above appeal:

Chairman: U. Oswald

technically qualified member: M. Ortega Plaza

legally qualified member: D. Prietzel-Funk

In the case of an extended Board:

technically qualified member: _____

legally qualified member: _____

2. The rapporteur shall be: M. Ortega Plaza

3. The additional rapporteur shall be: _____

4. Back to the Registry for further action.

Munich, 17.04.12

Chairman U. Oswald

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PATENT- UND
RECHTSANWÄLTE
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Our Ref.: P30048-EPOP SAN/lvo | April 23, 2012

Opposition against EP 1 768 649 B1 – Decision of the Opposition Division of December 22, 2011
Appeal No.: T0371/12-3.3.02
Opponent: Zentiva k.s.
Appellant/Patentee: UCB FARCHIM S.A, Allée de la Recherche 60, 1070 Bruxelles, Belgium

Further to the Notice of Appeal filed on February 17, 2012, a statement setting out the grounds of appeal according to Article 108 and Rule 99(2) EPC is submitted herewith:

I. REQUESTS

The requests submitted with our Notice of Appeal filed on February 17, 2012 are maintained. It is requested to set aside the decision of the Opposition Division of December 22, 2011 in its entirety.

Further, it is requested to maintain the European patent within the scope of the claims according to the main request as well as to the first and second auxiliary request on which the decision of the Opposition Division were based. A copy of

the decision and the attached claims according to the main, 1st and 2nd auxiliary requests is enclosed to this submission.

II. MAIN REQUEST

The Opposition Division came to the conclusion that the subject matter of claims 1 to 7 as granted fulfills the requirements of Article 54(1) and (2) EPC. The alleged prior use of documents D5, D6, D7, D8 and D11 allegedly proving that the products ZODAC® GTT and ZODAC® SIR were available to the public by prior use was rejected since it has not been proven without any remaining doubt.

However, the Opposition Division came to the conclusion that the subject matter of claim 1 according to the main request is not based on an inventive step according to Article 56 EPC.

Closest Prior Art Document

D1 still is considered to be the closest prior art document. D1, see example 5, discloses a liquid of an ophthalmic composition comprising cetirizine hydrochloride (3 mg/ml) and methylparaben (2 mg/ml) as well as propylparaben (1 mg/ml). Methylparaben and propylparaben are used as preservatives.

The difference of claim 1 of the opposed patent as granted over D1 thus is the amount of parabens used as preservatives which is restricted, according to claim 1 of the main request, to an amount of more than 0 and less than 1.5 mg/ml of parahydroxybenzoate esters.

Unexpected/surprising effects

The Opposition Division took the view that an unexpected or surprising effect has not been proven over the prior art by the experimental data contained in the opposed patent. The following conclusions were drawn by the Opposition Division in this respect:

1. The objective problem posed in the opposed patent was formulated as reducing the risk of adverse effects (such as allergic reactions) by reducing the concentration of preservatives and, at the same time, still providing a sufficient efficacy for antimicrobial preservation.

2. The Opposition Division outlined that neither experimental data is contained in the opposed patent nor had it been submitted which indeed shows that the reduction of the preservative concentration lowers the risk/occurrence of adverse allergic reactions. Therefore, the Opposition Division drew the conclusion that this advantage is speculative only.

3. Regarding the effect of providing/maintaining a sufficient antimicrobial efficacy in terms of fulfilling the recommended efficacy criteria, the Opposition Division outlined that this has been "sufficiently substantiated in the patent in suit".

4. However, the Opposition Division took the view that the compositions provided in the examples, in particular the formulations according to examples 3, 4, 6, 8 and 9 comprising parabens, comprise other additives and excipients which allegedly might exert a concomitant anti-microbial effect and, hence, fulfill the functional definition of a "preservative".

5. No "self-preserving" effect of the active ingredients, i.e. cetirizine, levocetirizine and efletirizine has been demonstrated in the opposed patent. According to the Opposition Division, it remains doubtful to which component or combination of components the antimicrobial stabilization effect shown in the compositions of the opposed patent is to be attributed.

Objective Technical Problem defined by the Opposition Division

With regard to the alleged absence of any unexpected or surprising effects (according to the opinion of the Opposition Division), the objective technical problem has been reformulated as being the provision of further useful liquid pharmaceutical compositions of cetirizine,

levocetirizine or efletirizine comprising parabens having the recommended efficacy of antimicrobial preservation.

Obviousness of the claimed invention - effects

Regarding the alleged obviousness of the presently claimed invention according to the main request in view of the prior art cited, the Opposition Division stated that the objective technical problem of providing a useful liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine comprising parabens showing "some degree of" antimicrobial preservative effectiveness has been actually solved across the whole area covered by claim 1 and that the solution provided in the opposed patent according to claim 1 of the main request was obvious for a skilled person based on D1 and D3.

In the following, the conclusions drawn by the Opposition Division are addressed:

ad 2: The Opposition Division, in our opinion provided a contradictive argumentation regarding the presence or absence of an effect of reducing the preservative concentration with regard to the lowering of risk/occurrence of adverse allergic reactions.

On the one hand, the Opposition Division outlined that "no evidence has been provided in support of this allegation". It, therefore, allegedly remains speculative whether there is any correlation between the amount of preservatives and the risk/occurrence of adverse allergic reactions. However, on the other hand, in terms of obviousness it was stated that "the skilled person is well aware that keeping the concentration of parabens in liquid pharmaceutical compositions at low levels is generally desired due to the controversial discussions ongoing at the time of priority of the opposed patent about the safety and toxicological concerns regarding the use of parabens as preservatives in pharmaceuticals". See p. 15, 4th paragraph of the decision of the Opposition Division. It is further outlined that this safety concern is recognized and discussed in D3.

From our point of view, it is highly contradictive to state that an effect has not been shown and is "speculative", but on the other hand to argue that this effect was clearly conceivable for a skilled

person at the time, the present patent was filed. Anyway, it is confirmed that the objective technical problem of reducing the risk of adverse side-effects by reducing the concentration of parabens is a self-explanatory effect which must not necessarily be demonstrated by experimental data.

ad 4. The Opposition Division stated that, although the antimicrobial efficacy of the compositions according to the examples of the opposed patent has been substantiated as a whole, there are further additives present in the compositions which could be regarded as having anti-microbial activity. Here, the opponent and the Opposition Division in particular referred to "traditional preservatives/antimicrobial agents, such as acetic acid and sodium acetate". The opponent cited new documents D12 to D15 related to vinegar (comprising acetic acid) and its use to manage wounds. D13 describes the use of acetic acid for disinfection and D14 allegedly is related to the use of sodium acetate as a preservative.

Therefore, having a view to examples 1 to 4, the opponent (and also the Opposition Division) came to the conclusion that some additives such as sodium acetate and acetic acid used in those examples might contribute to the antimicrobial preservative effectiveness and, therefore, to the overall antimicrobial characteristics of the pharmaceutical composition according to examples 1 to 4. Or, using the words of the Opposition Division, "it remains doubtful to which component or combination of components the antimicrobial stabilization effect shown in the compositions of the patent in suit is to be attributed" (see p. 12, 2nd paragraph of the decision).

In order to refute this allegation, supplementary examples according to **annex 1** have been performed by patentee.

Comparative example 1

In comparative example 1, sodium acetate and acetic acid in the amounts used in example 1 of the opposed patent have been tested for antimicrobial preservative effectiveness.

That is to say, a composition has been prepared comprising 4.2 mg sodium acetate and 0.500 mg acetic acid in 1 ml of purified water. It is noted that the amount of acetic acid (0.500 mg) provides a pH of 5.

The antimicrobial preservative effectiveness tests were realized according to the European Pharmacopoeia (Chapter 5.1.3.). The results are presented in Table 2 of the supplementary examples which should be compared with Table 2 according to example 1 of the opposed patent.

As it can be readily seen, the solution of comparative example 1 did not fulfill the requirements of the European Pharmacopoeia what clearly demonstrates that the solution of sodium acetate and acetic acid in the amounts used in the example 1 of the opposed patent as such had no preservative effect. In particular, it should be noted that the number of viable *Staphylococcus aureus* was extremely high as was the case for *Candida albicans* and *Aspergillus niger*.

A copy of Chapter 5.1.3. of the European Pharmacopoeia is attached to this submission as **annex 2**. Criteria of acceptance are detailed on page 448 column 2, the criteria are given in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum.

In order to explain the experimental setting and in order to avoid any doubts or confusion, it is noted that the number of viable microorganisms are differing from example to example.

At the beginning of the tests, the number of viable microorganisms is evaluated by an optical density method, and an estimation of the number of microorganisms is obtained without any possibility to differentiate between viable and non-viable microorganisms.

In fact, the number of viable micro-organisms can only be known after the beginning of the trials, they are counted on a Petri dish after incubation. This is the reason why it is impossible to introduce always the identical number of viable microorganisms in each lot of trials.

The supplementary examples strictly follow the requirement of the European Pharmacopoeia (see the "method" paragraph of the chapter 5.1.3 of the European Pharmacopoeia; 10^5 to 10^6 microorganisms per ml in the inoculum).

Comparative example 2

Further, turning now to comparative example 2 of the supplementary examples, an oral solution according to example 2, Table 4 of the opposed patent has been reproduced, however, without the addition of levocetirizine hydrochloride. As such, the exact amounts of glycerine 85%, sodium saccharinate, Tutti frutti flavour, sodium acetate and acetic acid as well as maltitol-lycasin 80-55 have been used as in the opposed patent.

Experimental tests regarding the antimicrobial preservative effectiveness have been performed according to the European Pharmacopoeia (chapter 5.1.3.). As it can be readily seen, the exemplified solution did not fulfill the requirements of the European Pharmacopoeia. The examples given in Table 4 of comparative example 2, clearly show that an oral solution without levocetirizine has no preservative effect and, therefore, in the composition according to Table 4, example 2 of the opposed patent, the auxiliaries do not have any preservative effect on the overall composition.

In order to draw a better comparison between the above experimental data and the compositions according to the present invention, a new example 3 according to the invention is submitted as well.

Example 3 (according to the present invention)

Here, the composition according to Table 4 (example 2) of the opposed patent has been reproduced and parahydroxybenzoate esters in a total amount of 0.1 mg/ml (0.090 mg/ml methyl p-hydroxybenzoate and 0.0100 mg/ml propyl p-hydroxy benzoate) have been added. According to Table 6 and Table 7 of new example 3, the results for oral solutions of levocetirizine and drops containing the same have been evaluated according to the regulations of the European Pharmacopoeia. In all cases, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* have disappeared in the inoculated samples. The number of *Aspergillus niger* has been significantly reduced.

This clearly shows that also a very small amount of parabens may be used in order to effectively preserve the overall composition according to the legal requirements of the European Pharmacopoeia.

As a result, the conclusion can be drawn that:

1. The further additives in the compositions disclosed in the examples of the opposed patent do not have any antimicrobial activity according to the European Pharmacopoeia test;

2. There is a clear "self-preserving" effect of levocetirizine demonstrated

Obviousness of the claimed invention – combination of D1/D3

As outlined above, the Opposition Division took the view that it would have been a straightforward consideration for a skilled person to keep paraben concentrations in compositions as low as possible considering, for example, the state of the knowledge according to D3.

As outlined during the first instance opposition proceedings, we respectfully disagree with this conclusion.

The skilled person indeed could have had the idea to lower the amount of preservatives in order to avoid the well-known toxicity and the allergic risk of this kind of preservatives. However, the decisive question is whether the skilled person in fact would simply lower the amount of preservatives bearing in mind the existing regulations and product requirements for pharmaceutical products in terms of product safety. Even in an attempt to reduce the potential side effects of preservatives, a skilled person in the first line would ensure that the product safety guidelines of the European Pharmacopoeia are met. In particular, in liquid pharmaceutical preparations, the question of microbial contamination is an omnipresent problem and, therefore, the general indications in D3 are not sufficient for a skilled person to simply combine D1 and D3 and to lower the amount of parabens in the pharmaceutical formulations and, thus, to arrive at the subject matter presently claimed.

The scientific information provided in D3 is unclear and, therefore, may not be regarded as a guideline for the skilled person in the meaning of a general textbook. The Opposition Division made the mistake not to scrutinize the data presented in D3 but to derive exactly that information from this document required to argue for the obviousness of the present invention.

The chapter of D3, discussing methylparaben (p. 340 etc.) indicates that methylparaben is widely used as an anti-microbial preservative in cosmetics, food products and pharmaceutical formulations. Although it is indicated, that it may be used alone, it can be derived from D3 that it is preferably used in combination with other parabens or with other anti-microbial agents, see section 7. of chapter "Methylparaben". Thus, the amounts of methylparaben indicated in the table of section 7. have to be evaluated quite carefully since the amounts of methylparaben indicated therein clearly do not reflect the methylparaben content used as the only preservative. Rather, the amounts of methylparaben have to be seen as intended for use in combination with other preservatives.

It is interesting to note that the first sentence on the right col. on p. 340 of D3 indicates that methylparaben is used together with propylparaben in an overall amount of 2 mg/ml for the "preservation of various parenteral pharmaceutical formulations". There is not any indication that the amounts indicated in the table are sufficient for methylparaben to act efficiently as the only preservative in a pharmaceutical formulation.

By comparing the contents of table I and the table in section 7. of chapter "Methylparaben" it can be easily determined that the minimum inhibitory concentrations as contained in table I do not fit to the concentrations indicated in the table of section 7. That is to say, a skilled person can easily derive from the latter table that the lower limits are only theoretical ones and that they are not suitable to provide a sufficient effect as a preservative alone in view of the best known pathogens which might occur in pharmaceutical compositions.

Table I of D3 indicates that the minimum inhibitory concentration of methylparaben has to be more than 4 mg/ml since a well-known and harmful pathogen (*Pseudomonas aeruginosa*) is leading to harmful infections of the eye and even to blindness, requiring a minimum inhibitory concentration of 4,000 µg/ml. Even if there should be some indication in D3 that lower amounts

of parabens might be used in liquid compositions, the existing doubts arising from the information presented in D3 as regards the general applicability of the one or the other information, in particular in the context of ophthalmic formulations, will deter a skilled person in the field of pharmaceutical products to simply lower the amounts of preservatives in liquid formulations.

The skilled person in the field of pharmaceutical technology, usually a pharmacist or specifically trained chemist, should be regarded as conservative and would not implement any new approach without careful consideration and without performing extensive tests. The skilled person in this field also works in an extraordinarily dense regulative network which does not allow him/her to design pharmaceutical products on a "trial and error" basis. Rather, there must be strong evidence for him/her in order to change one existing product (D1) into another. D3 does not provide such a strong evidence but leaves several questions open.

Further, as outlined before, in the absence of any information which is related to the self-preserving effect of cetirizine/levocetirizine and efletirizine, which effect has been shown in the opposed patent as well as the supplementary examples according to annex 1, a skilled person would not have sufficient motivation to combine the teachings of D1 and D3 in order to arrive at the subject matter presently claimed.

Therefore, the subject matter of the claims according to the main request is based on an inventive step according to Article 56 EPC.

III. 1st and 2nd Auxiliary Requests

The above remarks are also true for auxiliary request 1 as well as auxiliary request 2. The claims according to both requests are directed to more tailored pharmaceutical compositions in terms of the active substance and the amount of parabens used. Therefore, the above comments also apply with regard to auxiliary requests 1 and 2.

Further, it is noted that the opinion of the Opposition Division outlined on p. 23 of the decision "Final Remarks Regarding Auxiliary Requests 1 and 2" is not appropriate in view of the newly

submitted experimental data. In the last paragraph of this page, it was indicated that it is not credible that a concentration of 0.1 mg/ml of methylparaben/propylparaben in a ratio of 9/1 defined in claim 1 of auxiliary request 2 would be sufficient for solving the problem of fulfilling the recommended efficacy criteria, in particular in terms of providing preservative effectiveness against yeast/molds such as, in particular, Aspergillus etc.

Example 3 as submitted with annex 1 clearly shows that the allegations of the Opposition Division were incorrect. Therefore, the subject matter of auxiliary request 2 clearly fulfills the requirements of Article 56 EPC.

Respectfully submitted

Wolfgang Sandmann
European Patent Attorney

Enclosures:
Annex 1 and 2
Decision of the Opposition Division and Main Request, Auxiliary Requests 1 and 2

Europäisches Patentamt
European Patent Office
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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	05758582.0
Applicant's or representative's reference	P30048-EPOP SAN

	Description of document	Original file name	Assigned file name
1	Statement of grounds of appeal	P30048-EPOP Submission-23042012101316.pdf	APPEAL-GRDS-1.pdf
2	Annexes (other than cited documents) regarding review procedure	P30048-EPOP Decision-23042012101354.pdf	APPEALR-ANX-1.pdf
3	Annexes (other than cited documents) regarding review procedure	P30048-EPOP Annex I-23042012101433.pdf	APPEALR-ANX-2.pdf
4	Annexes (other than cited documents) regarding review procedure	P30048-EPOP Annex II-23042012101453.pdf	APPEALR-ANX-3.pdf

Signatures

Place:	**Munich**
Date:	**23 April 2012**
Signed by:	**DE, Isarpatent GbR, W. Sandmann 12098**
Capacity:	**(Representative)**

ANNEX I

Supplementary examples

Comparative example 1

A solution is prepared with the compositions given in table 1.

Table 1

Oral solution

Sodium acetate (mg)	4.2
Acetic acid	0.500 (ad pH 5)
Purified water (ml)	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the solution are inoculated with bacterial and yeast suspensions of Pseudomonas aeruginosa ATCC 9027, Escherichia Coli ATCC 8739, Staphylococcus aureus ATCC6538, 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 table 2.

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

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	2.5×10^5	3.2×10^5	4.1×10^5	2.6×10^5	3.9×10^5
0	1.9×10^5	3.2×10^5	4.2×10^5	3.2×10^5	2.2×10^5
7	< 100	$> 10^4$	1.8×10^4	$> 10^4$	2.9×10^5
14	< 1	< 1	< 1	3.4×10^5	3.8×10^5
21	< 1	6	< 1	3.4×10^5	4.5×10^5
28	< 1	< 1	< 1	3.4×10^5	3.1×10^5

The exemplified solution did not fulfill the requirements of the European Pharmacopoeia. The above example clearly shows that solution of sodium acetate and acetic acid has no preservative effect.

Comparative example 2

An oral solution containing no levocetirizine is prepared. The composition is given in table 3.

Table 3.

	Oral solution
Maltitol-Lycasin 80-55 (mg)	400
Glycerine 85 %(mg)	235.2
Sodium saccharinate (mg)	0.5
Tutti frutti flavour (mg)	0.15
Sodium acetate (mg)	3.4
Acetic acid (mg)	0.5
Purified water (ml)	ad 1

The antimicrobial preservative effectiveness tests are realized according to the European Pharmacopoeia (Chap. 5.1.3.). Samples of the oral solution 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 table 4.

Table 4. – Microbial content in inoculated sample of the oral solution

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	2.5×10^5	3.2×10^5	4.1×10^5	2.6×10^5	3.9×10^5
0	1.2×10^5	3.0×10^5	3.6×10^5	2.9×10^5	2.0×10^5
7	< 100	5.0×10^2	3.0×10^2	> 5.0×10^3	3.2×10^5
14	< 1	< 1	< 1	1.0×10^5	6.4×10^5
21	< 1	< 1	< 1	7.4×10^4	2.3×10^5
28	< 1	< 1	< 1	3.5×10^4	1.6×10^5

The exemplified solution did not fulfill the requirements of the European Pharmacopoeia. The above example clearly shows that an oral solution without levocetirizine has no preservative effect, therefore the preservative effect is not due to maltitol-Lycasin, glycerine, sodium saccharinate, tutti frutti flavor, sodium acetate, nor acetic acid.

Example 3 (according to the invention)

Oral solutions and drops containing levocetirizine and 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 0.1 mg/ml (0.090 mg/ml methyl p-hydroxybenzoate and 0.010 mg/ml propyl p-hydroxybenzoate) . The compositions are given in table 5.

Table 5. – 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)	0.50	10.0
Tutti frutti flavour (mg)	0.15	-
Sodium acetate (mg)	3.4	5.7
Acetic acid (mg)	0.5	0.53
Methyl p-hydroxybenzoate (mg)	0.090	0.090
Propyl p-hydroxybenzoate (mg)	0.010	0.010
Purified water (ml)	ad 1	ad 1

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 6 and 7.

Table 6. – Microbial content in inoculated sample of the oral solution containing 0.10 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	2.5×10^5	3.2×10^5	4.1×10^5	2.6×10^5	3.9×10^5
0	2.7×10^4	2.5×10^5	4.5×10^5	3.1×10^5	1.9×10^5
7	< 100	< 100	< 100	$> 10^4$	1.7×10^5
14	< 1	< 1	< 1	7.5×10^4	6.5×10^4
21	< 1	< 1	< 1	2.7×10^4	5.0×10^3
28	< 1	< 1	< 1	1.9×10^3	1.5×10^2

Table 7. – Microbial content in inoculated sample of the drops containing 0.10 mg/ml of p-hydroxybenzoate esters

Time (days)	Pseudomonas aeruginosa	Escherichia coli	Staphylococcus aureus	Candida albicans	Aspergillus niger
Inoculum	2.5×10^5	3.2×10^5	4.1×10^5	2.6×10^5	3.9×10^5
0	1.5×10^4	1.5×10^5	3.9×10^5	2.5×10^5	1.8×10^5
7	< 100	< 100	< 100	< 100	$< 10^4$
14	< 1	< 1	< 1	< 1	$< 10^3$
21	< 1	< 1	< 1	< 1	< 100
28	< 1	< 1	< 1	< 1	< 100

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 microorganisms is significantly reduced in the oral solution and in the drops.

In all cases the recommended efficacy criteria are achieved despite the very reduced amount of p-hydroxybenzoate esters.

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Application No. / Patent No.	Ref.	Date
05 758 582.0 - 2112 / 1 768 649 /	P30048-EPOP WB	22.12.2011
Proprietor UCB FARCHIM S.A.		

Decision revoking the European Patent (Art. 101(2) and 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 29.11.2011 - has decided:

European Patent No. EP-B- 1 768 649 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

Registered letter with advice of delivery
EPO Form 2331 12.07TRI

Chairman: Sindel, Ulrike
2nd Examiner: Giró, Annalisa
1st Examiner: Giménez Miralles, J

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Enclosure(s): 24 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97-98 EPC (Form 2019)
Minutes of oral proceedings
Main request, Aux. request 1, and Aux. request 2

to EPO postal service: 19.12.11

Registered letter with advice of delivery
EPO Form 2331 12.07TRI

Facts and submissions

I. The European patent EP 1 768 649 B1; based upon European patent application 05758582.0; date of filing: 07.07.2005; priority: 14.07.2004 (EP04016519); date of publication and mention of the grant of the patent: 23.09.2009 (Bulletin 2009/39);

Proprietor: UCB Farchim S.A., CH-1630 Bulle, Switzerland

has been opposed by:

Opponent: Zentiva k.s., 102 37 Prague, Czech Republic

II. With notice of opposition filed on 23.06.2010 the Opponent requested revocation of the opposed patent in its entirety based on the grounds of Art. 100(a) EPC for lack of novelty and inventive step (Art. 52(1), 54 and 56 EPC). Alternatively, oral proceedings pursuant to Art. 116 EPC were requested.

III. With letter of observations dated 13.10.2010 filed on 19.10.2010 the patent Proprietor requested rejection of the opposition and maintenance of the patent as granted (Main request), or amended in the form of Auxiliary request 1 or Auxiliary request 2 filed on same date. Alternatively, oral proceedings pursuant to Art. 116 EPC were requested.

IV. With official communication dated 03.08.2011 the Opposition Division gave a preliminary opinion and summoned to oral proceedings. In particular, Auxiliary request 1 (claim 3) was objected to under Rule 80 EPC.

V. With letter dated 29.09.2011 the patent Proprietor filed an amended Auxiliary request 1 replacing former Auxiliary request 1, and filed new Auxiliary requests 3 and 4, together with further arguments regarding inventive step.

VI. With letter dated 29.09.2011 the Opponent filed documents D12 to D15 and put forward further arguments regarding inventive step based on these new documents.

VII. Oral proceedings took place on 29.11.2011.

At the beginning of the oral proceedings the patent Proprietor confirmed his requests of maintenance of the contested patent as granted (Main request; see Annex I), or amended in form of Auxiliary request 1 (29.09.2011), Auxiliary request 2 (19.10.2010), Auxiliary request 3 (29.09.2011), or Auxiliary request 4 (29.09.2011). In the course of the proceedings, the Patentee withdrew Auxiliary requests 1 and 3. Auxiliary requests 2 and 4 were renumbered as Auxiliary requests 1 and 2 (see Annexes II and III), respectively. Further, the Patentee requested not to admit documents D12-D15 into the proceedings as being late filed and not prima facie more relevant than documents already on file.

The Opponent maintained the request to revoke the patent in its entirety based on the grounds mentioned in paragraph II above. Further, regarding Auxiliary request 1 (former Auxiliary request 2) the Opponent additionally raised the objection of lack of clarity (Art. 84 EPC). With regard to Auxiliary request 2 (former Auxiliary request 4), the Opponent raised objections under Art. 123(2) and 84 EPC.

The text of the claims under consideration in the form of the Main request and the Auxiliary requests 1 and 2 is appended to this decision (Annexes I to III).

For the essentials of the discussion during the oral proceedings, reference is made to the minutes.

VIII. In the course of the proceedings, the following documents have been submitted as evidence by the parties:

D1= EP0605203A2

D2= US5891913

D3= Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), pages 340-343 and 450-453

D4= Wang et al. (2001), Allergy 56, 339-343

D5= Marketing authorization for ZODAC GTT oral drops in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D6= Marketing authorization for ZODAC SIR syrup in the Slovak Republic, dated 29.11.2000, entering into force on 05.02.2001, accompanied by its translation into English

D7= Marketing authorization for ZODAC GTT drops in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D8= Marketing authorization for ZODAC SIR syrup in the Czech Republic, dated 18.04.2001, accompanied by its translation into English

D9= ZODAC GTT, Summary of Product Characteristics, date of last text revision 21.10.2009

D10= ZODAC SIR, Summary of Product Characteristics, date of last text revision 21.10.2009

D11= Thomson Reuters Newport Premium, Launched Drug Forms Detail (2010)

D12= Johnston et al. (2006), MedGenMed 8(2): 61

D13= Abstract of Ryssel et al. (2009), Burns 35(5), 695-700

D14= Abstract of Frech et al. (1979), Am. J. Hosp. Pharm. 36(12), 1672-1675

D15= Juslin et al. (2001) "Farmasian teknologia", 6th ed., Foy Fortis ry., page 450

IX. The arguments put forward by the parties can be summarised as follows:

IX.1 Novelty

The Opponent essentially alleges that novelty of claim 1 as granted is prejudiced by the public prior use of two pharmaceutical products named Zodac GTT and Zodac SIR which were launched in the Czech Republic and in Slovakia in 2001 and 2002, respectively, as demonstrated by the Launched Drug Forms Detail list D11. According to the Opponent, when the marketing authorisations were granted (D5 to D8), the patient information leaflets D9 and D10 (Summary of Product Characteristics) were published. The information contained in D9 and D10 was therefore available to the public before the date of priority of the contested patent. In D9 and D10 it is explained that the products Zodac GTT and Zodac SIR comprise 1.35 mg methylparaben and 0.15 mg propylparaben per 1 ml solution, this making a total amount of parabens of 1.5 mg/ml. The Opponent further alleges that, regardless of whether or not the information about the amounts of parabens in the products Zodac GTT and Zodac SIR was published before the priority date of the opposed patent, the compositions of these two products were part of the state of the art as soon as they were launched, since they could be analyzed by standard methods without undue burden. The Opponent argues that the products Zodac GTT and Zodac SIR publicly used before

the date of priority of the contested patent comprise a total amount of methylparaben and propylparaben of 1.5 mg/ml (as demonstrated by D9, D10 and D11), and the upper limit "lower than 1.5 mg/ml" for the concentration of preservatives defined in claim 1 of the contested patent is not novel over the prior use value 1.5 mg/ml, because under consideration of the margin of error inherent to any experimental measurement (tolerance area around an experimental value), as held in T594/01, the upper end point of the claimed range "lower than 1.5 mg/ml" cannot be distinguished from the experimental value 1.5 mg/ml of the public prior use.

The patent Proprietor essentially argues that the substantiation of the public prior use (in particular as to what was made available to the public) in the Notice of Opposition (i.e. within the opposition period) is insufficient. The Patentee holds that it is at least doubtful what was made available to the public through the use of the products Zodac GTT and Zodac SIR. According to the Patentee, D9 and D10 cannot be taken as evidence of the precise composition of Zodac GTT and Zodac SIR before the priority date of the opposed patent (14.07.2004), since it is evident from D9 and D10 themselves (chapters 9 and 10) that the publication date of these information sheets is later than 14.07.2004, and the text has been revised several times. Furthermore, D9 and D10 prove that there was a renewal of the authorisation in January 2009. It is therefore doubtful whether the Summary of Product Characteristics D9 and D10 truly and identically reflect the composition characteristics of the products Zodac GTT and Zodac SIR launched in 2001 and 2002, as the evidence provided is insufficient. For these reasons, the alleged public prior use has not been convincingly demonstrated beyond any remaining doubt. The Patentee further argues that, even if D9 and D10 could be taken as a proof of the composition of Zodac GTT and Zodac SIR as launched in 2001 and 2002, the amount of methylparaben and propylparaben of 1.5 mg/ml is outside the limit "less than 1.5 mg/ml" defined in claim 1 of the contested patent. According to the patent Proprietor, T594/01 is of no general applicability and is not relevant for the present case, in particular because in the pharmaceutical field the contents of any ingredients are determined very precisely due to regulatory requirements. Claim 1 as granted is therefore novel in view of the alleged prior use of Zodac GTT and Zodac SIR, and this even more applies to the subject-matter of the auxiliary requests where the amounts of parabens have been restricted.

IX.2 Inventive step

The Opponent argues that D1 (example 5) disclosing a liquid ophthalmic composition comprising cetirizine hydrochloride, and methylparaben (2 mg/ml) and propylparaben (1 mg/ml) as preservatives (page 3 line 52) represents the closest prior art. D1 does

not disclose the amount of parahydroxybenzoate esters (parabens) being "less than 1.5 mg/ml" as defined in claim 1 of the opposed patent. The technical effect of this feature, so the Opponent, is achieving the recommended efficacy criteria of antimicrobial preservation for different uses of the composition. According to the Opponent, the problem was therefore to provide a useful liquid composition of cetirizine, levocetirizine or efletirizine having the recommended efficacy of antimicrobial preservation. According to the Opponent, D1 itself indicates that the amount of additives (including preservatives) to be used can be determined by those skilled in the art within the ranges adopted for ordinary ophthalmic or nasal solutions (page 3 lines 56-57). Furthermore, the skilled person is well aware of the need to keep the concentration of parabens in liquid pharmaceutical compositions on the lowest possible levels due to the controversial discussions ongoing before and at the time of the priority of the opposed patent about the safety and toxicology concerns regarding the use of parabens as preservatives in pharmaceuticals. This provides a clear incentive to the skilled person to carefully consider the concentration of parabens. The skilled person would therefore turn to a handbook of pharmaceutical excipients such as D3. In D3 the skilled person finds information regarding the concentration of methylparaben and propylparaben suitable for ophthalmic and nasal solutions. D3 discloses using 0.15 to 2 mg/ml methylparaben and/or 0.05 to 0.1 mg/ml propylparaben in ophthalmic preparations; 0.15 to 2 mg/ml methylparabens and/or 0.1 to 0.2 mg/ml propylparaben in oral solutions/suspensions; and 0.33 mg/ml methylparaben and/or 0.17 mg/ml propylparaben in nasal solutions (see table in Section 7). This provides the indication for the skilled person to modify the ophthalmic formulation of D1 (example 5) to comprise 0.15-2 mg/ml methylparaben and/or 0.05-0.1 mg/ml propylparaben, thus ending up with combined amounts of parabens falling within the range "more than 0 and less than 1.5 mg/ml" defined in claim 1 of the contested patent, since three of the amounts explicitly disclosed in D3 fall within this range. With regard to the limitation to levocetirizine and/or specific combinations of parabens in the auxiliary requests, the Opponent argues that no particular technical effect is demonstrated in the patent in suit for these features, and hence this subject-matter merely represents obvious alternatives. Further, the use of levocetirizine instead of racemic cetirizine would be obvious from D4, as this enantiomer has enhanced activity. As for the use of methylparaben and propylparaben in combination in ratio 9/1 of methylparaben/propylparaben, the Opponent argues that this feature is also disclosed in D3 for parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7), and the skilled person would also apply this ratio to ophthalmic preparations. Using the lowest (0.05 mg/ml) and highest (0.1 mg/ml) amounts of propylparaben indicated in D3 for ophthalmic formulations and the ratio 9/1 of methylparaben to propylparaben also disclosed in D3, one ends up with total amounts of combined methylparaben + propylparaben of 0.5 mg/ml or 1.0 mg/ml

suitable for antimicrobial preservation of ophthalmic solutions, both concentrations falling within the range defined in the claims of the opposed patent (main request and auxiliary requests). The Opponent further argues that the examples of the patent in suit relate to the use of parabens together with other traditional preservatives/ antimicrobial agents such as acetic acid and sodium acetate, and none of the examples actually supports the claimed improved antimicrobial efficiency of only parabens alone combined with cetirizine/levocetirizine or efletirizine. Thus, it remains unclear whether the desired effect actually originates from one or more of the antimicrobial agents used not being parabens. The Opponent also contends that a "self-preserving" effect of cetirizine/levocetirizine or efletirizine has not been demonstrated in the opposed patent.

The patent Proprietor essentially argues that starting from D1 (example 5) the objective problem is that stated in the contested patent, paragraph [0008], namely providing a liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine with a reduced amount of preservatives (selected from parabens). He argues that the amounts of methylparaben indicated in the table of Section 7 of D3 are only amounts intended for use in combination with other preservatives, not for use as the only preservative. D3, so the Patentee, does not indicate that the amounts given in the table of Section 7 are sufficient for effective preservative effect when used as the only preservative. D3 in Section 11 (table I) provides information about the MICs (minimum inhibitory concentrations) of methylparaben in aqueous solutions. From table I in D3 one can derive that the minimum inhibitory concentration of methylparaben in ophthalmic solutions has to be more than 4 mg/ml (4000 microgram/ml) which is the minimum concentration required for inhibition of Pseudomonas aeruginosa, a pathogen involved in harmful eye infections. By comparing Sections 7 and 11 (table I) of D3 one easily understands that the amounts indicated in Section 7 (lower limits) are only theoretical and not suitable for providing sufficient preservative effect when methylparaben is used as the only preservative. Same considerations apply to propylparaben. Hence, D3 would teach that not even the concentration of parabens used in D1 (3 mg/ml) is sufficient to defeat well known pathogens which may occur in ophthalmic formulations. Furthermore, the skilled person, so the Patentee, would not have any motivation for combining D1 with D3, because D3 (Section 14) indicates that "although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for this type of formulations...". Hence, D3 would suggest that parabens should not be used in ophthalmic preparations. D1 and D3, so the Patentee, can be combined only with the use of hindsight. Indeed, in view of D3 the skilled person would be deterred from using parabens in liquid pharmaceutical formulations. Further, the Patentee contends that in the absence of any information which is related to the "self-preserving" effect of

cetirizine/levocetirizine and efletirizine, a skilled person would not have any motivation to simply lower the amounts of parabens based on D1 and D3, in particular in consideration of the fact that he has to expect that product safety would be considerably affected.

Reasons for the decision

1. The opposition, filed in due time, in proper form, and supported by reasoned statements, is formally admissible (Art. 99(1) and 100 EPC, and Rules 3(1) and 76 EPC).

2. Admissibility of D14

Whereas D12, D13 and D15 (D12 and D13 being post-published documents) merely represent the common general knowledge of any person skilled in the art, and there is no need to resort to them as a proof of said accepted common knowledge, this is not the case of D14. D14 is a document in the area of hospital parenteral nutrition, and hence in the field of pharmaceuticals, and reports on analogous problem of microbial contamination risk/preservation of aqueous solutions for pharmaceutical use. Indeed, during the oral proceedings D14 turned out to be useful for the discussion of the role of sodium acetate in the microbial growth inhibitory activity of the formulations of the patent in suit comprising sodium acetate (in particular examples 1-4), as D14 reports on antimicrobial activity of sodium acetate on same microorganisms (Staphylococcus, Escherichia, Pseudomonas, Candida) tested in the patent in suit. D14 is hence pertinent for understanding the role of the various ingredients of the compositions according to the opposed patent in the preservative effect(s) allegedly demonstrated in the patent. Although the patent Proprietor initially claimed that D14 is not relevant (at least not more relevant than other documents already on file), he himself used this document later on in favour of his argumentation of inventive step. For all these reasons, D14 late filed by the Opponent after expiry of the opposition period is considered as prima facie relevant for the present discussion, and the Opposition Division has decided to admit it into the proceedings.

Main request

3. Novelty - Alleged public prior use

D5, D6, D7, D8 together with D11 demonstrate that the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) were indeed launched to the market in the Czech Republic on 31.10.2001, and in Slovakia on 30.09.2002. The Summary of Product Characteristics and Patient Information Leaflet attached to each of D5, D6, D7 and D8 demonstrate that ZODAC GTT and ZODAC SIR comprise cetirizine dihydrochloride in aqueous solution containing methylparaben and propylparaben as preservatives. However, the concentration of methylparaben and propylparaben in the solution is not disclosed in D5 to D8.

On the other hand, D9 and D10 are the last revision of the Summary of Product Characteristics (dated 21.10.2009) for ZODAC GTT and ZODAC SIR in the Czech Republic. The Opponent's contention that D9 and D10 were published when the marketing authorisations were granted is not true. D9 and D10 have been last revised on 21.10.2009, and therefore their publication could not have occurred before that date. Further, D9 and D10 demonstrate that the first authorisation of ZODAC GTT and ZODAC SIR in the Czech Republic has been renewed once on 28.01.2009, and that the text of the Summary of Product Characteristics has been revised four times, once coinciding with the renewal of the authorisation (28.01.2009). The contents of D9 and D10 are different from those of the Summary of Product Characteristics and Patient Information Leaflet attached to D5, D6, D7 and D8. The evidence produced in form of D5, D6, D7, D8, D9 and D10 cannot exclude beyond any reasonable doubt the possibility that a variation of the excipient composition could have been introduced coinciding with one of those revisions or renewal after the products were first launched.

It has not been proven without any remaining doubt that the products launched in 2001 and 2002 in the Czech Republic and Slovakia and commercially available before the date of priority of the contested patent (14.07.2004) had exactly the same concentration of parabens as the products available in 2009 in the Czech Republic as described in D9 and D10.

D9 and D10 do not demonstrate the composition of the products publicly available before 14.07.2004, and the Opponent has not provided any further piece of evidence in this respect. The actual concentration of parabens in the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) publicly available in the Czech Republic and Slovakia before the priority date of the contested patent remains unknown.

The fact that, as alleged by the Opponent, the compositions of Zodac GTT and Zodac SIR publicly available from 2001 and 2002 and before 14.07.2004 could be or could have been analyzed by standard methods without any undue burden (which is not denied) does not change anything to this situation: It remains unknown what (which concentration of parabens) would have been found, had this analysis been carried out, and the Opponent has not provided sufficient evidence in this respect.

For the full substantiation of a public prior use, the burden was with the Opponent to prove up to the hilt that the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) publicly available before 14.07.2004 actually had a concentration of parabens of less than 1.5 mg/ml as defined in claim 1 of the opposed patent, so that this concentration was actually available to any member of the public who would have carried out a chemical analysis of the product composition. Yet, the actual concentration of parabens in the Zodac GTT and Zodac SIR products of the state of the art before 14.07.2004, and in particular before the revisions and authorisation renewal documented in D9 and D10, is not known. The paraben concentration is only known from D9 and D10 after said revisions and authorisation renewal after the priority date. The requirement of adequate substantiation within the opposition period for the proof of a public prior use by means of extensive evidence regarding this point (what was effectively made available, or what would have been actually available to the public through the analysis of the composition) before the priority date has not been fulfilled.

Under these circumstances, it is irrelevant to the question of novelty whether or not the upper limit for the concentration of preservative defined in claim 1 of the opposed patent as "less than 1.5 mg/ml" can be distinguished from the experimental concentration value 1.5 mg/ml within the unavoidable margin of error or tolerance associated with the experimental measurement of said amount in a pharmaceutical composition, since said experimental value 1.5 mg/ml does not form part of the prior art within the meaning of Art. 54(1) and (2) EPC for the reasons explained above.

4. Inventive step

4.1 Technical effect(s) and problem to be solved

4.1.1 D1 can be considered as the closest prior art. This has been acknowledged by both parties during the proceedings. D1, in example 5, discloses a liquid ophthalmic composition comprising cetirizine hydrochloride (3 mg/ml), and methylparaben (2 mg/

ml) and propylparaben (1 mg/ml) as preservatives (see page 3 line 52). The composition further comprises other excipients and additives such as sodium acetate (1 mg/ml) and propyleneglycol (20 mg/ml).

The difference of claim 1 of the opposed patent as granted with respect to D1 (example 5) is the definition of the concentration of parahydroxybenzoate esters (parabens) selected from methylparaben, ethylparaben, propylparaben, or mixtures thereof of "more than 0 and less than 1.5 mg/ml", whereas D1 discloses a total concentration of methylparaben and propylparaben of 3 mg/ml. It is noted that the wording of claim 1, however, does not exclude the presence of other additives, in particular other preservatives, in the composition.

4.1.2 The Opposition Division already expressed in the annex to the summons the view that the technical effect(s) which may be taken into account in view of this technical difference appear to relate to: i) the reduction of safety and toxicology concerns regarding the use of parabens in pharmaceuticals (lowering of well-known adverse effects in case of hipersensitivity to parabens), whilst ii) providing a sufficient efficacy for antimicrobial preservation (fulfilling the recommended efficacy criteria).

The advantage of reducing the concentration of preservatives leading to a reduction of the risk of an allergic reaction in sensitive patients is invoked in paragraph [0030] of the opposed patent. However, this passage does not relate specifically to parabens, but the patent describes the use of a number of different preservatives (see paragraphs [0011], [0018] and [0019], and the examples). Furthermore, the patent in suit does not contain any experimental details at all concerning this alleged effect or advantage. In particular, there is no demonstration in the patent of any effect of the parabens concentration values defined in claim 1 on an actual reduction of the risk of allergic reactions of the claimed compositions. The patent contains no information and no details whatsoever in this respect. Whereas the reduction of the risk of allergic reactions by reducing the concentration of preservatives may be considered as feasible in general in view of the common knowledge of the person skilled in the art, it is stressed that the contested patent is not concerned with this aspect (except for the assertion in paragraph [0030]), and it contains no evidence whatsoever making the achievement of this alleged effect in the present case at least plausible.

During the oral proceedings the patent Proprietor stated that there is a linear correlation between the reduction of preservative concentration and the lowering of risk/occurrence of adverse allergic reactions. However, no evidence has been provided in support of this allegation. It remains a matter of speculation whether this correlation is linear, or whether a statistically significant effect can be observed at all for the reduction of risk/occurrence of adverse effects when lowering the amount of

parabens to less than 1.5 mg/ml (as claimed in the opposed patent) when compared to parabens concentration of e.g. 3 mg/ml as described in the closest prior art D1 (example 5). Accordingly, in the absence of evidence supporting the comparison with the prior art this merely speculative advantage cannot be taken into consideration in determining the technical problem underlying the invention (Case Law of the BoA, 6th Ed., I.D.4.2).

The effect of providing/maintaining a sufficient antimicrobial efficacy in terms of fulfilling the recommended efficacy criteria is, however, sufficiently substantiated in the patent in suit. The examples in the patent specification describe a number of aqueous formulations of cetirizine, levocetirizine or efletirizine in form of oral solution or drops comprising different excipients and preservatives. The testing of the antimicrobial preservative effectiveness is carried out in terms of fulfilment of the recommended efficacy criteria according to the Eur. Pharmacopoeia (Chap. 5.1.3) by determining the number of viable microorganisms per ml 28 days after inoculation with bacterial (Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus) and yeast (Candida albicans, Aspergillus niger) suspensions. All the compositions described, except those of examples 1 and 2 in form of oral solution (see tables 2 and 5), show compliance with the recommended efficacy criteria (see example 1: table 3; example 2: table 6; example 3: tables 7-14; example 4: tables 15-20; example 5: paragraph [0047]; example 6: paragraph [0049]; example 7: paragraph [0051]; example 8: paragraph [0053]; example 9: paragraph [0055]).

In examples 1, 2, 5 and 7 the compositions do not comprise parabens, whereas the formulations of examples 3, 4, 6, 8 and 9 do. It is also apparent that all the compositions comprising parabens further comprise other additives and excipients which may exert a concomitant antimicrobial effect, and hence fulfil the functional definition "preservative". Thus, formulations of examples 3, 4 and 8 comprise sodium acetate and acetic acid; composition of example 6 comprises sodium phosphates and disodium edetate; composition of example 9 comprises boric acid. All of these additives are also preservatives within the meaning of the present patent (see paragraph [0019]). Other additives present in the compositions of the patent in suit such as propyleneglycol (examples 1-4 and 8) are known to have an enhancing effect on antimicrobial preservative efficacy of parabens (see D3, Section 7). Furthermore, it is stated in the patent in suit that the active ingredients (substituted benzhydryl piperazines such as cetirizine, levocetirizine or efletirizine) possess themselves a preservative effect in aqueous solution (see paragraphs [0007] and [0009]).

A great deal of discussion was devoted during the oral proceedings to the latter question of whether or not a "self-preserving" effect of the active agent itself is actually demonstrated in the patent. In the Opposition Division's opinion, the examples of the patent in suit do not allow to draw any conclusion in this respect, because all the

formulations comprise a combination of substances which may have an antimicrobial stabilising effect, and/or an antimicrobial enhancing effect, alone or in combination. In this context, the Patentee stated during the oral proceedings that sodium acetate used in examples 1-4, 7 and 8 in concentrations of up to 10 mg/ml has no preservative effect at all, and hence the preservative effect observed for compositions of examples 1 and 2 must be attributed to the self-preserving effect of the active agent. However, the Patentee has not provided any further evidence in support of this contention. Contrary to the Patentee's allegation, D14 discloses the growth inhibitory effect of sodium acetate on Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa in aqueous solution for parenteral nutrient therapy. The Patentee has further argued that D14, however, indicates that growth of Candida albicans is not inhibited by sodium acetate. Since examples 1 and 2 (tables 2, 3 and 6) do demonstrate an antimicrobial effect for Candida albicans, this effect must be attributed to the active agent.

Irrespective of the above controversy, the consideration of this effect –if it actually exists– is irrelevant for the formulation of the technical problem, as it does not derive from the technical difference of the subject-matter of claim 1 of the opposed patent over D1 (example 5), namely the lower concentration of parabens, but allegedly from the presence of the active agent, and hence this effect would have been also present, even if unrecognized, in the composition of D1 (example 5). The only decisive consequence of the above discussion in the present analysis, is that it remains doubtful to which component or combination of components the antimicrobial stabilisation effect shown in the compositions of the patent in suit is to be attributed.

Now, turning to the effect of the concentration of parabens, comparison of results in table 3 of the opposed patent (cetirizine drop formulation without parabens) and results in tables 11-14 (cetirizine drop formulation with various amounts of parabens) reveals no technical effect in terms of microbial preservation which could be attributed to the presence or absence of parabens. Same is true for levocetirizine formulations from the comparison of table 6 (no parabens) and tables 18-20 (with parabens). On the other hand, comparison of results in table 2 (oral solution formulation of cetirizine without parabens) and results in tables 7-10 (oral solution formulation of cetirizine with various amounts of parabens); and table 5 (oral solution formulation of levocetirizine without parabens) and results in tables 15-17 (oral solution formulation of levocetirizine with various amounts of parabens) reveals an effect of the presence of parabens in the stabilisation against yeast contamination (Candida albicans and in particular Aspergillus niger) which can be observed for concentration of parabens as low as 0.15 mg/ml (see table 7).

In view of the above analysis, it appears that the presence or absence of a technical effect in terms of microbial preservation which could be attributed to the presence or absence of parabens depends on the composition (concentration of active agent, amount of other additives such as propyleneglycol) of the pharmaceutical formulation, as it is not the same for oral solutions as for drops (see tables 1 and 4). It is stressed in this context, that claim 1 of the contested patent is not limited to drop formulations, and it does not exclude the presence of other additives.

4.1.3 Finally, the specification of the patent invokes an additional advantage, namely the ability of making the manufacturing process easier by avoiding the need of solubilising important amounts of preservatives not freely soluble in water (paragraph [0031]). However, no further details are provided in the specification in support of this speculative statement, and the Opposition Division concludes that in absence of supporting evidence this merely alleged advantage cannot be taken into consideration in determining the technical problem underlying the invention.

4.1.4 The Opposition Division stresses in particular that, in view of the evidence available, the correct formulation of the technical problem cannot be that of providing compositions having the lowest possible concentration of parabens still compatible with an effective antimicrobial activity fulfilling the recommended efficacy criteria. Compositions according to claim 1 of the opposed patent can comprise as much as "less than 1.5 mg/ml" of parabens. Neither the limit of the paraben concentration range "less than 1.5 mg/ml" defined in claim 1 of the opposed patent nor even the lowest paraben concentration value of 0.15 mg/ml used in various examples of the patent in suit have been shown to be critical in this respect, i.e. the lowest possible concentration of parabens still compatible with an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of cetirizine, levocetirizine and efletirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens. On the other hand, no significant difference is observed in tables 7 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.15, 0.375, 0.45, 0.75, 1.05 or 1.125 mg/ml of parabens. In this sense, the upper limit of less than 1.5 mg/ml of parabens defined in claim 1 of the opposed patent appears to be fully arbitrary.

It is also particularly stressed that the technical problem cannot be that as formulated by the patent Proprietor, namely providing a liquid pharmaceutical composition of cetirizine with a reduced amount of preservatives selected from parabens, as this

formulation merely amounts to a repetition of the technical difference vis-à-vis the closest prior art (D1, example 5), and includes a part of the solution in the statement of the problem, which necessarily results in an ex post facto view.

In summary, the Opposition Division comes to the conclusion that the objective technical problem can only be reasonably formulated in terms of **providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens having the recommended efficacy of antimicrobial preservation**. The Opposition Division therefore agrees with the Opponent's formulation of the technical problem.

4.1.5 Following the problem-solution analysis, it has to be first decided whether or not the problem as formulated above is shown in the patent to be actually solved across the whole area covered by claim 1 of the contested patent, in particular for any liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine comprising parabens in concentrations of "more than 0 and less than 1.5 mg/ml".

It is apparent from the evaluation of the disclosure of the patent in suit that this question has to be answered in the negative. Concentrations of parabens lower than 0.15 mg/ml have simply not been tested. However, it is apparent from tables 2, 5 and 7 that concentrations of parabens lower than 0.15 mg/ml, e.g. only slightly higher than 0 mg/ml (say concentrations as low as e.g. 0.0001 mg/ml as described in paragraph [0020] of the contested patent) may result, in particular in the case of oral solutions, in insufficient antimicrobial effectiveness against yeast contamination (Aspergillus and Candida), as the recommended efficacy criteria are not fulfilled. This is however not the case for drops formulations (see tables 3, 6 and 11), i.e. the achievement of the recommended efficacy criteria depends on the particular composition of the pharmaceutical formulation (concentration of active agent, amount of other additives/ excipients which may have a concomitant or enhancing effect). This demonstrates that the technical problem as formulated above is not effectively solved across the range of concentrations of parabens and across the variety of liquid pharmaceutical compositions covered by claim 1 of the opposed patent.

In view of this, the technical problem has to be reformulated less ambitiously, namely in terms of **providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens showing (some degree of) antimicrobial preservative effectiveness**.

4.2 Obviousness

The technical problem as formulated in paragraph 4.1.5 above is solved in the patent in suit by providing compositions comprising parahydroxybenzoate esters (parabens) in concentrations of more than 0 and less than 1.5 mg/ml. Examples 1-9 of the opposed patent demonstrate that this problem is actually solved across the whole area covered by claim 1.

It only remains to be ascertained whether this solution (use of parabens concentrations of more than 0 and less than 1.5 mg/ml) would have been obvious for the skilled person.

The Opposition Division agrees with the Opponent in that, confronted with the problem as formulated above, the skilled person would immediately resort to his general knowledge and to handbooks of pharmaceutical excipients such as D3 (chapters dealing with methyl- and propylparaben).

The motivation to resort to D3 is given first of all by the formulation of the problem itself, namely to find out suitable concentrations of parabens providing effective antimicrobial preservation in liquid pharmaceutical compositions. Secondly, the skilled person is well aware that keeping the concentration of parabens in liquid pharmaceutical compositions at low levels is generally desired due to the controversial discussions ongoing at the time of priority of the opposed patent about the safety and toxicology concerns regarding the use of parabens as preservatives in pharmaceuticals. This safety concern is even recognized and discussed in D3 (Section 14). Both facts provide a clear incentive for the skilled person to carefully consider the typical concentrations of parabens for various liquid pharmaceutical formulations disclosed in D3.

In D3 (tables under Section 7 on pages 340 and 450) the skilled person finds a clear indication regarding the usual concentrations of methylparaben and propylparaben to be employed for antimicrobial preservation of ophthalmic, nasal and oral solutions. D3 indicates using 0.15 to 2 mg/ml methylparaben and/or 0.05 to 0.1 mg/ml propylparaben in ophthalmic preparations; 0.15 to 2 mg/ml methylparabens and/or 0.1 to 0.2 mg/ml propylparaben in oral solutions/suspensions; and 0.33 mg/ml methylparaben and/or 0.17 mg/ml propylparaben in nasal solutions. The ranges of concentrations indicated in D3 almost completely overlap with the range of concentrations defined in claim 1 of the contested patent. The skilled person, in order to solve the technical problem as formulated in paragraph 4.1.5 above, would with every expectation of success, directly follow the indications provided in D3 (table under Section 7), and he would modify the ophthalmic formulation of D1 (example 5) to comprise 0.15-2 mg/ml methylparaben and/or 0.05-0.1 mg/ml propylparaben. In doing so, the skilled person would end up necessarily with combined amounts of parabens falling within the range "more than 0 and less than 1.5 mg/ml" defined in claim 1 of the contested patent in a straightforward manner.

The patent Proprietor has alleged that the skilled person would not use the concentrations of parabens indicated in Section 7 of D3 for three reasons:

i) Fisrtly, the amounts of methylparaben and propylparaben indicated in the tables under Section 7 of D3 (pages 340 and 450) are only amounts intended for use in combination with other preservatives, not for use of methylparaben, propylparaben or their combination as the only preservative(s).

However, this contention is of no merit, because, as explained above, claim 1 of the opposed patent does not require that parabens are the only preservatives present in the composition. The technical problem is not that of finding effective antimicrobial concentrations for use of parabens alone. In this sense, the Opponent's allegation that the patent in suit does not provide any demonstration of an effect for the combination of the active ingredient with parabens alone is irrelevant for the present analysis. It is apparent that the patent in suit does not disclose such antimicrobial use of parabens alone, but, to the contrary, it relates to the use of parabens always in combination with various other antimicrobial preservatives or preservative-enhancing agents. It is true that D3 teaches that parabens are generally used in combination with other antimicrobial and/or preservative-enhancing agents, and that additive and synergistic effects may occur (see Section 10). Precisely this, and nothing else, is what is disclosed also in the patent in suit. Furthermore, D3 in Section 10 also teaches that parabens are specially active against yeast and molds (such as Aspergillus and Candida). Thus, in order to achieve a broad-spectrum antimicrobial effect, the skilled person would indeed use the parabens concentrations indicated in D3 in combination with other antimicrobials and/or preservative-enhancing agents, thereby arriving at the subject-matter of the opposed patent. For these reasons, the Patentee's argument must fail.

ii) Secondly, according to the Patentee D3 does not indicate that the amounts of parabens given in the tables under Section 7 are sufficient for achieving an effective preservative effect when used as the only preservative. D3 in Section 11 (table I) provides information about the MICs (minimum inhibitory concentrations) of methylparaben and propylparaben in aqueous solutions. From table I on page 341 of D3 one can derive that the minimum inhibitory concentration of methylparaben in ophthalmic solutions has to be more than 4 mg/ml (4000 microgram/ml) which is the minimum concentration required for inhibition of Pseudomonas aeruginosa, a pathogen involved in harmful eye infections. By comparing Sections 7 and 11 (table I) of D3 one easily understands that the amounts indicated in Section 7 (lower limits) are only theoretical and not suitable for providing sufficient preservative effect when methylparaben is used as the only preservative. Same considerations apply to

propylparaben. Hence, D3 would teach that not even the concentration of parabens used in D1 (3 mg/ml) is sufficient to defeat well known pathogens which may occur in ophthalmic formulations.

This argumentation is also devoid of merit. Firstly, it is stressed again that claim 1 of the opposed patent does not require that parabens are the only preservatives present in the composition. Secondly, claim 1 does not require that the parabens include necessarily methylparaben; the parahydroxybenzoate ester can be e.g. propylparaben; in the case of propylparaben, the MIC value required for inhibition of Pseudomonas aeruginosa indicated in D3 (table I on page 451) is >1 mg/ml, which is, by the way, the concentration of propylparaben used in D1 (example 5), and fully overlaps with the range of less than 1.5 mg/ml defined in present claim 1. More importantly, the argumentation of the patent Proprietor appears to be only a deliberate attempt to create confusion. The MIC values of an antimicrobial agent is a property thereof defined as the lowest concentration of the antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation, which allows for comparison of the activity of antimicrobial agents. The MIC values reported in table I of D3 are not the minimum concentrations actually needed for providing sufficient or effective preservation in an aqueous solution. In the patent in suit, compliance with the recommended efficacy criteria according to the Eur. Pharmacopoeia requires the number of viable spores to be less than 1000 per ml after 28 days from the inoculation, which is a different criterion than that used in determining the MIC values. In D3, suitable/typical concentration values needed for providing effective antimicrobial preservation in various liquid pharmaceutical formulations are given in the tables under Section 7, not in tables I under Section 11; otherwise, the information provided in the tables under Section 7 would be simply superfluous and useless. It is apparent from D3 (Sections 7 and 10) that typical concentration values of parabens suitable for providing effective antimicrobial preservation in various liquid pharmaceutical formulations may be much lower than the MIC values reported on table I, as parabens are usually employed in combination and additive and synergistic effects occur (see Section 10). In summary, the information provided in table I of D3 would by no means deter the skilled person from using the typical values for paraben concentrations indicated under Section 7.

iii) Thirdly, the skilled person, so the Patentee, would not have any motivation for combining D1 with D3, because D3 (Section 14) indicates that "although parabens have also been used as preservatives in injections and ophthalmic preparations they are now generally regarded as being unsuitable for this type of formulations". Hence, D3 would suggest that parabens should not be used in ophthalmic preparations.

The Opposition Division also dismisses this contention. First of all, it is apparent that claim 1 of the contested patent is not limited to ophthalmic preparations. On the contrary, the patent in suit covers also e.g. oral solutions (see claim 7). D3 in the tables under Section 7 reflects the concerns existing before the date of priority of the contested patent regarding the use of parabens in injection and ophthalmic preparations in particular. These concerns are further explained in Section 14 of D3, as the Patentee correctly notes. However, under Section 14 it is also explained that parabens are widely used in e.g. oral pharmaceutical compositions, and in that application methylparaben is typically used in amounts as high as 2 mg/ml (see table under Section 7). In any event, it is true that D3 reflects the existing safety concerns at the date of priority of the patent in suit, and it reports that the WHO has set an estimated total acceptable daily intake for methyl-, ethyl- and propylparabens at up to 10 mg/kg body-weight (see Section 14). Following this explicit indication of D3, the skilled person would be by no means deterred from using the typical paraben concentration values for oral solutions of 0.15 to 2 mg/ml for methylparaben and/or 0.1 to 0.2 mg/ml for propylparaben indicated in the tables under Section 7, but would be inclined to use the lower values in the aforementioned ranges, thereby unavoidably ending up with concentration values falling within the area covered by claim 1 of the opposed patent.

For all these reasons, the Opposition Division comes to the conclusion that the subject-matter of claim 1 of the patent in suit as granted is obvious.

Finally, the following remarks are added: The line of reasoning underlying the patent Proprietor's argumentation of inventive step stresses the point that the discovery or realisation of a self-preserving effect of the active agents cetirizine, levocetirizine and efletirizine in liquid preparations for all strains except for Aspergillus is the decisive fact allowing the reduction of the amounts of parabens as claimed in the patent in suit. The Opposition Division underlines again that this line of reasoning is, however, based on an incorrect formulation of the objective technical problem following the problem-solution approach. Furthermore, irrespective of whether or not the alleged self-preserving effect of the active agent actually exists, the above analysis demonstrates that the discovery or realisation of this alleged effect is not the only motivation or incitation that the skilled person, starting from D1 (example 5), would have for carefully considering and looking at the concentration of parabens in liquid pharmaceutical compositions of cetirizine.

Auxiliary request 1

Claim 1 of Auxiliary request 1 is limited to liquid pharmaceutical compositions comprising levocetirizine and methylparaben/propylparaben in weight ratio 9/1 in concentrations of 0.01 to 1.125 mg/ml.

During the oral proceedings, the Opponent raised objections of lack of clarity and lack of inventive step.

Regarding clarity, the Opponent argues that it is unclear whether the amounts referred to in claim 1 relate to each of methylparaben and propylparaben independently, or to their combination; and/or whether the compositions as defined in claim 1 may comprise other preservatives, in particular other parabens.

The Opposition Division cannot agree with the Opponent's view. It is clear that claim 1 defines a fixed combination of methylparaben and propylparaben in fixed weight ratio methylparaben/propylparaben of 9/1, and hence the concentrations 0.01 to 1.125 mg/ml defined in claim 1 are the concentrations of the fixed combination. On the other hand, a composition comprising levocetirizine and the fixed combination methylparaben/propylparaben does not exclude the presence of any other additives or excipients, in particular those which may exert an antimicrobial and/or preservative-enhancing function, as already explained above for the Main request. Any other interpretation is only meaningless in view of the disclosure of the patent and/or an attempt to create confusion. Hence, claim 1 of Auxiliary request 1 meets the requirements of Art. 84 EPC.

Regarding inventive step, the additional features introduced in claim 1 of Auxiliary request 1 do not change anything to the problem-solution analysis as carried out above in respect of the Main request.

With regard to the limitation to levocetirizine, no particular technical effect in terms of antimicrobial preservation/stabilisation of the liquid composition is demonstrated in the patent in suit for the levorotatory enantiomer of cetirizine as compared to the racemic form (cetirizine). Furthermore, the use of levocetirizine instead of racemic cetirizine would be obvious from D4, as the levorotatory enantiomer has more therapeutic activity than racemic cetirizine, and hence less amounts of the pure enantiomer than of the racemic mixture are required in the formulation.

As for the use of methylparaben/propylparaben in fixed combination in weight ratio 9/1, this feature merely represents an obvious alternative, as it is not shown to be associated with any particular technical effect. The compositions of examples 3 and 4 of the patent in suit all comprise methylparaben/propylparaben in fixed combination in ratio 9/1; hence the analysis carried out above for the Main request applies mutatis mutandis to Auxiliary request 1.

As for the limits of the concentration range 0.01 to 1.125 mg/ml, both end point values are not shown to be linked to any technical effect in particular. Analogous considerations apply as for the range more than 0 and less than 1.5 mg/ml of the Main request.

It is stressed once more that the technical problem is not that of determining the lowest possible concentration of parabens having effective antimicrobial activity for the reasons explained above, and hence a limitation of the concentration range cannot change anything in the problem-solution analysis unless some further technical effect can be demonstrated within the limited range. The compositions according to claim 1 of Auxiliary request 1 may comprise as much as 1.125 mg/ml of parabens (methylparaben/propylparaben 9/1). However, the limit of the concentration range 1.125 mg/ml has not been shown to be critical in terms of achieving an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of levocetirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens (see table 6). On the other hand, no significant difference is observed in tables 15 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.375, 0.75 or 1.125 mg/ml of methylparaben/propylparaben 9/1. In this sense, the upper limit 1.125 mg/ml defined in claim 1 of Auxiliary request 1 appears to be a completely arbitrary choice.

In the absence of any further technical effect being demonstrated for these technical features, any possible ratios of methylparaben to propylparaben and any concentration values taken from those indicated in D3 (Section 7, tables) would equally solve the technical problem as formulated in paragraph 4.1.5 above with every expectation of success, and hence merely represent trivial alternatives. In this sense, the arbitrary choice of any possible limit values for the range of paraben concentrations in any weight ratios of methylparaben/propylparaben among those explicitly indicated in D3 (Section 7, tables) is equally obvious for the skilled person.

Furthermore, the fixed combination of methylparaben/propylparaben in weight ratio 9/1 defined in claim 1 of Auxiliary request 1 is also indicated in D3 in the context of parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7). Claim 1 of Auxiliary request 1 also covers parenteral formulations. The skilled person would therefore apply the ratio 9/1 in a straightforward manner to any typical/suitable concentrations of parabens as disclosed in D3 (Section 7, tables) for various liquid pharmaceutical compositions. Thus, e.g. taking the typical concentration values 0.05 mg/ml and 0.1 mg/ml of propylparaben indicated in D3 (Section 7, table), one ends up with total amounts of combined methylparaben/propylparaben in ratio 9/1 of (9x0.05 + 0.05 =) 0.5 mg/ml, or (9x0.1 + 0.1 =) 1.0 mg/ml, both concentration values falling within the range defined in claim 1 of Auxiliary request 1.

Accordingly, Auxiliary request 1 lacks an inventive step.

Auxiliary request 2

Claim 1 of Auxiliary request 2 is limited to liquid pharmaceutical compositions comprising levocetirizine and preservatives selected from methylparaben/ propylparaben in weight ratio 9/1 in concentrations of 0.1 to 1.125 mg/ml.

During the oral proceedings, the Opponent expressed objections of added matter (Art. 123(2) EPC), lack of clarity and lack of inventive step.

Regarding clarity, the Opponent argues in same way as with respect to the Auxiliary request 1.

Regarding Art. 123(2) EPC, the Opponent essentially alleges that the limitation to compositions comprising methylparaben/propylparaben as the only preservatives in the formulation is not disclosed in the originally filed patent application.

The patent Proprietor argues that support for this feature can be found in the patent application as originally filed (page 4 lines 22-24, corresponding to paragraph [0019] last sentence of the specification).

The Opposition Division, again, does not agree with the Opponent's contentions in this respect.

As for clarity, same reasons apply as for Auxiliary request 1. A technically sensible interpretation of the wording of claim 1 of Auxiliary request 2, in particular in the context of the actual disclosure of the specification, does not exclude that the liquid composition may comprise any other additives or excipients, in particular those which may exert an antimicrobial and/or preservative-enhancing function. Claim 1 is clear in this respect, and the requirements of Art. 84 EPC are met.

Precisely because the only technically sensible reading of claim 1 of Auxiliary request 2 is that as explained above, it follows that the requirements of Art. 123(2) EPC are also met. Basis for the claimed ratio 9/1 is found in the sentence "Best results have been obtained with a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight" on page 4 lines 22-24 of the original patent application. Claim 1 of Auxiliary request 2 does not limit in any manner the subject-matter to liquid compositions of levocetirizine containing methylparaben/propylparaben as the only preservatives exclusively. If an

interpretation of claim 1 with this intentional meaning were to be done, then claim 1 would find no basis in the aforementioned passage on page 4 lines 22-24, and it would indeed add subject-matter in contravention of Art. 123(2) EPC.

Regarding inventive step, the further limitation of claim 1 of Auxiliary request 2 to compositions comprising the fixed combination of methylparaben/propylparaben in weight ratio 9/1 in concentration values starting with 0.1 mg/ml does not change anything to the problem-solution analysis carried out in respect of Auxiliary request 1. Again, the end point values of the concentration range 0.1 to 1.125 mg/ml represent only a trivial variation and an arbitrary choice among the concentration values of parabens indicated in D3 (Section 7, tables) which the skilled person would equally use with every expectation of success to solve the technical problem as formulated in paragraph 4.1.5 above.

It is stressed again that the technical problem is not that of determining the lowest possible concentration of parabens having effective antimicrobial activity. Hence, a limitation of the concentration range cannot change anything in the problem-solution analysis unless some further technical effect can be demonstrated within the limited range. The compositions according to claim 1 of Auxiliary request 2 may comprise, again, as much as 1.125 mg/ml of methylparaben/propylparaben 9/1. Neither the upper limit of the concentration range 1.125 mg/ml nor the lower limit 0.1 mg/ml have been shown to be critical in terms of achieving an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of levocetirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens (see table 6). On the other hand, no significant difference is observed in tables 15 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.375, 0.75 or 1.125 mg/ml of methylparaben/propylparaben 9/1. In this sense, the upper limit 1.125 mg/ml defined in claim 1 of Auxiliary request 2 appears to be a completely arbitrary choice.

In the absence of any further technical effect being demonstrated for these technical features, any possible ratios of methylparaben to propylparaben and any concentration values taken from those indicated in D3 (Section 7, tables) would equally solve the technical problem as formulated in paragraph 4.1.5 above with every expectation of success, and hence merely represent trivial alternatives. In this sense, the arbitrary choice of any possible limit values for the range of paraben concentrations in any weight ratios of methylparaben/propylparaben among those explicitly indicated in D3 (Section 7, tables) is equally obvious for the skilled person.

Furthermore, the fixed combination of methylparaben/propylparaben in weight ratio 9/1 defined in claim 1 of Auxiliary request 2 is also indicated in D3 in the context of parenteral formulations (mixture of 0.18% methylparaben and 0.02% propylparaben; see Section 7). Claim 1 of Auxiliary request 2 also covers parenteral formulations. The

skilled person would apply the ratio 9/1 in a straightforward manner to any typical/ suitable concentrations of parabens as disclosed in D3 (Section 7, table) for various liquid pharmaceutical compositions. Thus, e.g. taking the concentration values 0.05 mg/ml and 0.1 mg/ml of propylparaben disclosed in D3 (Section 7, table), one ends up with total amounts of combined methylparaben/propylparaben in ratio 9/1 of (9x0.05 + 0.05 =) 0.5 mg/ml, or (9x0.1 + 0.1 =) 1.0 mg/ml, both concentrations falling within the range defined in claim 1 of Auxiliary request 2. Thus, the skilled person arrives at the subject-matter of claim 1 of Auxiliary request 2 in a straightforward manner.

Final remarks regarding Auxiliary requests 1 and 2

Finally, it is particularly stressed that a more ambitious formulation of the technical problem (as in point 4.1.4 above) in view of the limitation of Auxiliary request 2 to concentrations of methylparaben/propylparaben 9/1 starting with 0.1 mg/ml cannot be accepted.

D3 teaches the use of parabens, in particular in combination, to defeat specifically yeast/mold contamination, as it indicates that parabens are more active against yeast/ mold than against bacteria (see Sections 7 and 10). D3 clearly indicates minimum concentrations of methylparaben in oral solutions and ophthalmic preparations of 0.15 mg/ml, and minimum concentrations of 0.05 mg/ml for propylparaben (Section 7, tables). Hence, an expectation of success in meeting the recommended efficacy criteria (preservative effectiveness) on yeast/mold strains such as Aspergillus and Candida requires the use of the minimum concentrations disclosed in D3. Contrary to this, the concentration 0.1 mg/ml of methylparaben/propylparaben 9/1 defined in present claim 1 means concentration values of 0.09 mg/ml methylparaben and 0.01 mg/ml propylparaben; in particular the latter value is 5 times lower than the minimum concentration of propylparaben indicated in D3 (Section 7, table). It is therefore not credible that the concentration of 0.1 mg/ml of methylparaben/propylparaben 9/1 defined in claim 1 of Auxiliary request 2 would be sufficient for solving the problem of fulfilling the recommended efficacy criteria, in particular in terms of providing preservative effectiveness against yeast/molds such as in particular Aspergillus, and the patent specification does not provide any demonstration in this respect either. Rather to the contrary, it shows in table 7 that a concentration of 0.15 mg/ml of methylparaben/propylparaben 9/1 is on the borderline as to the fulfilment of the recommended efficacy criteria for Aspergillus in liquid compositions of cetirizine. For levocetirizine specifically, the lowest concentrations of methylparaben/propylparaben 9/1 tested in the patent in suit are even much higher than 0.15 mg/ml (0.375 mg/ml,

see tables 15-20). Comparison of results in tables 7 and 15 of the patent in suit demonstrates that in oral solutions of levocetirizine comprising 0.375 mg/ml of methylparaben/propylparaben 9/1 (table 15) the number of viable Aspergillus spores after 14 days from inoculation is even higher than in corresponding oral solutions of racemic cetirizine comprising only 0.15 mg/ml of methylparaben/propylparaben 9/1 (table 7). Hence, it is not plausible that a concentration of 0.1 mg/ml of methylparaben/ propylparaben 9/1 would be sufficient to meet the recommended efficacy criteria for Aspergillus.

These reasons even more apply to claim 1 of Auxiliary request 1 defining the lower limit of the concentration range 0.01 mg/ml.

Accordingly, the Opposition Division comes to the conclusion that the objective technical problem must remain as formulated in point 4.1.5 above. It follows that Auxiliary requests 1 and 2 do not involve an inventive step.

Annex I

[0053] 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 (reference), chlorhexidine acetate (reference) and p-hydroxybenzoate esters.

[0054] 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

[0055] 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, the preservative being 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.

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 preservatives is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight.

4. A liquid pharmaceutical composition according to claim 1 or 2, **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.

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

6. A liquid pharmaceutical composition according to any of the claims 1 to 4, **characterized in that** the active substance is levocetrizine.

7. 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.

Patentansprüche

1. Flüssige pharmazeutische Zusammensetzung, umfassend eine aktive Substanz, ausgewählt aus Cetirizin, Levocetirizin und Efletirizin, und mindestens ein Konservierungsmittel, wobei die Menge an Konservierungsmittel im Falle von Parahydroxybenzoatestern mehr als 0 und weniger als 1,5 mg/ml der Zusammensetzung beträgt, wobei das Konservierungsmittel aus der Gruppe von Methylparahydroxybenzoat, Ethylparahydroxybenzoat, Propylpara-

EP 1 768 649

~~2nd~~ **Auxiliary Request** 1

Kopie für Prüfer

AR 1

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.01 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

EP 1 768 649

~~4th~~ Auxiliary Request 2

AR2

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine and preservatives, wherein the preservatives are selected from methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight selected in the range of 0.1 and 1.125 mg/ml of the composition.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

- critical surfaces,
- container/closure sterilisation and transfer procedures,
- maximum holding period of the product before filling into the final container.

Process validation includes appropriate checks on all the above and checks on the process are regularly carried out by means of process simulation tests using microbial growth media which are then incubated and examined for microbial contamination (media fill tests). In addition, a suitable sample of each batch of any product that is sterilised by filtration and/or aseptically processed is tested for sterility (*2.6.1*) before the batch is released.

01/2005:50102

5.1.2. BIOLOGICAL INDICATORS OF STERILISATION

Biological indicators are standardised preparations of selected micro-organisms used to assess the effectiveness of a sterilisation procedure. They usually consist of a population of bacterial spores placed on an inert carrier, for example a strip of filter paper, a glass slide or a plastic tube. The inoculated carrier is covered in such a way that it is protected from any deterioration or contamination, while allowing the sterilising agent to enter into contact with the micro-organisms. Spore suspensions may be presented in sealed ampoules. Biological indicators are prepared in such a way that they can be stored under defined conditions; an expiry date is set.

Micro-organisms of the same bacterial species as the bacteria used to manufacture the biological indicators may be inoculated directly into a liquid product to be sterilised or into a liquid product similar to that to be sterilised. In this case, it must be demonstrated that the liquid product has no inhibiting effect on the spores used, especially as regards their germination.

A biological indicator is characterised by the name of the species of bacterium used as the reference micro-organism, the number of the strain in the original collection, the number of viable spores per carrier and the *D*-value. The *D*-value is the value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number. It is of significance only under precisely defined experimental conditions. Only the stated micro-organisms are present. Biological indicators consisting of more than one species of bacteria on the same carrier may be used. Information on the culture medium and the incubation conditions is supplied.

It is recommended that the indicator organisms are placed at the locations presumed, or wherever possible, found by previous physical measurement to be least accessible to the sterilising agent. After exposure to the sterilising agent, aseptic technique is used to transfer carriers of spores to the culture media, so that no contamination is present at the time of examination. Biological indicators that include an ampoule of culture medium placed directly in the packaging protecting the inoculated carrier may be used.

A choice of indicator organisms is made such that:

a) the resistance of the test strain to the particular sterilisation method is great compared to the resistance of all pathogenic micro-organisms and to that of micro-organisms potentially contaminating the product,

b) the test strain is non-pathogenic,

c) the test strain is easy to culture.

After incubation, growth of the reference micro-organisms subjected to a sterilisation procedure demonstrates that the procedure has been unsatisfactory.

Steam sterilisation. The use of biological indicators intended for steam sterilisation is recommended for the validation of sterilisation cycles. Spores of *Bacillus stearothermophilus* (for example, ATCC 7953, NCTC 10007, NCIMB 8157 or CIP 52.81) are recommended. The number of viable spores exceeds 5×10^5 per carrier. The *D*-value at 121 °C exceeds 1.5 min. It is verified that exposing the biological indicators to steam at 121 ± 1 °C for 6 min leaves revivable spores, and that there is no growth of the reference micro-organisms after the biological indicators have been exposed to steam at 121 ± 1 °C for 15 min.

Dry-heat sterilisation. Spores of *Bacillus subtilis* (for example, var. *niger* ATCC 9372, NCIMB 8058 or CIP 77.18) are recommended for the preparation of biological indicators. The number of viable spores exceeds 1×10^5 per carrier and the *D*-value at 160 °C is approximately 1 min to 3 min. Dry heat at temperatures greater than 220 °C is frequently used for sterilisation and depyrogenation of glassware. In this case, demonstration of a 3 log reduction in heat resistant bacterial endotoxin can be used as a replacement for biological indicators.

Ionising radiation sterilisation. Biological indicators may be used to monitor routine operations, as an additional possibility to assess the effectiveness of the set dose of radiation energy, especially in the case of accelerated electron sterilisation. The spores of *Bacillus pumilus* (for example, ATCC 27.142, NCTC 10327, NCIMB 10692 or CIP 77.25) are recommended. The number of viable spores exceeds 1×10^7 per carrier. The *D*-value exceeds 1.9 kGy. It is verified that there is no growth of the reference micro-organisms after the biological indicators have been exposed to 25 kGy (*minimum absorbed dose*).

Gas sterilisation. The use of biological indicators is necessary for all gas sterilisation procedures, both for the validation of the cycles and for routine operations. Gas sterilisation is widely used for medical devices, isolators, chambers, etc. Use for such purposes is outside the scope of the European Pharmacopoeia. The use of spores of *Bacillus subtilis* (for example, var. *niger* ATCC 9372, NCIMB 8058 or CIP 77.18) is recommended for ethylene oxide. The number of viable spores exceeds 5×10^5 per carrier. The parameters of resistance are the following: the *D*-value exceeds 2.5 min for a test cycle involving 600 mg/l of ethylene oxide, at 54 °C and at 60 per cent relative humidity. It is verified that there is no growth of the reference micro-organisms after the biological indicators have been exposed to the test cycle described above for 60 min and that exposing the indicators to a reduced temperature cycle (600 mg/l, 30 °C and 60 per cent relative humidity) for 15 min leaves revivable spores. Exposing the indicators to 600 mg/l of ethylene oxide at 54 °C for 60 min without humidification must leave revivable spores to ensure that the biological indicator is able to reveal insufficient humidification.

01/2005:50103

5.1.3. EFFICACY OF ANTIMICROBIAL PRESERVATION

If a pharmaceutical preparation does not itself have adequate antimicrobial activity, antimicrobial preservatives may be added, particularly to aqueous preparations, to prevent proliferation or to limit microbial contamination which, during normal conditions of storage and use, particularly for multidose containers, could occur in a product and present

a hazard to the patient from infection and spoilage of the preparation. Antimicrobial preservatives must not be used as a substitute for good manufacturing practice.

The efficacy of an antimicrobial preservative may be enhanced or diminished by the active constituent of the preparation or by the formulation in which it is incorporated or by the container and closure used. The antimicrobial activity of the preparation in its final container is investigated over the period of validity to ensure that such activity has not been impaired by storage. Such investigations may be carried out on samples removed from the final container immediately prior to testing.

During development of a pharmaceutical preparation, it shall be demonstrated that the antimicrobial activity of the preparation as such or, if necessary, with the addition of a suitable preservative or preservatives provides adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage and use of the preparation.

The efficacy of the antimicrobial activity may be demonstrated by the test described below. The test is not intended to be used for routine control purposes.

TEST FOR EFFICACY OF ANTIMICROBIAL PRESERVATION

The test consists of challenging the preparation, wherever possible in its final container, with a prescribed inoculum of suitable micro-organisms, storing the inoculated preparation at a prescribed temperature, withdrawing samples from the container at specified intervals of time and counting the organisms in the samples so removed.

The preservative properties of the preparation are adequate if, in the conditions of the test, there is a significant fall or no increase, as appropriate, in the number of micro-organisms in the inoculated preparation after the times and at the temperatures prescribed. The criteria of acceptance, in terms of decrease in the number of micro-organisms with time, vary for different types of preparations according to the degree of protection intended (see Tables 5.1.3.-1/2/3).

Test micro-organisms

Pseudomonas aeruginosa	ATCC 9027; NCIMB 8626; CIP 82.118.
Staphylococcus aureus	ATCC 6538; NCTC 10788; NCIMB 9518; CIP 4.83.
Candida albicans	ATCC 10231; NCPF 3179; IP 48.72.
Aspergillus niger	ATCC 16404; IMI 149007; IP 1431.83.

Single-strain challenges are used and the designated micro-organisms are supplemented, where appropriate, by other strains or species that may represent likely contaminants to the preparation. It is recommended, for example, that *Escherichia coli* (ATCC 8739; NCIMB 8545; CIP 53.126) is used for all oral preparations and *Zygosaccharomyces rouxii* (NCYC 381; IP 2021.92) for oral preparations containing a high concentration of sugar.

Preparation of inoculum

Preparatory to the test, inoculate the surface of agar medium B (*2.6.12*) for bacteria or agar medium C without the addition of antibiotics (*2.6.12*) for fungi, with the recently grown stock culture of each of the specified micro-organisms. Incubate the bacterial cultures at 30-35 °C for 18-24 h, the culture of *C. albicans* at 20-25 °C for 48 h, and the culture of *A. niger* at 20-25 °C for 1 week or until good sporulation is obtained. Subcultures may be needed after revival before the micro-organism is in its optimal state, but it is recommended that their number be kept to a minimum.

To harvest the bacterial and *C. albicans* cultures, use a sterile suspending fluid, containing 9 g/l of *sodium chloride R*, for dispersal and transfer of the surface growth into a suitable vessel. Add sufficient suspending fluid to reduce the microbial count to about 10^8 micro-organisms per millilitre. To harvest the *A. niger* culture, use a sterile suspending fluid containing 9 g/l of *sodium chloride R* and 0.5 g/l of *polysorbate 80 R* and adjust the spore count to about 10^8 per millilitre by adding the same solution.

Remove immediately a suitable sample from each suspension and determine the number of colony-forming units per millilitre in each suspension by plate count or membrane filtration (*2.6.12*). This value serves to determine the inoculum and the baseline to use in the test. The suspensions shall be used immediately.

METHOD

To count the viable micro-organisms in the inoculated products, use the agar medium used for the initial cultivation of the respective micro-organisms.

Inoculate a series of containers of the product to be examined, each with a suspension of one of the test organisms to give an inoculum of 10^5 to 10^6 micro-organisms per millilitre or per gram of the preparation. The volume of the suspension of inoculum does not exceed 1 per cent of the volume of the product. Mix thoroughly to ensure homogeneous distribution.

Maintain the inoculated product at 20-25 °C, protected from light. Remove a suitable sample from each container, typically 1 ml or 1 g, at zero hour and at appropriate intervals according to the type of the product and determine the number of viable micro-organisms by plate count or membrane filtration (*2.6.12*). Ensure that any residual antimicrobial activity of the product is eliminated by dilution, by filtration or by the use of a specific inactivator. When dilution procedures are used, due allowance is made for the reduced sensitivity in the recovery of small numbers of viable micro-organisms. When a specific inactivator is used, the ability of the system to support the growth of the test organisms is confirmed by the use of appropriate controls.

The procedure is validated to verify its ability to demonstrate the required reduction in count of viable micro-organisms.

CRITERIA OF ACCEPTANCE

The criteria for evaluation of antimicrobial activity are given in Tables 5.1.3.-1/2/3 in terms of the log reduction in the number of viable micro-organisms against the value obtained for the inoculum.

Table 5.1.3.-1. - *Parenteral and ophthalmic preparations*

		Log reduction				
		6 h	24 h	7 d	14 d	28 d
Bacteria	A	2	3	-	-	NR*
	B	-	1	3	-	NI**
Fungi	A	-	-	2	-	NI
	B	-	-	-	1	NI

*NR: no recover

**NI: no increase

The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.

Table 5.1.3.-2. - *Topical preparations*

		Log reduction			
		2 d	7 d	14 d	28 d
Bacteria	A	2	3	-	NI
	B	-	-	3	NI
Fungi	A	-	-	2	NI
	B	-	-	1	NI

The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.

Table 5.1.3.-3. - *Oral preparations*

	Log reduction	
	14 d	28 d
Bacteria	3	NI
Fungi	1	NI

The above criteria express the recommended efficacy to be achieved.

01/2005:50104

5.1.4. MICROBIOLOGICAL QUALITY OF PHARMACEUTICAL PREPARATIONS

The following chapter is published for information.

In the manufacture, packaging, storage and distribution of pharmaceutical preparations, suitable means must be taken to ensure their microbiological quality. The pharmaceutical preparations should comply with the criteria given below.

Category 1

Preparations required to be sterile by the relevant monograph on the dosage form and other preparations labelled sterile.

– Test for sterility (*2.6.1*).

Category 2

Preparations for topical use and for use in the respiratory tract except where required to be sterile and transdermal patches.

– Total viable aerobic count (*2.6.12*). Not more than 10^2 micro-organisms (aerobic bacteria plus fungi) per gram, per millilitre or per patch (including the adhesive and backing layer).
– Transdermal patches: absence of enterobacteria and certain other gram-negative bacteria, determined on 1 patch (including the adhesive and backing layer). Other preparations: not more than 10^1 enterobacteria and certain other gram-negative bacteria per gram or per millilitre (*2.6.13*).
– Absence of *Pseudomonas aeruginosa*, determined on 1 g, 1 ml or one patch (including the adhesive and backing layer) (*2.6.13*).
– Absence of *Staphylococcus aureus*, determined on 1 g, 1 ml or one patch (including the adhesive and backing layer) (*2.6.13*).

Category 3

A. *Preparations for oral and rectal administration.*
– Total viable aerobic count (*2.6.12*). Not more than 10^3 bacteria and not more than 10^2 fungi per gram or per millilitre.
– Absence of *Escherichia coli* (1 g or 1 ml) (*2.6.13*).

B. *Preparations for oral administration containing raw materials of natural (animal, vegetable or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts microbial contamination of the raw material exceeding 10^3 viable micro-organisms per gram or per millilitre. Herbal medicinal products described in category 4 are excluded.*
– Total viable aerobic count (*2.6.12*). Not more than 10^4 bacteria and not more than 10^2 fungi per gram or per millilitre.
– Not more than 10^2 enterobacteria and certain other gram-negative bacteria per gram or per millilitre (*2.6.13*).
– Absence of *Salmonella* (10 g or 10 ml) (*2.6.13*).
– Absence of *Escherichia coli* (1 g or 1 ml) (*2.6.13*).
– Absence of *Staphylococcus aureus* (1 g or 1 ml) (*2.6.13*).

Category 4

Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered).

A. *Herbal medicinal products to which boiling water is added before use.*
– Total viable aerobic count (*2.6.12*). Not more than 10^7 bacteria and not more than 10^5 fungi per gram or per millilitre.
– Not more than 10^2 *Escherichia coli* per gram or per millilitre (*2.6.13*, using suitable dilutions).

B. *Herbal medicinal products to which boiling water is not added before use.*
– Total viable aerobic count (*2.6.12*). Not more than 10^5 bacteria and not more than 10^4 fungi per gram or per millilitre.
– Not more than 10^3 enterobacteria and certain other gram-negative bacteria per gram or per millilitre (*2.6.13*).
– Absence of *Escherichia coli* (1 g or 1 ml) (*2.6.13*).
– Absence of *Salmonella* (10 g or 10 ml) (*2.6.13*).

01/2005:50105

5.1.5. APPLICATION OF THE F_0 CONCEPT TO STEAM STERILISATION OF AQUEOUS PREPARATIONS

The following chapter is published for information.

The F_0 value of a saturated steam sterilisation process is the lethality expressed in terms of the equivalent time in minutes at a temperature of 121 °C delivered by the process to the product in its final container with reference to micro-organisms possessing a *Z*-value of 10.

The total F_0 of a process takes account of the heating up and cooling down phases of the cycle and can be calculated by integration of lethal rates with respect to time at discrete temperature intervals.

When a steam sterilisation cycle is chosen on the basis of the F_0 concept, great care must be taken to ensure that an adequate assurance of sterility is consistently

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Acknowledgement of receipt

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Appeal number: T0371/12-3.3.02

Please find enclosed a copy of the statement setting out the grounds of Appeal.

Any reply must be filed within four months of this notification.

The Registrar N. Maslin
Tel.: 089 / 2399 - 3321

Annex(es):

Registered letter

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Opposition against EP 1 768 649
Appeal No.: T0371/12-3.3.02
Opponent: Zentiva k.s.
Proprietor/Appellant: UCB FARCHIM S.A

Further to our submissions dated February 17 and April 23, 2012 it is herewith indicated that the correct address of the Proprietor/Appellant reads as follows:

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P30048-EPOP WB	05758582.0 - 2112 / 1768649

Applicant/Proprietor
UCB FARCHIM S.A.

Communication

concerning the registration of amendments relating to

☐ a transfer (R. 22 and 85 EPC)

☑ entries pertaining to the applicant / the proprietor (R. 143(1)(f) EPC)

As requested, the entries pertaining to the applicant of the above-mentioned European patent application / to the proprietor of the above-mentioned European patent have been amended to the following:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
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Z.I. de Planchy,
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1630 Bulle/CH

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Date: 11-06-2012

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 2112 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy (copies) EPO Form 2544 dated 11.6.12.

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Eingereichte Unterlagen Anmeldenummer/Patentnummer Application Number/Patent Number Numéro de la demande/numéro du brevet	Items filed Ihr Zeichen Your reference Votre référence	Pièces produites ggfs. Art und Datum der Unterlagen[3] Nature and date of items (optional)[3] Nature et date des pièces (facultatif)[3]
1. EP 1768649	B0199PI-EP	Observation of opponent
2. EP 1768649	B0199PI-EP	D16 Batch record 020504
3. EP 1768649	B0199PI-EP	
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Page 1 of 12

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5 September 2012

Re.:	**European Patent No. 1768649** **European Patent Application No. 05758582.0**
Appeal File No.:	**T0371/12-3.3.02**
Proprietor:	**UCB Farchim S.A**
Opponent:	**Zentiva k.s.**
Agent's Case Ref.:	**B0199PI-EP**

REPLY TO GROUNDS OF APPEAL

Dear Sirs,

In response to the Grounds of Appeal (April 23, 2012) of the appellant/Proprietor UCB FARCHIM S.A our observations are submitted herewith:

1. Request

It is requested to maintain the decision of the Opposition Division of December 22, 2011, revoking EP 1768649 B1 in its entirety.

2. Cited documents

D1-D15 previously cited during the opposition proceedings

D16 Batch record for batch 020504 of ZODAC®GTT dated May 12, 2004

D16A English translation of D16

3. Argumentation regarding the Main Request

3.1 Art 54 EPC – Novelty

The Opposition Division came to the conclusion that D5, D6, D7, D8 together with D11 demonstrate that the products ZODAC GTT (oral drops) and ZODAC SIR (syrup) were indeed launched to the market in the Czech Republic on 31.10.2001, and in Slovakia on 30.09.2002. D5, D6, D7 and D8 demonstrate that ZODAC GTT and ZODAC SIR comprise cetirizine dihydrochloride in aqueous solution containing methylparaben and propylparaben as preservatives, but the Opposition Division pointed out that the concentration of methylparaben and propylparaben in the solution is not disclosed in D5 to D8. However, although the Summary of Product Characteristics D9 and D10 shows the concentration of parabens the Opposition Division in their decision took the view that it has not been proven without any remaining doubt that the products launched in 2001 and 2002 in the Czech Republic and Slovakia and commercially available before the date of priority of the contested patent (14.07.2004) had exactly the same concentration of parabens as the products available in 2009 in the Czech Republic as described in D9 and D10.

We enclose a batch record showing detailed manufacturing instructions for batch no. 020504 of the ZODAC®GTT product, dated back in May 2004 showing paraben amounts falling within the range of the Main Request, the proportion of parabens to cetirizine dihydrochloride being exactly according to the Summary of Product Characteristics (D9) (methyl paraben 1,349925 mg/ml and propyl paraben 0,15083 mg/ml). However, since this evidence was received so late during the Opposition proceedings we did not file it - but it is evident/clear that the registered composition of the ZODAC®GTT product had actually the same concentration of parabens as the products available in 2009 in the Czech Republic.

Independently of whether the information on the amounts of parabens of ZODAC®GTT and ZODAC®SIR was published at the priority date of B1 or not, the compositions of the products were part of the state of the art after the launch of the products since the composition of the products could be analyzed without undue burden. This is confirmed by T406/86 and G1/92.

<u>The margin of experimental error of a numerical range</u>

From D9 to D11 it is evident that both the ZODAC®GTT and ZODAC®SIR, publicly used before the priority date of B1, comprise a total amount of 1.5 mg/ml of methylparaben and propylparaben. Claim 1 of B1, comprises a range of "more than 0 and less than 1.5 mg/ml" of parahydroxybenzoates. Thus, the question is whether the claimed upper limit "lower than 1.5 mg/ml" is novel over the prior use value 1.5 mg/ml.

In T 594/01 the claimed subject matter was distinguished from a specific experimental value disclosed in the prior art only in the terms of an upper limit to be required to be "lower than" the specific value. In this decision the board stated that it is common general knowledge that experimental measurements cannot be dissociated from the margin of uncertainty attached to the measurement and therefore the claimed subject matter in this case was not distinguishable from the prior art within the margin of experimental error. Therefore the upper limit distinguished only by the terms "lower than" was not considered novel. Thus, since there is always a tolerance area around a certain value the upper end point of the claimed range "lower than 1.5 mg/ml" is not novel over the public prior use of 1.5 mg/ml.

Also the patentee has stated in their response of October 13, 2010 (page 4, third paragraph) that "there are established and very precise standard methods for determining the content of any ingredient of a pharmaceutical composition" and that "there are established and very precise standard methods for determining the content of any ingredient of a pharmaceutical composition" and that it thus would be quite unrealistic to assume a large margin of uncertainty regarding the measurement. However, any uncertainty regarding the

measurement is not relevant when discussing whether the intention to include a certain amount of an ingredient in the composition was in fact exactly present in the end product taking into account the different production steps. Thus the exact amount of parabens being 1.5 mg/ml or just below 1.5 mg/ml in a product on the market although the intention of course was that the amount is exactly as defined. As the patentee correctly stated the amounts can be precisely determined, but the amount of for example parabens in every batch is not necessary exactly identical.

Thus, all the features of claim 1 have been disclosed during the public prior use and therefore claim 1 lacks novelty.

3.2 Art 56 EPC – Inventive step

3.2.1 Closest prior art

The Opposition Division has considered D1 to be the closest prior art. This has also been acknowledged by both parties during the opposition proceedings.

D1 relates to a composition comprising cetirizine or a salt thereof as an active ingredient and parahydroxybenzoate esters as preservatives and the difference of claim 1 of the opposed patent as granted with respect to D1 (example 5) is the definition of the concentration of parahydroxybenzoate esters (parabens) selected from methylparaben, ethylparaben, propylparaben, or mixtures thereof of "more than 0 and less than 1.5 mg/ml", whereas D1 discloses a total concentration of methylparaben and propylparaben of 3 mg/ml. The Opposition Division has noted in their decision that the wording of claim 1, however, does not exclude the presence of other additives, in particular other preservatives, in the composition.

3.2.2 Reducing the risk of adverse effects

The Opponent agrees with the Opposition Division that there is no demonstration in the patent of any effect of the parabens concentration values defined in claim 1 on an actual reduction of the risk of allergic reactions of the claimed compositions. The patent contains no information and no details whatsoever in this respect. Whereas the reduction of the risk of allergic reactions by reducing the concentration of preservatives may be considered as feasible in general in view of the common knowledge of the person skilled in the art, it is stressed that the patent in suit does not contain any experimental details at all concerning this alleged effect or advantage.

In the decision the Opposition Division brought forward that no evidence has been provided in support that there is a linear correlation between the reduction of preservative concentration and the lowering of risk/occurrence of adverse allergic reactions stated by the patent Proprietor during the oral proceedings. No further evidence is provided in his Grounds of Appeal either.

3.2.3 Sufficient antimicrobial efficacy – further additives

Regarding the discussion of the "self-preserving" effect of the active ingredient itself the Opposition Division took the view that it remains doubtful to which component or combination of components the antimicrobial stabilisation effect shown in the compositions of the patent in suit is to be attributed. Especially since all the formulations comprise a combination of substances which may have an antimicrobial stabilising effect, and/or an antimicrobial enhancing effect, alone or in combination. The Opponent in this respect refers to documents D12-D15.

Although the Opposition Division did not admit D12, D13 and D15 (D12 and D13 being post-published documents) into the proceedings the Opposition Division stated that they represent the common general knowledge of any person skilled in the art, and that is why there is no need to resort to them as a proof of said accepted common knowledge.

Thereto the Opposition Division decided to admit D14 into the proceedings as prima facie relevant. The Opposition Division stated that D14 turned out to be useful for the discussion of the role of sodium acetate in the microbial growth inhibitory activity of the formulations of the patent in suit comprising sodium acetate (in particular examples 1-4), as D14 reports on antimicrobial activity of sodium acetate on same microorganisms (*Staphylococcus, Escherichia, Pseudomonas, Candida*) tested in the patent in suit. D14 is hence pertinent for understanding the role of the various ingredients of the compositions according to the opposed patent in the preservative effect(s) allegedly demonstrated in the patent especially since it is a document in the area of hospital parenteral nutrition, and hence in the field of Pharmaceuticals, and reports on analogous problem of microbial contamination risk/preservation of aqueous solutions for pharmaceutical use.

As pointed out before, none of the examples actually support the claimed improved antimicrobial efficiency of only parabens alone combined with the active ingredients cetirizine, levocetirizine and efletirizine. Especially there was no support that cetirizine, levocetirizine and efletirizine alone have any antimicrobial effect (for example at the lowest concentration of parabens of claim 1). Thus it remained unclear whether the desired effect actually originates from the use of one or more of the antimicrobial agents not being parabens or from any of the other components of the compositions, especially taking into account the disclosures presented in D12 to D15. Many of the compounds, for example propylene glycol, glycerol and sorbitol, which are used in the compositions of the Examples of the patent, influence on the antimicrobial stability and the new examples provided by the Patent Proprietor with the Grounds of Appeal does not as explained below clearly show from which components the desired effect originates.

Further, the Opponent wishes to point out that in the case any of cetirizine, levocetirizine or efletirizine alone had any antimicrobial effect, this would be an inherent property present already in the compositions of D1 and thus involving no inventive step.

3.2.3.1 Comparative example 1

The Patent Proprietor has in the Grounds of Appeal described a new Comparative example 1 which relates to preparing a solution of sodium acetate and acetic acid in the amounts specified in Example 1 of the patent in suit. However, none of the other compounds used in Example 1 of the patent, i.e. sorbitol, glycerine, propyleneglycol, which according to D3 and D15 have enhancing effects on the preservatives, are used in the solution. Since sorbitol, glycerine, propyleneglycol were excluded in the experimental setting of comparative example 1 the preservative efficiency of these compounds alone or their effect on sodium acetate and acetic acid has not been tested. Thus, this comparative example does not, contrary to the statement of the Patent Proprietor, show that further additives in the compositions disclosed in the examples do not have any antimicrobial activity as the test conditions are not the same as for example 1.

On the contrary, the effectiveness tests of comparative example 1 show that the solution of acetic acid and sodium acetate is in fact an effective antimicrobial preservative with regard to some of the tested microbial suspensions even without using compounds enhancing the preservative effect (such as propyleneglycol). For the bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus* the recommended efficacy criteria (log reduction = 3 at 14 d according to Table 5.1.3.-3. of Annex II) seems to be fulfilled since the result for

these microbes are <1 after 14 and 28 days according to the results in Table 2 of Annex 1. This comparative example clearly supports the contention that these compounds have antimicrobial effect.

Furthermore, it is also good to notice that for *Aspergillus niger* the count according to Table 2 of the patent in suit is also high in the oral solution after 28 days although the log reduction requirements of the European Pharmacopoeia seems to be fulfilled for the composition/solution of the patent.

3.2.3.2 Comparative example 2

Comparative example 2 relates to preparing a solution according to Example 2 (Table 4) of the patent, but without adding levocetirizine. In this example sodium acetate and acetic acid was used together with glycerine and sodium saccharinate.

From the results provided in Table 3 of Annex I, particularly when compared with the ones in Table 4 of Annex I, it can be seen that the antimicrobial effect, particularly with respect to *Eschericia coli, Staphylococcus aureus* and *Candida albicans* are improved, when glycerine and sodium saccharinate are added. This is evident in view of D12- D15.

In Annex I it is said that the exemplified solution did not fulfill the requirements of the European Pharmacopoeia. However, the results given in Table 4 of Annex I do not differ that much from the results of the patent in suit (Table 5). For *Pseudomonas aeruginosa*, *Escherichia coli* and *Stafylococcus aureus* the criteria where fulfilled since the result for these microbes are <1 after 14, 21 and 28 days according to the results in Annex 1 (Table 4). Further, the results for *Aspergillus niger* are quite the same as for Example 2 of the patent in suit. Thereto it seems that according to the results of Example 2 (Table 5) of the patent the solution prepared in that example comprising levocetirizine did also not totally fulfill the criteria for *Aspergillus niger*. The results for *Candida albicans* in Comparative example 2 (Table 4) seems somehow confusing since the microbial content after 14 days differs so much from the results after 7 and 21 days.

Although the Patent Proprietor says that the examples given in Table 4 of comparative example 2 clearly show that an oral solution without levocetirizine has no preservative effect, this statement does not seem to be true based on the above. Further, since the "self-preserving" effect of Levocetirizine was not the issue of the invention on hand this Comparative example 2 is not relevant for assessing the patentability of the patent in suit.

3.2.3.3 Example 3

Example 3 relates to preparing a solution according to example 2 (Table 4) of the patent, but by adding parahydroxybenzoate esters in a total amount of 0.1 mg/ml. In the patent the smallest amount of parahydroxybenzoate esters used in the examples was 0.15 mg/ml (for cetirizine) and 0.375 mg/ml (for levocetirizine).

Although it is said by the Patent Proprietor that the recommended efficacy criteria are achieved in all cases of Example 3 it seems that in Table 6 (annex I) the log reduction for 14 d according to the requirements of the European Pharmacopoeia, is not totally received for both *Candida albicans* and *Aspergillus niger* (log reduction = 1 for fungi at 14 d according to Table 5.1.3.-3. of Annex II), i.e. the reduction from **2.6**x10^5 to **7.5**x10^4 and **3.9**x10^5 to **6.5**x10^4 does not fulfill the criteria. For the drops the recommended efficacy criteria seem to be achieved (Table 7, Annex I).

When looking at tables 6 and 7 it can be clearly seen that the addition of propylene glycol enhances significantly the preservative effect of parabens for *Candida albicans* and *Aspergillus niger*, as could also be expected from the information provided in D3.

No examples or evidence are provided, supporting the contention that the combination of the active ingredient (cetirizine, levocetirizine or efletirizine), combined with parabens alone would provide the desired preservative effect. All of the examples in the patent and the new examples clearly show that at least sodium acetate, acetic acid, glycerol and sodium saccharinate have antimicrobial effect, and that propylene glycol has a clear enhancing effect on the effect of parabens. Thus it appears that at least some of these compounds are necessary for achieving the claimed effect.

Based on the new examples of the Patent Proprietor it is clearly shown that said self-preserving effect of levocetirizine is at least not true for all kind of microbes. On the contrary the other compounds of the compositions present in the Examples of the patent are shown to have a significant antimicrobial activity, preservative or preservative enhancing impact on different kinds of bacteria.

Further based on the Examples of the patent and on Example 3 (Annex I) it still not possible to draw any conclusions with regard to the how small amounts of parahydroxybenzoate esters are effective and the Patent Proprietor has shown no special technical effect of the tested amount of parabens in Example 3 (i.e. 0,1 mg/ml). Further this certain amount of parabens was discussed already during the Opposition proceedings and is also discussed below with regard to Auxiliary request 2.

3.2.4 Objective technical problem

In their decision the Opposition Division agrees with the Opponent's formulation of the technical problem and comes to the conclusion that the objective technical problem can only be reasonably formulated in terms of providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens having the recommended efficacy of antimicrobial preservation.

The Opposition Division stresses in particular that, in view of the evidence available, the correct formulation of the technical problem cannot be that of providing compositions having the lowest possible concentration of parabens still compatible with an effective antimicrobial activity fulfilling the recommended efficacy criteria. Compositions according to claim 1 of the opposed patent can comprise as much as "less than 1.5 mg/ml" of parabens. Neither the limit of the paraben concentration range "less than 1.5 mg/ml" defined in claim 1 of the opposed patent nor even the lowest paraben concentration value of 0.15 mg/ml used in various examples of the patent in suit have been shown to be critical in this respect, i.e. the lowest possible concentration of parabens still compatible with an effective antimicrobial activity. On the contrary, liquid pharmaceutical compositions of cetirizine, levocetirizine and efletirizine meeting the recommended efficacy criteria are demonstrated in the patent in suit even in the absence of parabens, but still in the presence of other known preservatives. On the other hand, no significant difference is observed in tables 7 to 20 in terms of fulfilling the recommended efficacy criteria (determination after 28 days) for compositions comprising 0.15, 0.375, 0.45, 0.75, 1.05 or 1.125 mg/ml of parabens. In this sense, the upper limit of less than 1.5 mg/ml of parabens defined in claim 1 of the opposed patent appears to be fully arbitrary.

The Opposition Division also addresses the question of whether or not a "self-preserving" effect of the active agent itself is actually demonstrated in the patent. In the Opposition Division's opinion, the examples of the patent in suit do not allow to draw any conclusion in this respect and thereto states that it is irrelevant for the formulation of the technical problem if it actually

exists, as it does not derive from the technical difference of the subject-matter of claim 1 of the opposed patent over D1 (example 5), namely the lower concentration of parabens, but allegedly from the presence of the active agent, and hence this effect would have been also present, even if unrecognized, in the composition of D1 (example 5).

After evaluating if the problem as formulated above is shown in the patent to be actually solved across the whole area covered by claim 1 of the contested patent, in particular for any liquid pharmaceutical composition of cetirizine, levocetirizine or efletirizine comprising parabens in concentrations of "more than 0 and less than 1.5 mg/ml" the conclusion of the Opposition Division is that the technical problem has to be reformulated even less ambitiously, namely in terms of providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens showing (some degree of) antimicrobial preservative effectiveness.

The Opposition Division pointed out in their decision that concentrations of parabens lower than 0.15 mg/ml have simply not been tested and that concentrations of parabens lower than 0.15 mg/ml, e.g. only slightly higher than 0 mg/ml (say concentrations as low as e.g. 0.0001 mg/ml as described in paragraph [0020] of the contested patent) may result, in particular in the case of oral solutions, in insufficient antimicrobial effectiveness against yeast contamination (*Aspergillus* and *Candida*), as the recommended efficacy criteria are not fulfilled.

3.2.5 Combination of D1 and D3

The Opponent agrees with the decision of the Opposition Division regarding lack of inventive step of the claims over the cited prior art publications D1 and D3.

As discussed above the Opposition Division expresses that the problem to be solved by the opposed patent is providing further useful liquid pharmaceutical compositions of cetirizine, levocetirizine or efletirizine comprising parabens showing (some degree of) antimicrobial preservative effectiveness.

The closest prior art D1 relates to a composition comprising cetirizine or a salt thereof as an active ingredient and parahydroxybenzoate esters as preservatives and the difference of claim 1 of the opposed patent as granted with respect to D1 (example 5) is the definition of the concentration of parahydroxybenzoate esters (parabens) selected from methylparaben, ethylparaben, propylparaben, or mixtures thereof of "more than 0 and less than 1.5 mg/ml", whereas D1 discloses a total concentration of methylparaben and propylparaben of 3 mg/ml.

In their decision the Opposition Division agreed with the Opponent that it was general knowledge of the person skilled in the art to reduce the concentration of parabens in order to lower the risk of allergic reactions due to the controversial discussions ongoing at the time of priority of the opposed patent about the safety and toxicology concerns regarding the use of parabens as preservatives in pharmaceuticals. The Opposition Division further agrees with the Opponent that the skilled person is therefore well motivated to take into account general knowledge represented by a handbooks of pharmaceutical excipients such as D3 (chapters dealing with methyl- and propylparaben) in order to find out suitable concentrations of parabens providing effective antimicrobial preservation in liquid pharmaceutical compositions.

According to D3 (tables under Section 7 on pages 340 and 450) the amount of methylparabens should be 0.15-2 mg/ml and/or the amount of propylparabens 0.05-0.1 mg/ml in an ophthalmic composition, as the one disclosed in D1 (Page 11, Example 5). Three of the explicitly disclosed points (0.15, 0.05 and 0.1) of the overlapping prior art ranges falls in the claimed range "more than 0 and less than 1.5 mg/ml". Also the Opposition Division came to the conclusion that the ranges of concentrations indicated in D3 almost completely overlap

with the range of concentrations defined in claim 1 of the contested patent and that the skilled person, in order to solve the technical problem as formulated above, would with every expectation of success, directly follow the indications provided in D3 (table under Section 7), and he would modify the ophthalmic formulation of D1 (example 5) to comprise 0.15-2 mg/ml methylparaben and/or 0.05-0.1 mg/ml propylparaben. In doing so, the skilled person would end up necessarily with combined amounts of parabens falling within the range "more than 0 and less than 1.5 mg/ml" defined in claim 1 of the contested patent in a straightforward manner.

Contrary to the statement of the Patent Proprietor (Grounds of Appeal p. 9, 2. paragraph) D3 only says that mixtures of different parabens are frequently used, but not that this is preferred or obligatory in any way. Therefore neither the statement of the Proprietor regarding it being unclear how the table of section 7 of the chapter "Methylparaben" should be interpreted nor the reference to section 10 regarding the activity of methylparaben bring any new relevant information the skilled person would take into account when checking D3 for usual amounts of methylparabens (or propylparabens) employed in ophthalmic drops or oral solutions. The same applies to section 14 indicating the irritant potential of the parabens. This section on the contrary discusses the widespread use of parabens, defines that parabens have been used also in ophthalmic preparations and states that reactions to parabens are relatively uncommon.

Also the Opposition Division pointed out that D3 reflects the existing safety concerns at the date of priority of the patent in suit, and it reports that the WHO has set an estimated total acceptable daily intake for methyl-, ethyl- and propylparabens at up to 10 mg/kg body-weight (see Section 14), but held that following this explicit indication of D3, the skilled person would be by no means deterred from using the typical paraben concentration values for oral solutions of 0.15 to 2 mg/ml for methylparaben and/or 0.1 to 0.2 mg/ml for propylparaben indicated in the tables under Section 7, but would be inclined to use the lower values in the aforementioned ranges, thereby unavoidably ending up with concentration values falling within the area covered by claim 1 of the opposed patent.

Therefore, since the concentration values of D3 overlap the range of concentrations defined in claim 1 of the Main request and also the ranges defined in claim 1 of Auxiliary requests 1 and 2 it is clear that these claims do not involve an inventive step.

3. Argumentation regarding the Auxiliary Requests

Auxiliary request 1

Claim 1 of Auxiliary request 1 is limited to liquid pharmaceutical compositions comprising levocetirizine and methylparaben/propylparaben in weight ratio 9/1 in concentrations of 0.01 to 1.125 mg/ml.

The Opponent totally agrees with the decision of the Opposition Division that regarding inventive step, the additional features introduced in claim 1 of Auxiliary request 1 do not change anything to the problem-solution analysis as carried out above in respect of the Main request.

With regard to the limitation to levocetirizine, no particular technical effect in terms of antimicrobial preservation/stabilisation of the liquid composition is demonstrated in the patent in suit for the levorotatory enantiomer of cetirizine as compared to the racemic form (cetirizine). Furthermore, the use of levocetirizine instead of racemic cetirizine would be obvious from D4, as the levorotatory enantiomer has more therapeutic activity than racemic cetirizine, and hence less amounts of the pure enantiomer than of the racemic mixture are required in the formulation.

As for the use of methylparaben/propylparaben in fixed combination in weight ratio 9/1, this specific ratio has been mentioned in D3 and thereto this feature merely represents an obvious alternative, as it is not shown to be associated with any particular technical effect. The compositions of examples 3 and 4 of the patent in suit all comprise methylparaben/propylparaben in fixed combination in ratio 9/1; hence the analysis carried out above for the Main request applies mutatis mutandis to Auxiliary request 1.

Since the technical problem is not that of determining the lowest possible concentration of parabens having effective antimicrobial activity a limitation of the concentration range cannot change anything in the problem-solution analysis especially since no further technical effect has been demonstrated within the limited range. The arbitrary choice of any possible limit values for the range of paraben concentrations in any weight ratios of methylparaben / propylparaben among those explicitly indicated in D3 (Section 7, tables) is equally obvious for the skilled person.

Auxiliary request 2

Claim 1 of Auxiliary request 2 is limited to liquid pharmaceutical compositions comprising levocetirizine and preservatives selected from methylparaben/ propylparaben in weight ratio 9/1 in concentrations of 0.1 to 1.125 mg/ml.

The Opponent again totally agrees with the decision of the Opposition Division that regarding inventive step, the further limitation of claim 1 of Auxiliary request 2 to compositions comprising the fixed combination of methylparaben/propylparaben in weight ratio 9/1 in concentration values starting with 0.1 mg/ml does not change anything to the problem-solution analysis carried out in respect of Auxiliary request 1. The end point values of the concentration range 0.1 to 1.125 mg/ml represent only a trivial variation and an arbitrary choice among the concentration values of parabens indicated in D3 (Section 7, tables) which the skilled person would equally use with every expectation of success to solve the technical problem.

4. Conclusion

In our opinion the set of claims of the Main request as well as Auxiliary requests 1 and 2 do not fulfill the requirements of the European Patent Convention.

If the Appeal Board would for some reason decide not to maintain the decision of the Opposition Division revoking the opposed patent in its entirety, then oral proceeding are kindly requested.

Drafted on behalf of the Opponent:
BORENIUS & Co Oy Ab

Jonna Sahlin
European Patent Attorney (09231490)

Zentiva, a.s., D.M.

Strana: 001

VÝROBNÍ PŘÍKAZ K VÝROBNÍ ZAKÁZCE

Číslo výr. zakázky :1726938

Název mat...: **Zodac # gtt, volně /**

Číslo mat....: **400424**
Číslo šarže..: **020504**
Vel. šarže...: **425,700 KG**
PZÚP*
Zahájení.....: **18.05.2004**

*Profit centrum...:***3112170**
VOLN TISK PŘKL CHPS KDPŘ KPŠA MAPO
Ukončení.....: **18.05.2004**

VÝROBNÍ STUPEŇ	1	2	3 MJ
Norm.ztráta v %:	1,000	0,000	0,000 %
Teoretický výtěžek:	430,000	0,000	0,000 KG
Normovaný výtěžek:	425,700	0,000	0,000 KG
Skutečný výtěžek	425,7 kg		
% plnění	100 %		

Řádek / Popis materiálu	Čís. materiálu	Sklad	Normované přepoč. koef. [P/D] / Šarže	Množství / Tříd. klíč	MJ
0010	25915	SAM1		1	KS
filtr OPTICAP POLYGARD CR,1um,KR0101TC1					
0009	1669	0077		178,590	KG
ČIŠTĚNÁ VODA				MZ1	
0002	1243	SUR2		0,537	KG
METHYLPARABENUM				MZ1	
0003	1344	SUR2		0,060	KG
PROPYLPARABENUM				MZ1	
0004	1896	SUR2		99,445	KG
GLYCEROLUM pur.pharm 85 PC z cisterny				NAV31	
0005	1621	SUR2		139,223	KG
PROPYLENGLYCOLUM				NAV32	
0008	1007	SUR4		0,211	KG
ACID. ACETICUM				NAV33	
0007	1260	SUR4		3,978	KG
NATRII ACETAS CRYSTALLISATUS				NAV34	
0006	1904	SUR2		3,978	KG
SACCHARINUM NATRICUM				NAV35	

Vystavil :04392 — Kontroloval : — Kontroloval :
Dne :12.05.2004 — Dne : 10.5.2004 — Dne :

ntiva, a.s., D.M. Strana: 002

VÝROBNÍ PŘÍKAZ K VÝROBNÍ ZAKÁZCE

Číslo výr. zakázky :1726938

dek	Čís. materiálu	Sklad	Normované přepoč. koef. [P/D]	Množství	MJ
is materiálu			Šarže	Tříd. klíč	
001	1950	SUR4		3,978	KG
TRIZINE DIHYDROCHLORIDUM				NAV36	

stavil :04392 Kontroloval : Kontroloval :

e :12.05.2004 Dne : Dne :

D16A

Zentiva, a.s.

Material name: Zodac gtt
Material number: 400424
Batch number: 020504
Batch amount: 425,700 kilograms

Starting date: 18.05.2004 Finishing date: 18.05.2004

	1	2	3	UNIT
Loss standards:	1,000	0,000	0,000	%
Theoretical yield:	430,000	0,000	0,000	KG
Standard yield:	425,700	0,000	0,000	KG
Actual yield:	*425,7 kg*			
% yield	*100 %*			

Material		unit
OPTICAP POLYGARD CR, 1 um, KR0101TC1	1	KS
WATER	178,590	KG
METHYL PARABEN	0,537	KG
PROPYL PARABEN	0,060	KG
GLYCEROL	99,445	KG
PROPYLENEGLYCOL	139,223	KG
ACETIC ACID	0,211	KG
CRYST. SODIUM ACETATE	3,978	KG
SODIUM SACCHARINATE	3,978	KG
CETIRIZINE DIHYDROCHLORIDE	3,978	KG

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
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Friedrichstrasse 31
80801 München
ALLEMAGNE

Datum/Date
11.09.12

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.02**

Please find enclosed a copy

☐ of a letter of the patent proprietor dated

☑ of a letter of the opponent dated 05.09.12

☐

for your information.

The Registrar N. Maslin
Tel.: 089 / 2399 - 3321

Annex(es):

Registered letter

Europäisches Patentamt
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European Patent Office
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Appeal number: T0371/12-3.3.07

Order

Change of the composition of the Board

compare to order of 17.04.12

1.

Chairman: J. Riolo

technically qualified member: R. Hauss

technically qualified member:

legally qualified member: D. T. Keeling

legally qualified member:

2. The rapporteur shall be: R. Hauss

3. The additional rapporteur shall be:

4. Reasons:
Change in the business distribution scheme of the board for the current year.

5. Back to the Registry for further action.

Munich, 02.01.13

Chairman J. Riolo

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Datum/Date
21.02.13

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Change of responsibility of a Board of Appeal
Article 1(2) Business Distribution Scheme for the Technical Boards of Appeal

According to the amended business distribution scheme for the Technical Boards of Appeal for the year 2013 , this case has been transferred to Board 3.3.07 as from 02.01.13.

The new reference number is: **T0371/12-3.3.07**

Please quote the new reference number cited above in any further communications.

The Registrar I. Aperribay
Tel.: 089 / 2399 - 3371

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Datum/Date
21.02.13

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Change of responsibility of a Board of Appeal
Article 1(2) Business Distribution Scheme for the Technical Boards of Appeal

According to the amended business distribution scheme for the Technical Boards of Appeal for the year 2013 , this case has been transferred to Board 3.3.07 as from 02.01.13.

The new reference number is: **T0371/12-3.3.07**

Please quote the new reference number cited above in any further communications.

The Registrar I. Aperribay
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*1 European Patent Attorney
*2 European Trade Mark Attorney
*3 European Design Attorney

26 April 2013

Re: **Change of company name**

Dear Sir or Madame,

We have changed our name from BORENIUS & Co Oy Ab to Boco IP Oy Ab as of today 26 April 2013.

Please update your records accordingly. Our email addresses are now in the form @bocoip.com and our webpage is www.bocoip.com.

I understood that also the software relating to our smart cards will be updated, but that the cards themselves do not need to be renewed at this point.

Please do not hesitate to contact me if you have any questions.

Faithfully yours,
Boco IP Oy Ab

Jonna Sahlin
ID 09231490

Association 472 (Boco)
Deposit account 28150010

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Date
22-05-2013

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 1460 / 1768649
Applicant/Proprietor	
UCB FARCHIM S.A.	

Communication of amended entries in the Register of European Patents

It is confirmed that, according to the request dated 26.04.13

1. ☐ the name
   ☐ the address
   ☐ of the (co-)applicant / patentee,
   ☐ of the opponent

   as from , has/have been amended as follows:

2. ☐ the appointment of a representative
   ☐ the authorisation
   ☐ the withdrawal from representation
   ☒ the new firm of the representative

   has/have been registered as from 26.04.13 .

Enclosure(s):

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Client Data Registration
Tel.: +49 (0)89 2399 2780

isarpatent

PATENT- UND
RECHTSANWÄLTE
| PATENT ATTORNEYS
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CERTIFIED IP-LAWYERS

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Europäisches Patentamt
Erhardtstraße 27
80298 München

Our Ref.: P30048-EPOP SAN/lvo | June 25, 2013

Opposition against European Patent No. EP 1 768 649
Proprietor/Appellant: UCB FARCHIM S.A
Opponent/Respondent: Zentiva k.s.
Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Appeal No.: T0371/12-3.3.07

This is in reply to the Submission of the Opponent dated September 5, 2012:

I. REQUESTS

Our requests submitted on February 17, 2012 and April 23, 2012 are fully maintained. That is to say, it is requested to set aside the decision of the Opposition Division of December 22, 2011 and to maintain the European patent within the scope of the claims according to the main request or according to the first / second auxiliary request.

Further, it is requested not to admit document D16/D16A into the appeal proceedings.

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II. CLAIMS ACCORDING TO THE MAIN, 1ST AND 2ND AUXILIARY REQUEST

2.1 Article 54 EPC - Novelty

Opponent outlined in the submission of September 5, 2012 that claim 1 according to the main request is not novel in view of the alleged prior use of products ZODAC®GTT (oral drops) and ZODAC®SIR (syrup) based on documents D5, D6, D7 and D8.

In order to summarize, the marketing authorizations for the above products were granted on November 29, 2000 in Slovakia and on April 18, 2001 in the Czech Republic. The products were actually launched then on October 31, 2001 and September 30, 2002.

In order to support the alleged prior use, further documents D9 and D10 have been submitted during the opposition period. These documents should prove what kind of medicinal product was available to the public before the priority date of the opposed patent, i.e. July 14, 2004. However, as outlined earlier, there is no proof in D9 or D10 that the composition described therein indeed reflects the products launched on the market in Slovakia and the Czech Republic before July 14, 2004. That is to say, Chapters 9 and 10 clearly indicate that the publication date of the information submitted in D9 and D10 is later than July 14, 2004. The original text has been revised four times between October 2006 and October 2009 for both documents, D9 and D10. Furthermore, it can be derived from D9 and D10, see point 9, that there was a renewal of the marketing authorization in January 28, 2009.

Thus, it is not convincing that the summary of product characteristics of D9 and D10 identically reflects the characteristics of ZODAC®SIR and ZODAC®GTT as launched in 2001 and 2002.

The established case law of the boards gives a clear guideline whether information has been made available to the public by prior use or not. This definition is as follows:

(i) when did the prior use occur,
(ii) what was made available to the public through that use,
(iii) where, how and by whom was the information made public through that use.

As outlined above, it is at least doubtful, what was made available to the public through the use of the products named ZODAC®GTT and ZODAC®SIR.

The opponent has filed documents D16 and D16A on September 5, 2012 in order to remove all remaining doubts regarding the public prior use of products ZODAC®GTT and ZODAC®SIR. As it can be seen from the English translation of document D16 (D16A), a product named ZODAC®GTT has been produced in one batch having an actual yield of 425.7 kg on May 18, 2004. Allegedly, document D16/D16A supports the novelty destroying function of document D9, i.e. the summary of product characteristics of the medicinal product ZODAC®GTT.

However, by carefully reviewing D9 and D16 (and the batch of ZODAC®GTT described therein) it remains doubtful, whether both products have the same composition. Document D16/D16A indicates a precise composition of ZODAC®GTT drops:

WATER	178,590	KG
METHYL PARABEN	0,537	KG
PROPYL PARABEN	0,060	KG
GLYCEROL	99,445	KG
PROPYLENEGLYCOL	139,223	KG
ACETIC ACID	0,211	KG
CRYST. SODIUM ACETATE	3,978	KG
SODIUM SACCHARINATE	3,978	KG
CETIRIZINE DIHYDROCHLORIDE	3,978	KG

which, however, cannot be found in document D9. D9 only describes that 1 ml solution of the product contains 10 mg cetirizine dihydrochloride, 1.35 mg methylparaben, 0.15 mg propylparaben, glycerol 85%, propylene glycol, saccharin sodium dihydrate, sodium acetate trihydrate, acetic acid 99 percent (M/M) and purified water. Thus it is not clear whether D16/D16A reflects the composition described in D9 qualitatively or quantitatively.

Further, it is not clear whether D16/D16A indeed reflects the product described in document D9 since the publication date of document D9 is January 28, 2009. This is more than 4.5 years after the production date of batch 020504 according to document D16/D16A.

Finally, it should be noted that in case of an alleged public prior use, particular substantiation is required in the notice of opposition itself, i.e. within the time period for filing an opposition. Thus,

if an opponent wishes to rely upon prior use, the notice of opposition must indicate within the opposition period all the facts which make it possible to determine the date of prior use, what has been used and the circumstances relating to the prior use.

The case law mentioned by the opponent in this context, i.e. T406/86 and G1/92, does not change the fact that the alleged prior use has not been proven beyond all doubts, neither in the notice of opposition nor later.

T406/86 is not related to the problem of an alleged prior use at all.

G1/92 defined that the chemical composition of a product is state of the art when the product as such is available to the public and can be analyzed and reproduced by the skilled person, irrespective of whether or not particular reasons can be identified for analyzing the composition. However, this is not the question here, since it is still doubtful what has been made available to the public by prior use. Until today, it has not been shown convincingly by the opponent that the products ZODAC®GTT and ZODAC®SIR with the composition outlined in documents D9 and D10 were available to the public before the priority date of the opposed patent.

Furthermore, it should be noted that, as outlined above, an alleged prior use has a high standard of proof. Thus, stricter standards have been set by the boards of appeal regarding admissibility of late-filed evidence of public prior use.

Notably, document D16/D16A is derived from the opponent/respondent Zentiva k.s. itself. According to T17/91, an allegation of prior use based on the opponent's own activities filed two years after the expiry of the opposition period may constitute an abuse of the proceedings and a breach of the principle of good faith. In T17/91, the potential relevance of the document and the allegation of prior use was disregarded under Article 114(2) EPC. A similar case has been decided in T534/89.

Furthermore, T481/99 clearly outlined that late-filed facts, evidence and related arguments regarding prior use should only exceptionally be admitted into the proceedings and that submissions and/or documents relating to late allegation of prior use showing inconsistencies or contradictions should be disregarded pursuant to Article 114(2) EPC without further enquiries.

Thus, it is requested not to admit document D16/D16A into the present appeal proceedings.

Considering the above, the discussion of the margin of experimental error of a numerical range as led by the opponent/respondent seems to superfluous.

Therefore, the decision of the Opposition Division that the subject matter of claim 1 according to the main request is novel in view of the alleged prior use is correct. The same applies *mutatis mutandis* also to claim 1 according to the 1st and 2nd auxiliary request.

2.2 Article 56 EPC – Inventive Step

Combination of D1/D3

Regarding the closest prior art document, we agree that D1 is the most relevant piece of prior art. D1 discloses a liquid of an ophthalmic composition comprising cetirizine hydrochloride and methylparaben / propylparaben in an overall amount of 3 mg/ml. The difference between claim 1 of the opposed patent as granted and D1, thus, resides in the amount of parabens used as preservative which is restricted, according to claim 1 of the main request, to an amount of more than 0 and less than 1.5 mg/ml of parahydroxybenzoate esters.

Regarding the alleged obviousness of the claimed invention based on D1 in view of D3, we fully refer to our substantiation of the appeal as submitted on April 23, 2012.

Sufficient antimicrobial efficacy – further additives

In the following, the arguments provided by the opponent regarding the anti-microbial efficacy will be addressed.

The key point in the discussion led so far was the self-preserving effect of the active pharmaceutical ingredient, defined in claim 1 according to the main request as *cetirizine, levocetirizine and efletirizine*. The opponent outlined that this self-preserving effect and the experimental data submitted by the appellant along with the substantiation of the appeal is not

convincing. In particular, it was pointed out that none of the present examples actually would support the claimed improved anti-microbial efficacy of parabens alone combined with the active ingredients cetirizine, levocetirizine and efletirizine. Rather, it was stated that the desired effect might actually originate from the use of other ingredients of the liquid pharmaceutical composition used in the examples, notably of sodium acetate (and others).

a) General Remarks

The opponent tried to create the impression that the experimental data submitted in the opposed patent and the substantiation of the notice of appeal are meaningless since the experimental results are different for the microorganisms used, i.e. *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*. For example, the opponent outlined regarding comparative example 2 submitted along with the substantiation of the appeal that "for *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus* the criteria were fulfilled... whereas this is not the case for *Candida albicans* and *Aspergillus niger*".

It should be noted that the test requirements of the European Pharmacopoeia have to be considered (and fulfilled) in their entirety. Test results on one single microorganism or even a sub-group of the microorganisms identified therein cannot serve as a basis for "fulfilling" or "not-fulfilling" the requirements of the European Pharmacopoeia. It is clear from the European Pharmacopoeia that the efficacy has to be demonstrated for all of the microorganisms indicated, i.e. for the complete set of microorganisms defined in chapter 5.1.3 of the European Pharmacopoeia 5.0 (see Annex II as submitted along with the substantiation of the appeal). In chapter "Criteria of Acceptance", there are clear limits which have to be fulfilled for both types of microorganisms, i.e. bacteria and fungi. According to table 5.1.3.-3 – oral preparations – the log reduction for bacteria at 14 days must be 3, for fungi 1, whereas at 28 days, no increase (n.i.) is allowed to occur.

Therefore, the efficacy of antimicrobial preservation according to 5.1.3 of the European Pharmacopoeia can be only "fulfilled" or "not fulfilled" *in toto*. Thus, the differentiation into different subgroups of microorganisms as opponent did is meaningless.

Furthermore, in comparing the different test results which are at hand, it should be borne in mind that there is a certain margin of experimental error in counting microorganisms. Counting microorganisms is not similar to chemical testing and it is not possible to obtain the same precision here as well. Thus, it does not make sense to consider only single types (or subgroups) of microorganisms since the overall experimental results, in light of the regulations of the European Pharmacopoeia, are decisive for the question whether there is a sufficient anti-microbial activity or not.

b) Comparative Example 1

Comparative example 1 provides a microbial efficacy test on an oral solution comprising sodium acetate and acetic acid (as used in the composition of example 1 of the opposed patent). The test results depicted in table 2 clearly indicate that the requirements of the European Pharmacopoeia are not met for *Candida albicans* and *Aspergillus niger* since on day 14, the number of microorganisms remained stable and a reduction by 1 log did not occur. Furthermore, on day 28 there is an increase in the number of microorganisms, therefore violating the requirements of table 5.1.3.-3. of European Pharmacopoeia 5.0.

Therefore, it is self-explanatory that sodium acetate and acetic acid do not have any anti-microbial effectiveness for *Candida albicans* and *Aspergillus niger* and, therefore, both substances could not have contributed to the positive test results shown in tables 2 and 3 of the opposed patent. Rather, comparative example 1 shows that the alleged anti-microbial efficacy of sodium acetate derived from document D14 does not influence the microbial count of *Candida albicans* and *Aspergillus niger* at all. Further, it should be noted that the rate of reducing *Escherichia coli* and *Staphylococcus aureus* is much higher in tables 2 and 3 according to the opposed patent compared to the results of comparative example 1. As such, the microbial content at day 7 for these two types of bacteria was < 100 according to tables 2 and 3 of the opposed patent, whereas comparative example 1 showed counts of > 10^4 and 1.8 x 10^4 at day 7 (i.e. a more than 100 times higher microbial count). Thus, sodium acetate and acetic acid do not contribute to the anti-microbial activity of cetirizine hydrochloride in example 1 of the opposed patent.

In this connection, it should be noted that we fully agree with the opponent that the test results contained in table 2 of the opposed patent comply with the requirements of the European

Pharmacopoeia. A 3 log reduction for all bacteria can be seen from table 2, furthermore, the log reduction for fungi is remarkable as well (and much higher than a 1 log reduction). For *Aspergillus niger*, an almost 3 log reduction can be seen on day 14. This is remarkable and much more than required by the European Pharmacopoeia.

As a summary, sodium acetate and acetic acid are not responsible in the composition of example 1 of the opposed patent for fulfilling the criteria of the European Pharmacopoeia 5.0. The absence of cetirizine hydrochloride in the composition of comparative example 1 leads to a lack of compliance with the regulations of the European Pharmacopoeia.

c) Comparative Example 2

Comparative example 2, table 3 discloses the same composition as example 4 of the opposed patent, but without the API levocetirizine hydrochloride.

The opponent compared tables 3 and 4 of Annex I regarding their results, however, we would like to note that table 3 describes the composition of the oral solution and table 4 the microbial content in inoculated samples of said oral solution (therefore, a comparison does not seem to be useful). Rather, a comparison between table 4 of comparative example 2 and table 5 of the opposed patent should be done. From table 4, it becomes clear that, again, for *Candida albicans* and *Aspergillus niger* the requirements of the European Pharmacopoeia are not fulfilled. Notably, for *Aspergillus niger* there was an increase of from 3.9×10^5 (inoculum) and 2.0×10^5 (day 0) to 6.4×10^5 at day 14. It is obvious that neither acetic acid, sodium acetate nor glycerin (or sodium saccharinate) contribute to an anti-microbial efficacy against *Candida albicans* and *Aspergillus niger* in the oral solution. Therefore, it can be clearly derived from a comparison of table 4 of Annex I and table 5 of the opposed patent that the addition of levocetirizine in the indicated amounts allows the overall composition to fulfill the requirements of the European Pharmacopoeia which are not met in absence of levocetirizine hydrochloride.

Basically, the opponent takes the view that the results in table 4 of Annex I do not differ "that much" from the results of the opposed patent, table 5. However, the count of *Candida albicans* in table 5 is 1 log (= 10 times) lower than in table 4 of comparative example 2. It is surprising that the opponent indicated that this is not "that much". Furthermore, in reviewing the contents of table

4 of Annex I and table 5 of the opposed patent in detail, it becomes clear that the reduction of microorganisms also for bacteria is much faster in table 5 than in table 4 of Annex I. For *Escherichia coli*, the microbial content on day 7 is 500, for *Staphylococcus aureus* 300. This is again supporting the fact that levocetirizine has an anti-microbial activity by itself.

In light of this, the arguments submitted by opponent regarding comparative example 2 seem to be moot.

d) Example 3 of Annex I

The composition of example 3 of annex I corresponds to the levocetirizine composition of table 4 of the opposed patent but additionally adds p-hydroxybenzoate esters in a total amount of 0.1 mg/ml.

In this connection, the opponent stated that the recommended efficacy criteria have not been achieved according to table 6 of Annex I since the criteria for log reduction at 14 days required by the European Pharmacopeia is not met for *Candida albicans* and *Aspergillus niger*. However, table 6 clearly indicates that the reduction is by 1 log, namely from 10^5 to 10^4.

The opponent further stated regarding tables 6 and 7 of Annex I that it can be "clearly seen that the addition of propylene glycol enhances significantly the preservative effect of parabens for *Candida albicans* and *Aspergillus niger*". However, this statement is incorrect. At first, there is no reason to assume that the addition of propylene glycol enhances the preservative effect of parabens. If any, propylene glycol has its own effects, but it is not plausible at all that it enhances the preservative effect of any other substance. Further, although table 6 of Annex I reflects the results for an oral solution not containing propylene glycol whereas table 7 is directed to the results for drops containing propylene glycol, this is not a scientific evidence that propylene glycol itself has an anti-microbial activity in the amounts used in this example.

Rather, it should be noted that the concentration of levocetirizine HCl in the drops and in the oral solution is completely different, more precisely differs by a factor of 1:10. Therefore, the better anti-microbial efficacy in table 7 is clearly due to the higher amount of levocetirizine hydrochloride

and not to propylene glycol. Thus, a comparison of tables 6 and 7 rather supports the anti-microbial efficacy of levocetirizine hydrochloride.

Therefore, as a summary, the antimicrobial activity of the active pharmaceutical ingredients according to claim 1 of the main request, 1st and 2nd auxiliary request has been well evidenced by the present experimental data.

As such, the subject-matter presently claimed is based on an unexpected and surprising effect which cannot be derived from the prior art cited. Therefore, all presently pending claims fulfill the requirements of Art. 56 EPC.

Respectfully submitted,

Wolfgang Sandmann
European Patent Attorney

Europäisches Patentamt
European Patent Office
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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	05758582.0
Applicant's or representative's reference	P30048-EPOP

	Description of document	Original file name	Assigned file name
1	Letter relating to Appeal procedure	P30048-EPOP.pdf	APPEAL-LETT-1.pdf

Signatures

Place:	**Munich**
Date:	**25 June 2013**
Signed by:	**DE, Isarpatent GbR, W. Sandmann 12098**
Capacity:	**(Representative)**

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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	2188634
Application number	EP05758582.0
Date of receipt	25 June 2013
Receiving Office	European Patent Office, The Hague
Your reference	P30048-EPOP
Applicant	All applicants as on file
Documents submitted	package-data.xml epf1038.pdf (1 p.) ep-sfd-request.xml APPEAL-LETT-1.pdf\P30048-EPOP.pdf (10 p.)
Submitted by	CN=W. Sandmann 12098,O=Isarpatent GbR,C=DE
Method of submission	Online
Date and time receipt generated	25 June 2013, 15:39 (CEST)
Message Digest	97:D1:D9:82:67:21:C6:F0:8B:4C:FF:D5:26:BD:32:39:86:37:31:DF

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Datum/Date
01.07.13

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Please find enclosed a copy

☑ of a letter of the patent proprietor dated 25.06.13

☐ of a letter of the opponent dated

☐

for your information.

The Registrar I. Aperribay
Tel.: 089 / 2399 - 3371

Annex(es):

Registered letter

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Appeal number: T0371/12-3.3.07

Order

Change of the composition of the Board

compare to order of 02.01.13

1.

Chairman: J. Riolo

technically qualified member: A. Usuelli

technically qualified member: _____

legally qualified member: D. T. Keeling

legally qualified member: _____

2. The rapporteur shall be: A. Usuelli

3. The additional rapporteur shall be: _____

4. Reasons:
Change in the business distribution scheme of the board for the current year.

5. Back to the Registry for further action.

Munich, 04.11.13

Chairman J. Riolo

Sonera Sähköpostifaksi

To: FAX EPO Munich
Fax: *498923994465

From:Boco IP Oy Ab
Date: 15.1.14

Subject:Request to transfer files to association/LYP

Dear Sirs,

Please find enclosed our request regarding transfer of our files to association.

Yours sincerely,

On behalf of Ms. Jonna Sahlin

Laura Ylä-Pietilä
Patent Assistant
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*1 European Patent Attorney
*2 European Trade Mark Attorney
*3 European Design Attorney

15 January 2014

Re.: **REQUEST TO TRANSFER FILES TO ASSOCIATION**

Dear Sirs,

We hereby respectfully request to transfer all active files of the individual representatives of the Association No. 472 to the Association in question (No. 472, Boco).

If you have any questions, please do not hesitate to contact us (jonna.sahlin@bocoip.com).

Yours faithfully,

Boco IP Oy Ab

Jonna Sahlin

European Patent Attorney (Reg. No. 09231490)

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Date: 17-02-2014

Reference	Application No./Patent No.
B0199PI-EP OPPO 01	05758582.0 - 1460 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

Communication of amended entries in the Register of European Patents

It is confirmed that, according to the request dated 15.01.14

1. ☐ the name
   ☐ the address
   ☐ of the (co-)applicant / patentee,
   ☐ of the opponent

   as from , has/have been amended as follows:

2. ☐ the appointment of a representative
   ☐ the authorisation
   ☐ the withdrawal from representation
   ☒ the association No 472

   has/have been registered as from 15.01.14.

Enclosure(s):

Receiving Section/For the Examining Division/For the Opposition Division/For the Legal Division

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Date: 17-02-2014

Reference	Application No./Patent No.
P30048-EPOP WB	05758582.0 - 1460 / 1768649
Applicant/Proprietor: UCB FARCHIM S.A.	

BRIEF COMMUNICATION

Subject:
- ☐ Your letter of
- ☐ Our telephone conversation of
- ☐ Communication of
- ☐

Enclosure(s):
- ☐ Letter from the proprietor of the patent of
- ☐ Letter from the opponent of
- ☒ Copy (copies) of Form 2575

Communication:

☐ A letter from the opponent /proprietor was received on ..... . The documents specified as patent documents in this letter are available via the European Patent Register at **www.epo.org/register.** Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2009, 434).

☐

For the Opposition Division

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   ☐ of the opponent

   as from , has/have been amended as follows:

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   ☐ the authorisation
   ☐ the withdrawal from representation
   ☒ the association No 472

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2399-4465

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Dipl.-Ing. Oliver Hassa [1,2]
Dipl.-Phys. Ralf Peckmann [1,3]
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Dipl.-Phys. Dr. Christoph Hecht [1,2]
B. Eng. (Hons) Philip Gehrig [1,2,4,6]
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Europäisches Patentamt München
22. Mai 2015
Dir. 5.2.3

Ihr Zeichen: | Unser Zeichen: A0044 rsw/zzsa_vat | 20. Mai 2015

Zusammenschluss Nr. 73, Laufendes Konto Nr. 28000484
Korrektur des Namens Zusammenschluss
Korrektur allgemeine Vertreteradresse
Aktualisierung der Mitglieder des Zusammenschlusses

1. Aktualisierung Anschrift Zusammenschluss

Hiermit wird höflich darum gebeten, amtsseitig den Namen bzw. die Anschrift unseres Zusammenschlusses Nr. 73 wie folgt zu ändern:

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C - 22.05.2015
SM
OJ 07/2015

2. Aktualisierung lfd. Konto

Es wird die entsprechende Aktualisierung für unser laufendes Konto Nr. 28000484 wie unter 1. beantragt. ØCSC

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*AMTSGERICHT MÜNCHEN
PARTNERSCHAFTSREG. 1262

E.Behe/Colv.

DE

3. Aktualisierung Vertreteradresse / Aktualisierung im Register

Es wird die entsprechende Aktualisierung wie unter 1. für unsere Vertreteradresse beim EPA beantragt, mit der wir in allen von unserer Sozietät vertretenen Akten im Register als Vertreter geführt werden. Die entsprechenden Einträge im Register bitten wir ebenso zu aktualisieren.

Es wird höflich darum gebeten, dass amtsseitig nur noch diese eine Adresse verwendet wird.

4. Aktualisierung Mitglieder Zusammenschluss / Verfügungsberechtigung laufendes Konto

Hiermit wird eine aktualisierte Übersicht über alle beim EPA zugelassenen Vertreter übermittelt, die in unserem Zusammenschluss Nr. 73 zu führen sind. Der identische Personenkreis erhält gleichzeitig Verfügungsbefugnis über unser laufendes Konto Nr. 28000484. Es wird höflich darum gebeten, dies amtsseitig zu vermerken.

BEHNISCH, Dr. Werner
BARTH, Dr. Stephan Manuel
CHARLES, Glyndwr
HASSA, Oliver Michael
PECKMANN, Ralf
SANDMANN, Wolfgang
HECHT, Dr. Christoph Joachim
GEHRIG, Philip Walter
KOLB, Dr. Pamela
SCHAUPP, Dr. Christoph Simon
TATZEL, Dr. Stephan

Es wird gleichzeitig darum gebeten, die unter 1. aufgeführte Anschrift sowie Kontaktdaten auch bei den jeweiligen zugelassenen Vertretern in der Liste der Vertreter zu vermerken und entsprechend im Amtsblatt zu veröffentlichen. ø List

Für die Sozietät

Dr. Werner Behnisch
Patentanwalt

Europäisches Patentamt
European Patent Office
Office européen des brevets

05758582.0 - 1460 / 1768649 03.06.15

Client Database System (CDS) - clean up.

Application Nr.: 05758582.0

Following clean up action in CDS the entries concerning the **Representative for the applicant (association)** have been amended and are now as follows:

Isarpatent
Patentanwälte Behnisch Barth Charles
Hassa Peckmann & Partner mbB
Friedrichstraße 31
80801 München
DE

Where appropriate, the European Patent Register at www.epo.org/register will be updated to show the amended details.

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05758582.0 - 1460 / 1768649 03.06.15

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Application Nr.: 05758582.0

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Fax +49 (0)89 2399-4465

Appeal number: **T0371/12-3.3.07**

Order

Oral proceedings are to be held

on 11.03.16

at 09:00 hours

Room N° 0132

Munich 05.10.15

The Chairman J. Riolo

Europäisches Patentamt
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Boco IP Oy Ab
Itämerenkatu 5
00180 Helsinki
FINLANDE

Date
08.10.15

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582 / 1768649

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
UCB FARCHIM S.A.

Appeal number: **T0371/12-3.3.07**

Summons to oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to the oral proceedings concerning the above appeal.
The proceedings are scheduled to take place

on 11.03.16 at 09:00 hrs in Room 0132

Bob-van-Benthem-Platz 1, 80469 Munich (DE)

The proceedings will be public.

Room 115 is available as a waiting-room.

You are requested to attend outside the appointed room **10 minutes** before the hearing.

Registered letter with advice of delivery

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Appeal number: **T0371/12-3.3.07**

You are reminded that

- if a party who has been duly summoned to oral proceedings does not appear, the proceedings may continue without that party (Rule 115(2) EPC).
- oral proceedings will only be postponed at the request of a party for serious reasons (see Notice in Special edition No. 3 OJ EPO 2007, 115).
- as regards filing authorisations for representatives or company employees, see Decision of the President of the EPO dated 12.7.2007 on the filing of authorisations in Special edition No. 3 OJ EPO 2007, 128.
- concerning the language of the proceedings, attention is drawn to Rule 4 EPC. Notice given pursuant to Rule 4(1) EPC before the first instance is not valid in proceedings before the Boards of Appeal.
- According to Rule 103(2) EPC it is possible to obtain a 50% reimbursement of the appeal fee if the appeal is withdrawn under certain circumstances (OJ EPO 2014, A3).

Composition of the Board

Chairman: J. Riolo

Member: A. Usuelli

Member: D. T. Keeling

For all urgent communications in connection with the oral proceedings please use <u>only</u> fax No. + 49 (0) 89 2399 3014.

If you are planning not to attend the oral proceedings or if you are aware of any matter that could have a bearing on the appointment of interpreters, you are requested to inform the Board of this, preferably in writing, at the earliest possible opportunity.

The Registrar S. Fabiani

Tel.: 089 / 2399 - 3371

Annex(es): ☑ Confirmation of receipt Form 3936

☐ Communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal

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Patentanwälte Behnisch Barth Charles
Hassa Peckmann & Partner mbB
Friedrichstrasse 31
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ALLEMAGNE

Date
08.10.15

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR	05758582 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

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Appeal number: **T0371/12-3.3.07**

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Member: D. T. Keeling

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The Registrar S. Fabiani
Tel.: 089 / 2399 - 3371

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Tracking Information

EP/ECT/PCT No.:	**05758582 .**
Name:	Isarpatent
Adress:	Patentanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31
City:	80801 München
Country:	DE
Formtype:	T0371/12-3.3.07 F3011
Send Date:	Thursday, October 08, 2015

Delivery Information:

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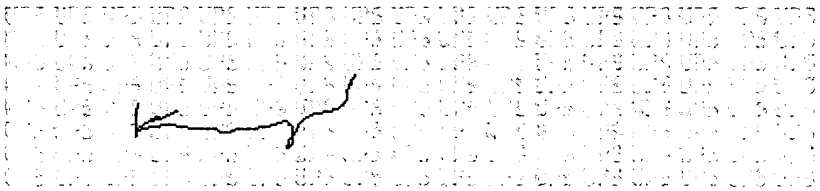
Signature:	

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Boards of Appeal

The Registry

Name: S. Fabiani

Tel.: 089 / 2399 - 3371

Date: 08.10.15

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR	05758582 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: T0371/12-3.3.07

EPA/EPO/OEB Formblatt/Form/Formulaire: 3011

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl. EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately:**

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

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- **per Fax / by fax / par téléfax (+49 (0) 89 2399-4465 or +31 (0)70 340-3016)**
- oder per Post / or by post / ou par courrier

Empfangen am / Received on / Reçu le:

München, 12.10.2015

Unterschrift / Signature:

Isarpatent
Patent- und Rechtsanwälte
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Tel. +49 89 381610-0, Fax +49 89 3

Empfangsberechtigter/authorised recipient/
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Fax: *498923994465

From:Boco IP Oy Ab
Date: 23.10.2015

Subject:Our ref: B0199PI-EP , application no 05758582 / mp

Dear Sirs,

Enclosed please find the signed confirmation of receipt form 3936.

Yours faithfully,

Merja Pynnönen
IP Specialist,
administration and formalities
Boco IP Oy Ab
Direct: +358 9 6866 8474
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Boards of Appeal

The Registry

Name: S. Fabiani
Tel.: 089 / 2399 - 3371

Date: 08.10.15

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: T0371/12-3.3.07

EPA/EPO/OEB Formblatt/Form/Formulaire: 3011

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

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Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
- **per Fax / by fax / par téléfax (+49 (0) 89 2399-4465 or +31 (0)70 340-3016)**
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23 October 2015

Unterschrift / Signature:

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Datum / Date
10.11.2015

Zeichen/Reference/Référence		Anmeldung Nr. / Application No. / Demande n°. // Patent Nr. / Patent No. / Brevet n°.
B0199PI-EP	OPPO 01	05758582.0 // 1768649
Anmelder / Applicant / Demandeur // Patentinhaber / Proprietor / Titulaire		
UCB FARCHIM S.A.		

Appeal number: **T0371/12-3.3.07**

Communication of the Board of Appeal

The Rapporteur A. Usuelli

The Registrar S. Fabiani

Tel.: 089 / 2399 - 3371

Registered letter

This document: 12 page(s) including this page

Annex(es):

Communication text

I. This communication, which is sent pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA; OJ EPO 2007, 536), serves to prepare the oral proceedings and conveys the Board's provisional opinion, which is thus not binding as regards the final decision. The communication is not meant to represent

an exhaustive study of all the points to be dealt with at the oral proceedings. Its purpose is rather to make known the concerns which at present the Board has in relation to some of the arguments or requests presented.

Original grounds of opposition

II. European Patent 1 768 649 was opposed under Article 100 (a, EPC on the grounds that its subject-matter lacked novelty and inventive step.

Decision under appeal

III. The appeal of the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on the patent as granted as main request and on two auxiliary requests filed on 19 October 2010 (auxiliary request 1) and 29 September 2011 (auxiliary request 2).

According to the decision under appeal:

a) The late filed document D14 (Abstract of Am. J. Hosp. Pharm. 1979, 36(12), 1672-5) was to be admitted into the proceedings in that it was *prima facie* relevant.

b) Documents D5 (Marketing authorization for Zodac GTT in the Slovak Republic), D6 (Marketing authorization for Zodac SIR in the Slovak Republic), D7 (Marketing authorization for Zodac GTT in the Czech Republic), D8 (Marketing authorization for Zodac SIR in the Czech Republic) and D11 (Thomas Reuter Newport Premium; launched Drug Fors Detail) demonstrated that the products Zodac GTT and Zodac SIR were available on the market before the priority date of the patent.

However, none of these documents disclosed the concentration of parabens (i.e. methylparaben and propylparaben) in the products. This information could not be taken from D9 (Zodac GTT, Summary of product Characteristics, date of last revision 21 October 2009) or D10 (Zodac SIR, Summary of product Characteristics, date of last revision 21 October 2009) since it was not sufficiently proven that the products available on the market had the same concentration of parabens disclosed in these documents. Hence, the public availability of the products Zodac GTT and Zodac SIR was not prejudicial to the novelty of the main request.

c) Document D1 (EP 605203) was the closest prior art for the assessment of inventive step. This document disclosed in example 5 a liquid ophthalmic composition comprising *inter alia* cetirizine hydrochloride and 3 mg/ml of a mixture of parabens. The composition defined in claim 1 of the patent in suit differed from the composition of example 5 of D1 in the lower concentration of of parabens, i.e. more than 0 and less than 1.5 mg/ml.

The patent did not contain any data supporting the alleged effect of reducing the risk of allergic reaction. Furthermore, the amount of parabens in the compositions tested was always at least 0.15 mg/ml. Thus, it was not shown that the problem of providing further compositions having the recommended efficacy of antimicrobial concentration, was actually solved over the whole scope of the claim. Hence, the technical problem was to be defined as the provision of further liquid "compositions of cetirizine, levocetirizin or efletirizine comprising parabens showing (some degree of) antimicrobial effectiveness".

Document D3 (Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), 340-342 and pages 450-453) disclosed the standard concentrations of methylparaben and propylparaben when used in the antimicrobial preservation of ophthalmic, nasal and oral solutions. The ranges of concentrations disclosed in this document overlapped with the range recited in claim 1 of the patent in suit. The skilled person faced with the technical problem would have modified the amount of parabens of the composition of D1 in the light of the teaching of D3 thereby obtaining compositions falling in claim 1 of the patent in suit. Hence, the main request did not comply with the requirements of Article 56 EPC.

d) The limitations introduced in the auxiliary requests did not change the assessment of inventive step. Thus, auxiliary requests 1 and 2 were not inventive either.

Parties and requests

IV. Appellant UCB Farchim SA (patent proprietor) requests that the decision under appeal be set aside and the patent be maintained according to the sets of claims filed on 23 April 2012 as main request and auxiliary requests 1 and 2, these requests being identical to the requests forming the basis of the appealed decision. The appellant also requests the Board not to admit documents D16 and D16a into the appeal proceedings.

V. Respondent Zentiva k.s. (opponent) requests that the appeal dismiss be dismissed.

New items of evidence

VI. With the statement setting out the grounds of appeal the appellant submitted the following pieces of evidence:

D17: Supplementary examples
D18: European Pharmacopoeia 5.0 - Efficacy of antimicrobial preservation

(*numbering attributed by the Board*)

With the reply to the grounds of appeal the respondent submitted the following documents:

D16: Batch record for batch 2 May 2004 of Zodac GTT dated 12 May 2004
D16A: English translation of D16

The following points inter alia appear to need consideration at the oral proceedings:

1. *Admissibility of the new items of evidence*

The question may arise whether the additional evidence filed on appeal need be admitted into the proceedings. Attention is drawn to the Case Law of the Boards of Appeal of the EPO (7th edition 2013, IV.C.1) and to Articles 12 and 13 of the Rules of Procedure of the Boards of Appeal.

Main request

2. Novelty

2.1 The Board tends to concur with the conclusions reached by the opposition division in relation to the alleged public prior use (see point 3 of the decision). In particular, the evidence submitted during the first instance proceedings does not appear to prove that the

products Zodac GTT and Zodac SIR, which were available on the market before the priority date of the patent (i.e. 14 July 2004), had the same concentration of parabens disclosed in documents D9 and D10 which bear as a "date of revision of the text" the 21 October 2009.

2.2 The relevance of documents D16/D16A in relation to the above issue will be considered if necessary during the oral proceedings, after discussion of their admissibility.

2.3 As to the remarks made by the respondent in relation to possibility of analysing the products on the market and the reference to the decision of the Enlarged Board of Appeal G1/92, the Board observes that the precise composition of these products is not yet known. Thus it is unclear which amount of parabens would have been found if the commercial products had been analysed. Thus, at present this argument appears to be of no relevance.

3. Inventive step

3.1 Inventive step will be considered on the basis of the problem-solution approach. This will involve assessing (a) which document is the closest prior art, (b) what is the objective technical problem vis-à-vis that document and (c) whether the claimed subject-matter is obvious with regard to the closest prior-art document, possibly in combination with the other documents on file.

Closest prior art

3.2 The parties agree that document D1 represents the closest prior art. It is also not disputed that the composition of the patent differs from the composition

disclosed in example 5 of D1 in the amount of parabens which is "more than 0 and less than 1.5 mg/ml", whereas in the composition of D1 the parabens concentration is 3 mg/ml.

The Board sees no reason to deviate from the approach followed by the parties.

Technical problem

3.3 The invention addresses the problem of providing pharmaceutical compositions containing as active ingredient a substance selected from cetirizine, levocetirzine and efletirizine and having a reduced amount of preservatives, in particular parabens (see [0007] to [0010]). It is explained in paragraph [0030] of the patent, that reducing the amount of preservatives leads to a reduction of the risk of allergic reactions in sensitive patients. At the same time the composition maintains its capacity to resist microbial contamination (see [0009]). The possibility of reducing the amount of preservatives is based on the recognition that the active agents themselves possess a preservative effect.

3.4 In its decision the opposition division considered that in the absence of any data supporting the alleged reduction of allergic reactions, this effect was to be disregarded in the assessment of inventive step.

The Board notes that according to D3, methylparaben and propylparaben may be irritant to the skin, eye and mucous membranes. These substances are considered unsuitable for certain types of formulations in view of their irritant potential. It is furthermore stated that hypersensitivity reactions to parabens, appearing as contact dermatitis, have been reported (see sections

"Safety" and "Handling precautions" on pages 342 and 452).

In the light of this general knowledge as to the potential side-effects associated to the use of parabens, the Board considers it credible, even in the absence of any experimental evidence, that the compositions of the patent in suit will cause fewer allergic reactions than the composition of example 5 of D1 because they contain a reduced amount of parabens.

3.5 As to the antimicrobial properties of the compositions the following is observed.

Tables 2, 3, 5 and 6 of examples 1 and 2 show the antimicrobial properties of cetirizine and levocetirizine compositions which do not contain parabens. The objective of the experiments described in these examples is to demonstrate that the active ingredients have a preservative effect. As observed by the respondent and by the opposition division, the formulations of examples 1 and 2 contain, however, other substances such as sodium acetate that may have an antimicrobial effect. It is therefore unclear whether the antimicrobial properties of the compositions of examples 1 and 2 are to be attributed to the active ingredient or to other substances and in particular to sodium acetate.

3.6 In this context the Board observes that document D14 describes the inhibitory effect of sodium acetate on microorganism growth in protein hydrolysate solutions. It is affirmed that this substance inhibits growth of S aureus and E coli whilst it is not effective against C albicans.

Tables 2, 3, 5 and 6 show the antimicrobial preservative effect of the compositions of examples 1

and 2 against various bacteria and yeasts, including C albicans. Since sodium acetate does not inhibit the growth of C albicans (see above), in the Board's opinion the experiments of the patent suggest that the active ingredients possess some antimicrobial properties.

3.7 Given that the active ingredients of the claimed composition appear to have some antimicrobial properties, it appears credible that compositions having very low amounts of parabens as claimed in claim 1 of the patent are resisting to some extent microbial contamination.

3.8 It remains however questionable in the Board's opinion, whether the composition of the patent in suit fulfils the requirements of the European Pharmacopoeia as to the efficacy of antimicrobial preservation.

The compositions of examples 1 and 2 of the patent and of example 3 of D17, which fulfil these requirements, contain sodium acetate. Although this substance is not effective against some bacteria (see above), it appears that it may contribute to the antimicrobial preservation of the compositions in which it is included. Thus, it is not clear whether compositions containing as preservative agents only small amounts of parabens would meet the criteria of acceptance of the European Pharmacopoeia.

3.9 The above issues will be further considered at the oral proceedings in the context of defining the technical problem. The Board is of the preliminary opinion that the technical problem formulated in the appealed decision (point 4.1.5) should be modified by the indication that the compositions present a reduced risk of allergic reaction (e.g. providing liquid pharmaceutical compositions comprising cetirizine,

levocetirizine or efletirizine as active ingredient and parabens as preservative agents, showing some degree of antimicrobial effectiveness and presenting a reduced risk of allergic reaction).

Obviousness

3.10 Document D3 describes the use of methyl- and propylparaben as antimicrobial preservative agents in cosmetic and pharmaceutical formulations. As discussed above, document D3 also indicates that parabens may be irritant and may cause hypersensitivity reactions.

The decisive issue in relation to the obviousness of the invention is whether the skilled person trying to improve the safety profile of the composition of D1 and at the same time concerned with the problem of maintaining the antimicrobial properties of the composition, would reduce the concentration of parabens down to the levels recited in claim 1.

3.11 As noted by the opposition division, D3 indicates that methylparaben is normally used in ophthalmic preparations and in oral solutions in an amount ranging from 0.15 to 2 mg/ml (page 340, section 7). The amount of propylparaben used for the same preparations is even lower (page 450, section 7). These quantities are partially within the range recited in claim 1. It appears that it would also be possible to combine methyl- and propylparaben in amounts within the limits disclosed for each of these substances in D3 whilst still respecting the maximum amount allowed by claim 1 (i.e. 1.5 mg/ml).

3.12 Thus, D3 indicates that parabens can be used in concentrations which are well below the concentration in which these substances are present in the composition of D1 (i.e. 3 mg/ml) and within the range

of claim 1 of the patent in suit. In the Board opinion's, the skilled person concerned with the issue of reducing the risk of allergic reaction would prepare compositions having the low amounts of parabens suggested in D3 and verify whether these compositions still maintain an acceptable capacity to resist microbial contamination.

The above issues will be further considered during the oral proceedings.

Auxiliary requests

4. Article 123(3) EPC

The wording of claim 1 of both requests does not exclude compositions comprising, in addition to methyl- and propylparaben, also other parabens (e.g. ethylparaben) in any amount, since the range 0.01 to 1.125 refers only to methyl- and propylparaben.

Claim 1 as granted included as limiting feature the requirement that the total amount of parabens was below 1.5 mg/ml. Thus, auxiliary requests 1 and 2 appear to cover also compositions which were not included in the granted patent (e.g. compositions comprising 1.6 mg/ml of ethylparaben).

5. The requirements of novelty and inventive step of the auxiliary requests will be assessed along the same general lines discussed in respect to the main request.

Final remarks

6. Other relevant issues may also be addressed, if necessary.

7. Should the appellant in reaction to this communication wish to file further submissions, attention is drawn to Article 13 (1) and (3) RPBA. The admissibility of any such amendment would have to be considered at the oral proceedings.

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Boards of Appeal
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Zeichen/Reference/Référence	Anmeldung Nr. / Application No. / Demande n°. // Patent Nr. / Patent No. / Brevet n°.
P30048-EPOP WB APPR	05758582.0 // 1768649
Anmelder / Applicant / Demandeur // Patentinhaber / Proprietor / Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Communication of the Board of Appeal

The Rapporteur A. Usuelli

The Registrar S. Fabiani

Tel.: 089 / 2399 - 3371

Registered letter

This document: 12 page(s) including this page

Annex(es):

Communication text

I. This communication, which is sent pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA; OJ EPO 2007, 536), serves to prepare the oral proceedings and conveys the Board's provisional opinion, which is thus not binding as regards the final decision. The communication is not meant to represent

an exhaustive study of all the points to be dealt with at the oral proceedings. Its purpose is rather to make known the concerns which at present the Board has in relation to some of the arguments or requests presented.

Original grounds of opposition

II. European Patent 1 768 649 was opposed under Article 100 (a, EPC on the grounds that its subject-matter lacked novelty and inventive step.

Decision under appeal

III. The appeal of the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on the patent as granted as main request and on two auxiliary requests filed on 19 October 2010 (auxiliary request 1) and 29 September 2011 (auxiliary request 2).

According to the decision under appeal:

a) The late filed document D14 (Abstract of Am. J. Hosp. Pharm. 1979, 36(12), 1672-5) was to be admitted into the proceedings in that it was *prima facie* relevant.

b) Documents D5 (Marketing authorization for Zodac GTT in the Slovak Republic), D6 (Marketing authorization for Zodac SIR in the Slovak Republic), D7 (Marketing authorization for Zodac GTT in the Czech Republic), D8 (Marketing authorization for Zodac SIR in the Czech Republic) and D11 (Thomas Reuter Newport Premium; launched Drug Fors Detail) demonstrated that the products Zodac GTT and Zodac SIR were available on the market before the priority date of the patent.

However, none of these documents disclosed the concentration of parabens (i.e. methylparaben and propylparaben) in the products. This information could not be taken from D9 (Zodac GTT, Summary of product Characteristics, date of last revision 21 October 2009) or D10 (Zodac SIR, Summary of product Characteristics, date of last revision 21 October 2009) since it was not sufficiently proven that the products available on the market had the same concentration of parabens disclosed in these documents. Hence, the public availability of the products Zodac GTT and Zodac SIR was not prejudicial to the novelty of the main request.

c) Document D1 (EP 605203) was the closest prior art for the assessment of inventive step. This document disclosed in example 5 a liquid ophthalmic composition comprising *inter alia* cetirizine hydrochloride and 3 mg/ml of a mixture of parabens. The composition defined in claim 1 of the patent in suit differed from the composition of example 5 of D1 in the lower concentration of of parabens, i.e. more than 0 and less than 1.5 mg/ml.

The patent did not contain any data supporting the alleged effect of reducing the risk of allergic reaction. Furthermore, the amount of parabens in the compositions tested was always at least 0.15 mg/ml. Thus, it was not shown that the problem of providing further compositions having the recommended efficacy of antimicrobial concentration, was actually solved over the whole scope of the claim. Hence, the technical problem was to be defined as the provision of further liquid "compositions of cetirizine, levocetirizin or efletirizine comprising parabens showing (some degree of) antimicrobial effectiveness".

Document D3 (Handbook of Pharmaceutical Excipients, 3rd Ed. (2000), 340-342 and pages 450-453) disclosed the standard concentrations of methylparaben and propylparaben when used in the antimicrobial preservation of ophthalmic, nasal and oral solutions. The ranges of concentrations disclosed in this document overlapped with the range recited in claim 1 of the patent in suit. The skilled person faced with the technical problem would have modified the amount of parabens of the composition of D1 in the light of the teaching of D3 thereby obtaining compositions falling in claim 1 of the patent in suit. Hence, the main request did not comply with the requirements of Article 56 EPC.

d) The limitations introduced in the auxiliary requests did not change the assessment of inventive step. Thus, auxiliary requests 1 and 2 were not inventive either.

Parties and requests

IV. Appellant UCB Farchim SA (patent proprietor) requests that the decision under appeal be set aside and the patent be maintained according to the sets of claims filed on 23 April 2012 as main request and auxiliary requests 1 and 2, these requests being identical to the requests forming the basis of the appealed decision. The appellant also requests the Board not to admit documents D16 and D16a into the appeal proceedings.

V. Respondent Zentiva k.s. (opponent) requests that the appeal dismiss be dismissed.

New items of evidence

VI. With the statement setting out the grounds of appeal the appellant submitted the following pieces of evidence:

D17: Supplementary examples
D18: European Pharmacopoeia 5.0 - Efficacy of antimicrobial preservation

(*numbering attributed by the Board*)

With the reply to the grounds of appeal the respondent submitted the following documents:

D16: Batch record for batch 2 May 2004 of Zodac GTT dated 12 May 2004
D16A: English translation of D16

The following points inter alia appear to need consideration at the oral proceedings:

1. *Admissibility of the new items of evidence*

The question may arise whether the additional evidence filed on appeal need be admitted into the proceedings. Attention is drawn to the Case Law of the Boards of Appeal of the EPO (7th edition 2013, IV.C.1) and to Articles 12 and 13 of the Rules of Procedure of the Boards of Appeal.

Main request

2. Novelty

2.1 The Board tends to concur with the conclusions reached by the opposition division in relation to the alleged public prior use (see point 3 of the decision). In particular, the evidence submitted during the first instance proceedings does not appear to prove that the

products Zodac GTT and Zodac SIR, which were available on the market before the priority date of the patent (i.e. 14 July 2004), had the same concentration of parabens disclosed in documents D9 and D10 which bear as a "date of revision of the text" the 21 October 2009.

2.2 The relevance of documents D16/D16A in relation to the above issue will be considered if necessary during the oral proceedings, after discussion of their admissibility.

2.3 As to the remarks made by the respondent in relation to possibility of analysing the products on the market and the reference to the decision of the Enlarged Board of Appeal G1/92, the Board observes that the precise composition of these products is not yet known. Thus it is unclear which amount of parabens would have been found if the commercial products had been analysed. Thus, at present this argument appears to be of no relevance.

3. Inventive step

3.1 Inventive step will be considered on the basis of the problem-solution approach. This will involve assessing (a) which document is the closest prior art, (b) what is the objective technical problem vis-à-vis that document and (c) whether the claimed subject-matter is obvious with regard to the closest prior-art document, possibly in combination with the other documents on file.

Closest prior art

3.2 The parties agree that document D1 represents the closest prior art. It is also not disputed that the composition of the patent differs from the composition

disclosed in example 5 of D1 in the amount of parabens which is "more than 0 and less than 1.5 mg/ml", whereas in the composition of D1 the parabens concentration is 3 mg/ml.

The Board sees no reason to deviate from the approach followed by the parties.

Technical problem

3.3 The invention addresses the problem of providing pharmaceutical compositions containing as active ingredient a substance selected from cetirizine, levocetirzine and efletirizine and having a reduced amount of preservatives, in particular parabens (see [0007] to [0010]). It is explained in paragraph [0030] of the patent, that reducing the amount of preservatives leads to a reduction of the risk of allergic reactions in sensitive patients. At the same time the composition maintains its capacity to resist microbial contamination (see [0009]). The possibility of reducing the amount of preservatives is based on the recognition that the active agents themselves possess a preservative effect.

3.4 In its decision the opposition division considered that in the absence of any data supporting the alleged reduction of allergic reactions, this effect was to be disregarded in the assessment of inventive step.

The Board notes that according to D3, methylparaben and propylparaben may be irritant to the skin, eye and mucous membranes. These substances are considered unsuitable for certain types of formulations in view of their irritant potential. It is furthermore stated that hypersensitivity reactions to parabens, appearing as contact dermatitis, have been reported (see sections

"Safety" and "Handling precautions" on pages 342 and 452).

In the light of this general knowledge as to the potential side-effects associated to the use of parabens, the Board considers it credible, even in the absence of any experimental evidence, that the compositions of the patent in suit will cause fewer allergic reactions than the composition of example 5 of D1 because they contain a reduced amount of parabens.

3.5 As to the antimicrobial properties of the compositions the following is observed.

Tables 2, 3, 5 and 6 of examples 1 and 2 show the antimicrobial properties of cetirizine and levocetirizine compositions which do not contain parabens. The objective of the experiments described in these examples is to demonstrate that the active ingredients have a preservative effect. As observed by the respondent and by the opposition division, the formulations of examples 1 and 2 contain, however, other substances such as sodium acetate that may have an antimicrobial effect. It is therefore unclear whether the antimicrobial properties of the compositions of examples 1 and 2 are to be attributed to the active ingredient or to other substances and in particular to sodium acetate.

3.6 In this context the Board observes that document D14 describes the inhibitory effect of sodium acetate on microorganism growth in protein hydrolysate solutions. It is affirmed that this substance inhibits growth of S aureus and E coli whilst it is not effective against C albicans.

Tables 2, 3, 5 and 6 show the antimicrobial preservative effect of the compositions of examples 1

and 2 against various bacteria and yeasts, including C albicans. Since sodium acetate does not inhibit the growth of C albicans (see above), in the Board's opinion the experiments of the patent suggest that the active ingredients possess some antimicrobial properties.

3.7 Given that the active ingredients of the claimed composition appear to have some antimicrobial properties, it appears credible that compositions having very low amounts of parabens as claimed in claim 1 of the patent are resisting to some extent microbial contamination.

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The compositions of examples 1 and 2 of the patent and of example 3 of D17, which fulfil these requirements, contain sodium acetate. Although this substance is not effective against some bacteria (see above), it appears that it may contribute to the antimicrobial preservation of the compositions in which it is included. Thus, it is not clear whether compositions containing as preservative agents only small amounts of parabens would meet the criteria of acceptance of the European Pharmacopoeia.

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The decisive issue in relation to the obviousness of the invention is whether the skilled person trying to improve the safety profile of the composition of D1 and at the same time concerned with the problem of maintaining the antimicrobial properties of the composition, would reduce the concentration of parabens down to the levels recited in claim 1.

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4. Article 123(3) EPC

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Final remarks

6. Other relevant issues may also be addressed, if necessary.

7. Should the appellant in reaction to this communication wish to file further submissions, attention is drawn to Article 13 (1) and (3) RPBA. The admissibility of any such amendment would have to be considered at the oral proceedings.

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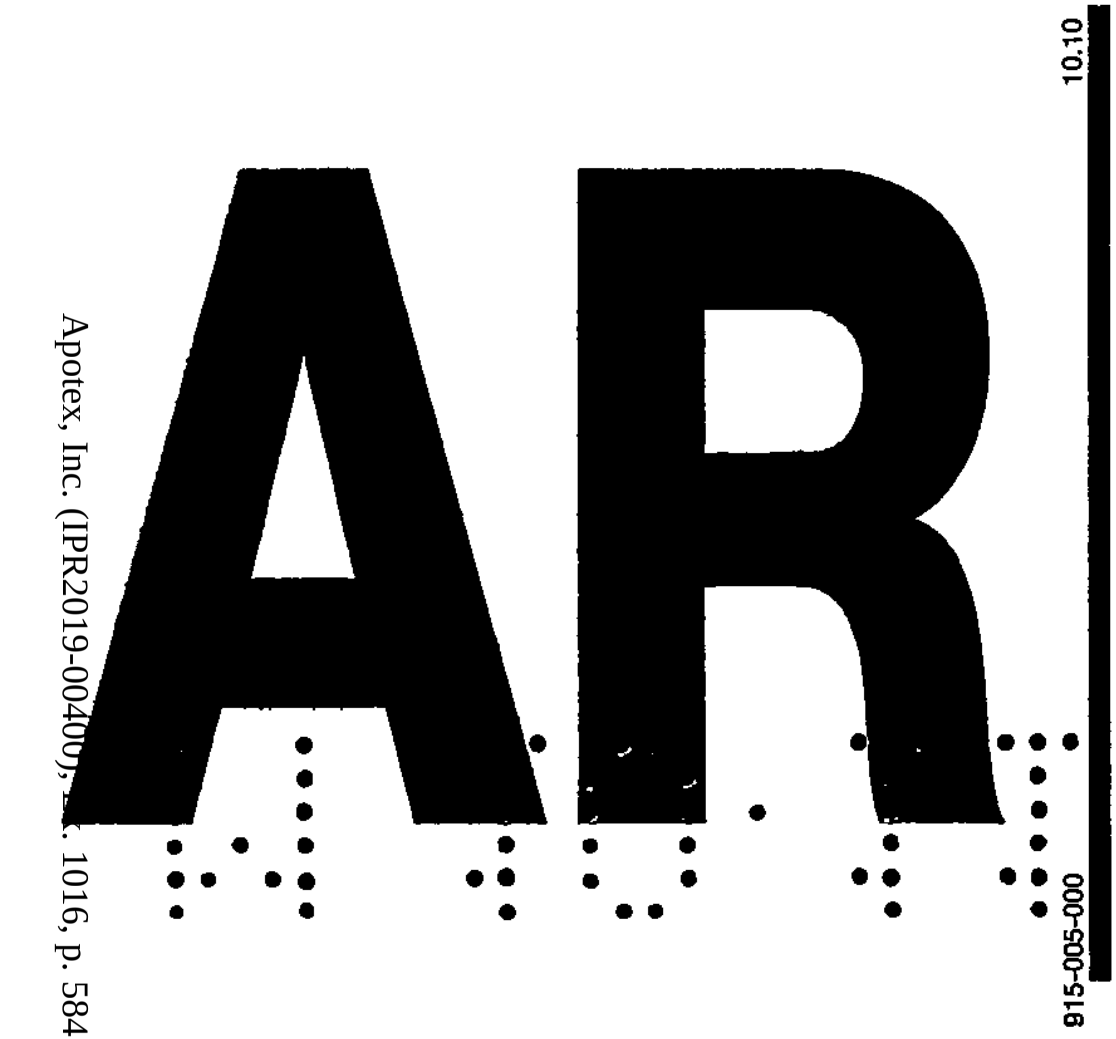

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- representing the opponent(s):	Zentiva, k.s.
Opponent/representative's reference	B0199PI-EP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1768649
Application No.	EP05758582.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	23 September 2009
Title of the invention	Pharmaceutical composition of piperazine derivatives
Proprietor of the patent	UCB FARCHIM S.A.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Any annexes (other than citation) to an opposition letter - Letter relating to representation and language during the oral proceedings	B0199PI-EP - Oral proceedings (ID 578301).pdf	OTHER-1.pdf

Signatures

Place:	**Helsinki**
Date:	**10 February 2016**
Signed by:	**Jonna Sahlin 24501**
Association:	**Boco IP Oy Ab**
Representative name:	**Jonna Sahlin**

Capacity: **(Representative)**

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10 February 2016

Re.: **Appeal File No.: T0371/12-3.3.07**
Opposition to European Patent Patent No. 1768649
Patent owner/Appelant: UCB FARCHIM S.A.
Opponent/Appelee: ZENTIVA k.s.

Dear Sirs,

During the Oral proceedings scheduled for 11 March 2016 the Opponent/Appelee will be represented by me, Mrs. Jonna Sahlin (09231490), as professional representative and by Mr. János Őri as accompaning person.

Please be informed that we will use the English language during the proceedings and wish to get interpretation if the French or German is used.

Yours faithfully,
Boco IP Oy Ab

Jonna Sahlin
Professional Representative (09231490)

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Acknowledgement of receipt

We hereby acknowledge receipt of the following submission by the opponent:

Submission number	4112944
Application number	EP05758582.0
Patent number	EP1768649
Date of receipt	10 February 2016
Your reference	B0199PI-EP
Opponent	Zentiva, k.s.
Title	Pharmaceutical composition of piperazine derivatives
Documents submitted	package-data.xml ep-oppo.pdf (2 p.) ep-opposition-data.xml OTHER-1.pdf\B0199PI-EP - Oral proceedings (ID 578301).pdf (1 p.)
Submitted by	CN=Jonna Sahlin 24501
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/European Patent Office/

Am J Hosp Pharm 36:1672–1675 (Dec) 1979

Sodium acetate as a preservative in protein hydrolysate solutions

Gary Frech, Loyd V. Allen, Jr., M. Lou Stiles and **R. Saul Levinson**

The inhibitory effect of sodium acetate on microorganism growth in protein hydrolysate solutions was studied.

Solutions of 5% protein hydrolysate and 5% dextrose in water (seven parts) and 50% dextrose in water (three parts) containing 0, 30, 50 and 90 mEq/liter of sodium acetate were inoculated with *Staphylococcus aureus, Escherichia coli, Candida albicans* and *Pseudomonas aeruginosa*. The number of colony-forming units in the solutions after inoculation was compared with that after incubation for 24 hours at 37 C.

Sodium acetate inhibited growth of *S aureus* and *E coli*. Growth of *P aeruginosa* was inhibited in protein hydrolysate solutions with and without sodium acetate; inhibition could not be attributed solely to sodium acetate and may have been related to *p*H of the solutions (4.7 to 5.4). Growth of *C albicans* was not inhibited by sodium acetate.

Sodium acetate reduced growth of some common contaminants of protein hydrolysates. Sodium acetate is known to reduce metabolic acidosis, a reported complication of parenteral nutrient therapy and a possible predisposing factor in *C albicans* sepsis. Addition of sodium acetate to protein hydrolysate solutions should be considered seriously.

Key words: Contamination; Dextrose; Preservatives; Protein hydrolysates; Sodium acetate; Solutions

Total parenteral nutrition (TPN) has achieved status as an accepted method of administering nutrients to patients who cannot ingest food orally, require supplemental feeding or have gastrointestinal complications that contraindicate oral feeding. TPN solutions usually contain a caloric source (e.g., dextrose), a nitrogen source (e.g., amino acids) and various electrolytes, depending on the status of the patient. TPN solutions prepared with protein hydrolysates as the nitrogen source will support growth of some bacteria and fungi[1] and are certain to be a source of septicemia if improper environment, manipulation or use of nonsterile materials is involved.[2,3] In vitro studies indicate that *Candida albicans, Klebsiella* sp, *Staphylococcus aureus, Escherichia coli, Serratia* sp, *Proteus* sp and *Enterobacter* sp grow at various rates in TPN solutions prepared using protein hydrolysate.[2–4]

It has been demonstrated in peritoneal dialysis solutions, that certain factors contribute to inhibition of growth of selected microorganisms. These factors include low *p*H, acetate base and dextrose.[5] Sodium acetate, in place of sodium lactate, has been used successfully to decrease infection associated with peritoneal dialysis solutions.[6,7]

For many years acetic acid as well as lactic acid has been used to preserve food. It has been shown that the toxic effect of acetic acid on microorganisms implicated in food spoilage was not entirely attributable to the level of hydrogen ion concentration and that acetic acid had a greater effect than did lactic or hydrochloric acid.[8] Using *Staphylococcus* microganisms, one study demonstrated an antibacterial effect of acetic acid which could not be accounted for entirely by alterations in *p*H.[9] Phillips and others reported that dilute solutions of acetic acid were useful in the treatment of superficial wounds infected by *Pseudomonas aeruginosa*.[10] Martin and Bookrajian[11] reported preventing bacilluria from indwelling foley catheters using acetic acid solutions.

The similarity of acetic acid to the components of the tricarboxylic acid and glyoxylate cycles of bacteria seems to suggest that acetate facilitates bacteria's metabolic processes. However, reports indicate that cells of *Pseudomonas fluorescens* grown with acetate as their principal source of carbon did not oxidize tricarboxylic acid intermediates as well as did cells grown with other sources of carbon.[12] Similarly, other investigators showed that in *Pseudomonas putida*, production of malate synthase, an important enzyme of the glyoxylate cycle, was suppressed by acetate, pyruvate and lactate with acetate having the greatest suppressive effect.[13]

It seems plausible to suggest that sodium acetate might inhibit the growth rate of certain microorganisms in TPN solutions prepared with protein hydrolysates. An added advantage of using sodium acetate is that it also is effective in treating moderate metabolic acidosis caused by mild renal insufficiency, diarrhea, diabetic ketosis or infusion of excessive acidifying substances.[14–17]

The purpose of this investigation was to determine the effect of varying concentrations of sodium acetate on the proliferation rate of selected microorganisms in TPN solutions containing protein hydrolysate.

Materials and Methods

This investigation was divided into preliminary, intermediate and final segments. The preliminary segment, using brain heart infusion broth (BHIB), an agar for growth of microorganisms, established standard transmittance and standard volume of inoculum (an unknown quantity of organisms), and experimental methods, and equipment and filtration techniques to be used in the intermediate phase

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of the investigation.

Standard Transmittance and Standard Volume. The standard transmittance and standard volume of inoculum (Table 1) were determined by preliminary experimentation so that the number of colony-forming units (CFU) would not be too numerous to count on a 47-mm petri dish (Millipore Corp.) after incubation for 24 hours at 37 C. Inocula of each of four microorganisms (*C albicans, E coli, P aeruginosa* and *S aureus*) were diluted with a series of sterile 0.9% sodium chloride solution dilution blanks (10^1 to 10^8). After the transmittance of each dilution was obtained, numerous 1-ml samples of inoculate were filtered (see Filtration Method). The mean number of CFUs obtained from the 1-ml samples of inoculate determined a predictable number of CFUs for a given standard transmittance, dilution and volume of inoculate.

Preparation and Storage of TPN Solutions. Four aliquots of a TPN solution containing seven parts 5% protein hydrolysate derived from casein (Amigen) and 5% dextrose in water, and three parts 50% dextrose in water (McGaw Laboratories, lots G230A0-E, 51100-G25222 and 51281-G3K191) were prepared to contain 0, 30, 50 or 90 mEq/liter of sodium acetate (using dry crystals, Baker Chemicals, lot 30186). A one-liter vacuum filter flask fitted with a 300-ml Pyrex filter-holder apparatus (Millipore Corp.) containing a 47-mm, 0.22-μm membrane filter (Millipore Corp.) was used to cold sterilize each aliquot (see Filtration Method). A sterile pipet was used to transfer 9.9 ml of the sterile TPN solution into appropriately labeled 16-mm by 150-mm, autoclaved test tubes fitted with vented, plastic closures. The TPN solutions were returned to room temperature. The *p*H of the TPN solutions ranged from 4.7 (no sodium acetate) to 5.4 (90 mEq/liter sodium acetate).

Filtration Method. The filtration method used a filter-holder apparatus containing a premoistened, 47-mm, 0.45-μm, gridded membrane filter. The sterile filter-holder apparatus was inserted into a specially constructed, four-place, vacuum filter-holder support. Vacuum was provided by a portable vacuum pump. Approximately 25 ml of sterile 0.9% sodium chloride was used to premoisten the filter. After the sample was passed through the filter, the filter-holder apparatus was rinsed with additional sterile aqueous 0.9% sodium chloride and additional vacuum provided.

The filter was removed by carefully disassembling the filter-holder apparatus and removing the filter with smooth-tipped forceps (Millipore Corp.) which were alcohol flame sterilized. The filter was peeled from the base of the holder apparatus and gently drawn over the edge of an open 47-mm petri dish until the far edge of the filter fell into position on the edge of the broth pad (Millipore Corp.) or agar surface. The petri dish with the lid replaced was properly labeled, inverted and incubated 24 hours at 37 C and the number of CFU counted.

Indicator Agar and Broth. Table 2 lists the indicator agar or broth used to nourish microorganisms for this investigation. After preparing each agar according to the instructions on the agar bottle, 6 to 7 ml was transferred into a 47-mm petri dish using sterile pipets.

Table 1. Standard Transmittance and Volume of Inoculum Used To Test Inhibitory Effect of Sodium Acetate

Organism	Transmittance (%)	Dilution	Volume (ml)
Pseudomonas aeruginosa	80	10^6	1.43
Staphylococcus aureus	74	10^6	1.6
Candida albicans	72	10^6	3.0
Escherichia coli	74	10^6	1.6

Table 2. Commercial Indicator and Growth Agar/Broth Used to Nourish Organisms for Protein Hydrolysate Solutions

Commercial Agar/Broth	Organism Nourished
Vogel Johnson Agar[a]	*Staphylococcus aureus*
Les Endo Agar[b]	*Escherichia coli*
Pseudocell Agar[c]	*Pseudomonas aeruginosa*
Yeast and Mold (M-Green) Medium[d]	*Candida albicans*

[a] B.B.L., Division of Becton, Dickinson and Co., Cockeysville, MD, lot C7DOFS.
[b] Difco Laboratories, Detroit, MI, lot 613183.
[c] B.B.L., lot K6DCPD.
[d] Millipore Corp., lot A7D96897.

A sterile, plastic syringe was used to aseptically transfer the yeast and mold broth (M-Green) from a 2-ml ampul into a covered sterile, plastic 47-mm petri dish containing a sterile, absorbent pad.

The agar and broth were prepared, placed into the petri dish and kept in the refrigerator if necessary. Prior to use the petri dish was returned to room temperature.

Microorganisms. The microorganisms used in this investigation have been reported in the literature as common contaminates of TPN solutions. The organisms were furnished on sheep blood agar by the Oklahoma Health Sciences Center. *C albicans* was obtained from isolations of cultures of patient specimens. *P aeruginosa, E coli* and *S aureus* were obtained from America Type Culture Collection numbers 27853, 25922 and 25923, respectively.

Incubation of Inoculum of Microorganisms. Using aseptic bacteriological technique, the organisms were transferred to slants of BHIB agar via a wire loop and incubated for 24 hours at 37 C. Subsequently, using bacteriological technique, the BHIB agar slant was washed with approximately 3 ml of sterile, 0.9% sodium chloride solution. The resultant suspension was transferred to a one-liter Roux bottle containing a large surface of the BHIB agar and incubated at 37 C for another 24 hours.

Transfer and Dilution of Microorganisms. After incubation of microorganisms on the BHIB agar in the Roux bottle, a sterile glass micropipet was used to transfer 0.1 ml of the resultant suspension into 9.9 ml of sterile, 0.9% sodium chloride solution contained in a 16-mm by 150-mm, autoclaved test tube fitted with a vented plastic closure. The suspension was mixed three consecutive times using a vortex mixer. A spectrophotometer, at a wavelength of 530 nm, was used to determine the transmittance of the suspension. Dilution with sterile 0.9% sodium chloride solution was necessary to obtain the recommended standard transmittance (Table 1) for each organism. Subsequently, the suspension was diluted to 10^6 and the recommended standard

volume (Table 1) was placed into 16 test tubes (four samples of each sodium acetate concentration—0, 30, 50 and 90 mEq/liter) containing 9.9 ml of the sterile TPN solution.

Determining CFUs. Time-zero colony counts were made by filtering (see Filtration Method) a 1-ml sample of protein hydrolysate solution removed from each of the 16 test tubes. Colony counts also were made by filtering a sample of 0.1-ml of protein hydrolysate solution from the same 16 test tubes after incubation for 24 hours at 37 C.

Results

The effect of various concentrations of sodium acetate (0, 30, 50 and 90 mEq/liter) on the growth of microorganisms in protein hydrolysate solutions was evaluated by determining if the number of CFUs of the four microorganisms (*S aureus, C albicans, P aeruginosa, E coli*) present at inoculation of the solution was significantly greater than that present after incubation for 24 hours at 37 C. Differences in growth of microorganisms in protein hydrolysate solutions with and without sodium acetate were measured to evaluate inhibition properties of sodium acetate.

Inhibition of S aureus. Table 3 shows the growth of *S aureus* in protein hydrolysate solutions with various concentrations of sodium acetate. The samples without sodium acetate showed copius growth in 24 hours while the samples with concentrations of 30 to 90 mEq/liter showed obvious inhibition of growth.

Inhibition of E coli. Table 3 shows the growth of *E coli* in protein hydrolysate solutions with various concentrations of sodium acetate. The samples without sodium acetate showed growth in 24 hours while samples with concentrations of 30 to 90 mEq/liter of sodium acetate showed obvious inhibition of growth. Inhibition of growth increased as the concentration of sodium acetate increased from 30 mEq/liter.

Inhibition of C albicans. Table 3 shows the growth of *C albicans* in protein hydrolysate solutions containing various concentrations of sodium acetate. Samples with and without sodium acetate experienced similar copious growth, with the number of CFUs too numerous to count in all instances. Sodium acetate, in concentrations used in this investigation, apparently had no inhibitory effect on growth of *C albicans*.

Inhibition of P aeruginosa. Table 3 shows the growth of *P aeruginosa* in protein hydrolysate solutions containing various concentrations of sodium acetate. All samples showed substantial inhibition of microorganism growth, including samples that contained no sodium acetate. Bergey[18] emphasized that *P aeruginosa* is incapable of growth in solutions with a *p*H less than 6; thus, the marked inhibition noted may not be attributed to sodium acetate alone.

Discussion

The presence of acetic acid in the tricarboxylic acid (Krebs) cycle and the glyoxylate (modified Krebs) cycle of bacterial enzymatic processes is well known. Bacteria, using the glyoxylate cycle consisting of enzymes in the mitochondria of the cell, convert acetate into acetyl coenzyme A and four-carbon dicarboxylic acids (fumarate, oxyalacetate, malate and succinate) which are valuable intermediaries in the tricarboxylic acid cycles. Therefore, consideration should be given to factors which affect cell enzyme activity such as concentration of hydrogen ion and enzyme inhibitors.[19]

The inhibition of growth of *S aureus* and *E coli* in this investigation could be due to the concentration of an inhibitor of enzyme activity. Sodium acetate may be such an inhibitor of enzymatic activity.

One group of investigators reported that enzyme levels in pseudomonades grown at *p*H 6.8 to 7.0 on a number of carbon sources including acetate were repressed greatest by acetate or a product formed from acetate (possibly acetyl coenzyme A). Repression of enzyme activity was thought to be due to suppression of malic enzyme formation by acetate, although no complete inhibition of malic enzyme was reported.[13] When sodium acetate was added to our protein hydrolysate solution, the *p*H shifted from 4.7 to 5.4 which is more favorable for growth of microorganisms. However, since the shift of *p*H did not stimulate the growth of microorganisms, inhibition of enzyme activity of *E coli* and *S aureus* must be considered a possible factor. This concept is in agreement with others who showed that the toxic effect of acetic acid on Staphylococci and other microorganisms implicated in food spoilage was not attributable entirely to hydrogen ion concentration.[8] Owens also demonstrated an antibacterial effect of acetate which could not be accounted for entirely by alterations in hydrogen ion concentration.[9]

Table 3. Number of CFUs[a] of Four Organisms in Protein Hydrolysate Solutions Containing Sodium Acetate

Organism	Sample Times (hrs)	Sodium Acetate Concentration of Protein Hydrolysate Solution			
		0 mEq/liter	30 mEq/liter	50 mEq/liter	90 mEq/liter
Staphylococcus	0	77.35 ± 29.48	69.35 ± 25.03	83.00 ± 3.61	60.67 ± 20.53
aureus	24	TNTC[b]	1.25 ± 0.96	0.75 ± 0.96	1.50 ± 1.00
Escherichia	0	166.33 ± 16.26	161.67 ± 12.10	157.00 ± 11.36	163.00 ± 6.56
coli	24	TNTC	4.00 ± 4.24	3.25 ± 2.63	1.75 ± 0.50
Candida	0	26.00 ± 5.61	24.20 ± 2.77	27.00 ± 4.30	25.00 ± 5.10
albicans	24	TNTC	TNTC	TNTC	TNTC
Pseudomonas	0	165.00 ± 14.73	169.33 ± 6.11	143.67 ± 14.15	173.67 ± 18.50
aeruginosa	24	3.50 ± 2.12	3.25 ± 1.50	5.50 ± 4.36	10.50 ± 8.23

[a] Colony-forming units expressed as mean values ± one standard deviation.
[b] TNTC = CFUs too numerous to count; estimated at 300 CFUs for *S aureus* and *E coli* and 500 CFUs for *C albicans*.

Although Richardson and Borchardt[6,7] conducted their experiments using peritoneal dialysis fluids, their observation of a reduction in the number of viable organisms in solutions containing sodium acetate was strikingly similar to our results with protein hydrolysates. *S aureus* in our protein hydrolysates similarly was almost completely eradicated by sodium acetate. *E coli* also was affected but to a lesser degree, until the concentration of sodium acetate rose to 90 mEq/liter.

An effect of sodium acetate on protein hydrolysate solutions containing *C albicans* was not observed. Use of sodium acetate to reduce the incidence of candidal sepsis may be of merit because it will assist in reducing acidosis which may predispose the patient to invasion by *C albicans*.

An effect of sodium acetate on the growth of *P aeruginosa* was not detected by this investigation. The *p*H of the protein hydrolysate solution in this investigation (4.7 to 5.4) was lower than that reported by other investigators (*p*H 5.2 to 5.8).[7] Bergey reported that *p*H below 6 was unfavorable for growth of *P aeruginosa*.[18]

The advantages to following strict protocol when preparing TPN solutions are obvious; however, the wise use of sodium acetate is advocated because of its effect as an alkalinizing agent and inhibitor of bacterial growth.

Conclusions

This in vitro study did not show inhibition of growth of *C albicans*, one of the most predominant organisms causing sepsis with protein hydrolysates. The study did show that sodium acetate is useful in inhibiting growth of *E coli* and *S aureus* and possibly *P aeruginosa* in protein hydrolysate solutions.

Sodium acetate is a useful agent in reducing metabolic acidosis, a reported complication of parenteral nutrient therapy and reportedly a possible predisposing factor to *C albicans* sepsis. The use of sodium acetate, a readily metabolized product, as an additive in protein hydrolysate solutions should be considered seriously.

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Appeal No.: T0371/12-3.3.07
Opposition against EP 1 768 649
Title: PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES
Proprietor: UCB FARCHIM S.A
Opponent: Zentiva k.s.

This is in reply to the Communication of the Board of Appeal dated November 10, 2015, and in preparation of the oral proceedings of March 11, 2016:

I. Language used during the oral proceedings:

We will use the English language during the oral proceedings (speaking). Assuming that the opponent will use the English language as well, no simultaneous translation is required (listening).

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Formally, it is noted that the undersigned will be accompanied by Ms. Monique Lechien, European patent attorney and employee of the patent proprietor.

II. Requests

It is still requested to set aside the decision of the Opposition Division of December 22, 2011, and to maintain the European patent EP 1 768 649 within the scope of the claims according to the main request or according to the first/second auxiliary request (as enclosed to this submission).

Two further auxiliary requests are submitted, i.e. claims according to the 3rd and 4th auxiliary request. Both correspond to the claims according the 1st and 2nd auxiliary request, however are restricted to oral solutions. A basis for this amendment may be found in claim 12 as originally filed (WO 2006/005507).

Furthermore, it is requested not to admit document D16/D16a into the appeal proceedings.

III. The Communication of the Board of Appeal dated November 10, 2015

We thank the Board of Appeal for sending a detailed summary of the case and of the points which appear to need consideration at the oral proceedings. In the following, we will address some of these points in preparation of the oral proceedings:

III.1. Admissibility of the new items of evidence

In the communication, it was correctly noted that the question may arise whether the additional evidence filed on appeal needs to be admitted into the proceedings.

According to Art. 12(1)(a) of the Rules of Procedure of the Boards of Appeal, the appeal proceedings are based, among others, on the Notice of Appeal and the statement of grounds of appeal filed pursuant to Art. 108 EPC. Thus, formally, new documents D17 and D18 (in particular the supplementary examples according to D17) have been filed within the required time frame of Art. 12(1)(a).

Art. 12(4) of the Rules indicates that the Board might hold facts, evidence or requests inadmissible which could have been presented or were not admitted in the first instance proceedings. Considering that only the first alternative is applicable here, the following is noted: The new experimental data submitted as document D17 address the decision of the Opposition Division as outlined in our letter dated April 23, 2012, (substantiation of the appeal), see points 1-5 on page 3 of the submission. Point 5 deals with the "self-preserving" effect of the active ingredients cetirizine, levocetirizine and efletirizine which has not been acknowledged by the Opposition Division. Furthermore, according to point 4 on page 3 of our substantiation of the appeal, the Opposition Division's view has been addressed that the composition provided in the examples of the present patent, i.e. formulations according to examples 3, 4, 6, 8 and 9, comprise other additives and excipients which might exert a concomitant anti-microbial effect.

D17 could not be filed earlier, i.e. in the first instance proceedings since it addresses the decision of the Opposition Division. Furthermore, the discussion on the relevance of other additives and excipients which might exert a concomitant anti-microbial effect (such as sodium acetate and acetic acid) were first raised and substantiated by the opponent in the submission of September 29, 2011, i.e. on the last day of the term fixed by the Opposition Division according to Rule 116 EPC. At that time, documents D12-D15 were presented by the opponent. It was impossible to prepare and file suitable experimental data in the remaining time, i.e. prior to the oral proceedings and thus during the first instance.

Therefore, D17 (and document D18 belonging to it) cannot be regarded as late-filed and it is thus requested to admitted them into the appeal proceedings.

III.2. Main request

III.2.1 Novelty

The Board noted in its preliminary opinion that it tends to concur with the conclusions reached by the Opposition Division regarding the alleged public prior use. In order to avoid any necessary reiteration, it is fully referred to our letter dated June 25, 2013, and our arguments regarding the alleged prior use of products Zodac® GTT (oral drops) and Zodac® SIR (syrup).

It is fully referred to our argumentation submitted on June 25, 2013, page 3, regarding D16/D16a. There is no evidence, whatsoever, that the composition described in document D16/D16a corresponds to that disclosed in D9. In terms of preservatives (methylparaben and propylparaben), D9 discloses a concentration of 1.5 mg paraben per one ml solution. That is to say, the concentration is given in terms of mass/volume.

In D16/D16a, however, the concentration of the parabens and the other ingredients is only indicated in terms of mass. In order to convert the values indicated in D16/D16a into mass/volume, the exact volume of the different ingredients has to be known, in particular the exact volume of glycerol, propylene glycol, and acetic acid which corresponds to the indicated mass. The exact volume, however, is not known and a comparison thus can't be made.

As a summary, the evidence submitted during the first instance proceedings does not appear to prove that the products Zodac® GTT and Zodac® SIR, available on the market before the present patent was filed, had the same concentrations of parabens as those disclosed in documents D9 and D10. Furthermore, even if, *arguendo*, this should be the case, D9 and D10 disclose a concentration of 1.5 mg parabens per ml solution and not "less than 1.5 mg/ml" as it is the case in present claim 1 according to the main request. The same is even more true for

the subject-matter of Auxiliary Requests 1 and 2, where the amount of parabens is restricted to 0.01 - 1.125 and 0.1 to 1.125 mg/ml, respectively.

Therefore, the alleged lack of novelty based on prior public use has not been proven beyond any doubt.

III.2.2 Inventive step

Also in this respect, we refer to our previous submissions, in particular the Notice of Opposition, the substantiation of our appeal filed on April 23, 2012, and our submission of June 25, 2013.

Closest prior art

The role of document D1 as closest prior art document remains undisputed.

Technical problem

As also noted in the preliminary opinion of the Board of Appeal, we see a dual technical problem of the claimed invention vs. the composition of D1, i.e.

a) reducing the risk of allergic and other adverse reactions in sensitive patients by reducing the amount of parabens, and
b) at the same time, maintaining a sufficient capacity to resist microbial contamination.

Solution of the technical problem

Regarding the first problem, the Board already noted that, considering D3, it seems to be credible that lowering the amount of parabens in a liquid pharmaceutical composition will cause fewer allergic reactions.

The other technical problem/effect of the liquid pharmaceutical composition according to claim 1 of the main request, however, seems to need a more detailed discussion.

According to the preliminary opinion of the Board, it still seems that the role of auxiliaries contained in the formulations of the examples of the opposed patent (as well as in document D17), in particular sodium acetate, has to be elucidated.

The role of sodium acetate as a preservative in protein hydrolysate solutions has been described in document D14. D14 explicitly states that growth of *Candida albicans* was not inhibited by sodium acetate in each of the concentrations used. Considering the experimental results in tables 2, 3, 5 and 6 of the opposed patent (formulations which do not include parabens) and the reduction of the microbial content regarding *Candida albicans*, it is clear that the active pharmaceutical ingredients cetirizine and levocetirizine must have their own anti-microbial activity.

Having a detailed look on the full paper of D14 (enclosed to this submission), it gets clear that sodium acetate furthermore has no inhibitory effect on the growth of *Pseudomonas aeruginosa*.

As it can be seen from table 3 on page 1674 of D14, also solutions containing 0 mEq/liter of sodium acetate reduced the number of *Pseudomonas aeruginosa* considerably. On page 1675, left column, third paragraph, it is clearly outlined that an effect of sodium acetate on the growth of *Pseudomonas aeruginosa* was not detected by the investigation performed in D14.

It is in fact correct that the compositions of examples 1 and 2 contained in the opposed patent and of example 3, submitted as D17, are directed to formulations comprising certain amounts of sodium acetate. However, D17 provides comparative examples 1 and 2 elucidating the role of sodium acetate as a preservative.

Comparative example 1 of D17 exclusively contains sodium acetate, acetic acid and purified water. The amount of sodium acetate intentionally was selected as in the formulations according to examples 1 and 2 of the opposed patent. Acetic acid has been used to acidify the formulation to give a pH of 5, i.e. exactly in the same way as it has been used in example 1 of the opposed patent.

The results indicated in table 2 of D17 are striking: It is confirmed that sodium acetate is not at all effective against *Candida albicans* confirming, by the way, the conclusions drawn in document D14. The amount of the microorganisms (*Candida albicans*) in the end of the test was higher than in the beginning. The correct conclusion drawn in our document D17 was that the exemplified solution does not fulfill the requirements of the European Pharmacopoeia, see D18.

The European Pharmacopoeia requires an adequate reduction of 4 test microorganisms, i.e. *Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans und Aspergillus niger*. If only one of these strains is not properly reduced (see table 5.1.3.-1 of D18), the test criteria for efficacy of anti-microbial preservation of the European Pharmacopoeia are not fulfilled.

Although it is admitted that sodium acetate has an anti-microbial effect on *Staphylococcus aureus*, it will not bring any pharmaceutical formulation into a condition to fulfill the test criteria of the European Pharmacopoeia, regardless of the concentration used, since it is not effective against *Candida albicans, Pseudomonas aeruginosa and Aspergillus niger.*

Similar effects can be seen in comparative examples 2 of D17.

The opposed patent exemplifies total amounts of para-hydroxybenzoate esters in formulations according to the invention as follows: 0.1 mg/ml (example 3 of D17), 0.15 mg/ml (example 3 opposed patent), 0.375 mg/ml (example 4 opposed patent), 0.45 mg/ml (example 3 opposed patent), 0.75 mg/ml (examples 3 and 4 opposed patent), 1.05 mg/ml

(example 3 opposed patent), and 1.125 mg/ml (example 4). All of these formulations reduce the number of microorganisms as required by the European Pharmacopoeia.

As a summary, regarding the effects underlying the present invention, we assume that both have been supported by sufficient evidence, i.e. the reduced risk of allergic reactions and of antimicrobial effectiveness due to the self-preserving function of the active pharmaceutical ingredients.

The above-mentioned arguments are also true for the subject-matter of auxiliary requests 1 and 2 which contain restricted selections of the active pharmaceutical ingredient levocetirizine and of the range of parabens used in the composition (0.01-1.125 mg/ml in auxiliary request 1; 0.1-1.125 mg/ml in auxiliary request 2).

Obviousness

Regarding the question of obviousness, the following is stated:

The Board referred to documents D1 and D3 and correctly noted that D3 indicates that methylparaben is normally used in ophthalmic preparations and in oral solutions in amounts ranging from 0.15-2 mg/ml. The amounts of propylparabens used in these preparations is indicated in a lower range on page 450, right column of D3. However, many question marks remain regarding the disclosure of D3. For example, in the list indicating the concentration of 0.15-2 mg/ml methylparaben for ophthalmic preparations (page 340, right column), it is not indicated where these proposed values have been derived from and whether they may fulfill the requirements of the European Pharmacopoeia (see D18).

Furthermore, it is noted that D1 generally refers to the active pharmaceutical ingredient cetirizine and discloses a huge number of different formulations and proposed auxiliaries/ excipients for use therein. On page 3, D1 proposes the use of preservatives such as p-hydroxybenzoates, benzalkonium chloride and chlorobutanol for ophthalmic or nasal

solutions. The compositions proposed in table 1 on page 4 do not contain any parabens at all. There is only one out of several examples making use of parabens, i.e. example 5, however, it is not indicated that the use of methyl and propylparaben used therein is of any particular advantage.

Therefore, a combination of documents D1 and D3 is somewhat artificial since it is not clear whether a skilled person really would envision a pharmaceutical composition with cetirizine HCl etc. and methyl/propylparaben and why there should be any motivation to further modify exactly this formulation in light of the relatively vague teachings of D3 in order to arrive at the subject presently claimed.

Rather, it seems that hindsight is required to arrive at the subject-matter of claim 1 according to the main request since there is nothing in D1 which would immediately prompt the skilled person to use parabens. D1 and D3 do not provide a "one way situation" which would make the development of a pharmaceutical composition as presently claimed a straight-forward approach.

In particular, we do not see a true motivation based on D1 and D3 to reduce an overall amount of parabens of 3 mg/ml to less than 1.5 since D3 actually indicates that parabens usually are used in combination with each other and that the use of single compounds is not a promising approach in the field of parabens. The statement: *"a mixture of parabens is thus frequently used to provide effective preservation"* according to D3, page 340, left paragraph is a clear indication in this regard. See, further, the repeated statement regarding the combination of methylparaben and propylparaben on page 340, right column, first paragraph, and page 450, left column, last paragraph.

Therefore, the subject-matter of claim 1 according to the main request is based on an inventive step in view of prior art documents D1 and D3.

III.2. Auxiliary requests

The Board noted that claim 1 of both requests (auxiliary request 1 and 2) potentially could violate Art. 123(3) EPC.

Regarding claim 1 of the 1st and 2nd auxiliary request, we are submitting a slightly revised version of them based on the [0020] of the published version of EP 1 768 649 B1.

The Board noted that, theoretically, the present claim wording could include other parabens such as ethylparaben resulting in an overall amount of para-hydroxybenzoate esters of more than "< 1.5 mg/ml".

Amended claim 1 of the 1st auxiliary request now clearly defines that the amount of para-hydroxybenzoate esters in total is 0.01-1.125 mg/ml where the para-hydroxybenzoate esters are methyl p-hydroxybenzoate/propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight.

The same wording has been used for claim 1 according to the 2nd auxiliary request which is directed to a more narrow range of 0.1-1.125 mg/ml of total parabens.

The newly submitted 3rd and 4th auxiliary requests are restricted to oral solutions. Since D1 refers to an ophthalmic formulation, it is submitted that there would be an even smaller motivation for a skilled person to use this document in combination with D3 in order to arrive at the subject-matter claimed.

All sets of claims, according to the 1st to 4th auxiliary request, meet the requirements of Art. 123(3) EPC.

Respectfully,

Wolfgang Sandmann
European Patent Attorney

Enclosure(s):
Document D14 (full version)
Auxiliary requests 1-4

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

Representative:

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	05758582.0
Applicant's or representative's reference	P30048-EPOP

	Description of document	Original file name	Assigned file name
1	Letter dealing with oral proceedings during the appeal procedure	P30048-EPOP_Submission.pdf	APPEAL-ORAL.pdf
2	Patent Document cited during the appeal procedure	P30048-EPOP_D14.pdf	APPEAL-CP-1.pdf
3	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 1 (clean version).pdf	DG3-CLMS-HWA.pdf
4	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 1 (annotated version).pdf	DG3-CLMS-HWA-1.pdf
5	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 2 (clean version).pdf	DG3-CLMS-HWA-2.pdf
6	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 2 (annotated version).pdf	DG3-CLMS-HWA-3.pdf
7	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 3 (clean version).pdf	DG3-CLMS-HWA-4.pdf
8	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 3 (annotated version).pdf	DG3-CLMS-HWA-5.pdf
9	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 4 (clean version).pdf	DG3-CLMS-HWA-6.pdf
10	Amended claims with annotations (appeal procedure)	P30048-EPOP_Auxiliary request 4 (annotated version).pdf	DG3-CLMS-HWA-7.pdf

Signatures

Place: **Munich**

Date: **11 February 2016**

Signed by: **Wolfgang Sandmann 12098**

Association:	**isarpatent - Patentanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB**
Representative name:	**Wolfgang Sandmann**
Capacity:	**(Representative)**

4th Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition in the form of an oral solution comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.1 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3rd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition in the form of an oral solution comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

1st Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

2nd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.1 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight ~~selected in the range of 0.01 and 1.125 mg/ml of the composition~~.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

2nd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.1 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

1st Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight ~~selected in the range of 0.01 and 1.125 mg/ml of the composition~~.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

3. 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 and ear drops.

3rd Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition in the form of an oral solution comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight ~~selected in the range of 0.01 and 1.125 mg/ml of the composition~~.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

~~3. 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 and ear drops.~~

4th Auxiliary Request

CLAIMS:

1. A liquid pharmaceutical composition in the form of an oral solution comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.1 and 1.125 mg/ml of the composition, where the p-hydroxy-benzoate esters are methyl p-hydroxybenzoate / propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight ~~selected in the range of 0.01 and 1.125 mg/ml of the composition~~.

2. A liquid pharmaceutical composition according to claim 1, characterized in that it is an aqueous composition.

~~3. 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 and ear drops.~~

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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	4117020
Application number	EP05758582.0
Date of receipt	11 February 2016
Receiving Office	European Patent Office, The Hague
Your reference	P30048-EPOP
Applicant	All applicants as on file

Documents submitted

package-data.xml	ep-sfd-request.xml
epf1038.pdf (2 p.)	APPEAL-ORAL.pdf\P30048-EPOP_Submission.pdf (11 p.)
APPEAL-CP-1.pdf\P30048-EPOP_D14.pdf (4 p.)	DG3-CLMS-HWA.pdf\P30048-EPOP_Auxiliary request 1 (clean version).pdf (1 p.)
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DG3-CLMS-HWA-7.pdf\P30048-EPOP_Auxiliary request 4 (annotated version).pdf (1 p.)	

Submitted by	CN=Wolfgang Sandmann 12098

Method of submission	Online
Date and time receipt generated	11 February 2016, 16:01 (CET)
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Correction by the EPO of errors in debit instructions filed by eOLF

Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Datum/Date
15.02.16

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR	05758582 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Please find enclosed a copy

☐ of a letter of the patent proprietor dated

☑ of a letter of the opponent dated 10.02.16

☐

for your information.

The Registrar S. Fabiani
Tel.: 089 / 2399 - 3371

Annex(es):

Registered letter

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Datum/Date
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Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: **T0371/12-3.3.07**

Please find enclosed a copy

☑ of a letter of the patent proprietor dated 11.02.16

☐ of a letter of the opponent dated

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Tel.: 089 / 2399 - 3371

Annex(es):

Registered letter

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BEHNISCH • BARTH • CHARLES
HASSA • PECKMANN
& PARTNER mbB*

PATENT- UND
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Dipl.-Ing. Oliver Hassa [1,2]
Dipl.-Phys. Ralf Peckmann [1,2]
M.P.H. Wolfgang Sandmann [1,2]
Dipl.-Phys. Dr. Christoph Hecht [1,2]
B. Eng. (Hons) Philip Gehrig [1,2,5,6]
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Dipl.-Ing. Dominik Cabrerizo [4]
Dipl.-Ing. Adrian Huissel [1]
Dipl.-Ing. Dr. Han Bong Ko [1]
Dipl.-Chem. Dr. Tobias Roßteuscher [1]

Franz Stangl [3,4]
Sandra V. Pilgram, LL.M. [3,4]
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PARTNERSCHAFTSREG. 1262

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Europäisches Patentamt
80298 München

Ihr Zeichen:	Unser Zeichen:	Datum:
	A0044 H	**10. März 2016**

Zusammenschluss Nr. 73, Laufendes Konto: 28000484
Namensänderung Zusammenschluss
Korrektur allgemeine Vertreteradresse

1. Aktualisierung Anschrift Zusammenschluss

Hiermit wird höflich darum gebeten, amtsseitig den Namen bzw. die Anschrift unseres Zusammenschlusses Nr. 73 wie folgt zu ändern:

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Email: info@isarpatent.com
URL: www.isarpatent.com

2. Aktualisierung lfd. Konto

Es wird die entsprechende Aktualisierung des Namens des Kontoinhabers für unser laufendes Konto Nr. 28000484 beantragt.

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3. Aktualisierung Vertreteradresse / Aktualisierung im Register

Es wird die entsprechende Aktualisierung wie unter 1. für unsere Vertreteradresse beim EPA beantragt, mit der wir in allen von unserer Sozietät vertretenen Akten im Register als Vertreter geführt werden. Die entsprechenden Einträge im Register bitten wir ebenso zu aktualisieren.

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Mit freundlichen Grüßen

Oliver Hassa
Patentanwalt

Anlage(n):
Ausdruck Registerblatt des Registergerichts

Amtsgericht München -Registergericht-

PR 1262

Aktueller Ausdruck aus dem Registerblatt

Datum der letzten Eintragung: 08.02.2016

Datum des Abrufs: 10.02.2016

Ersteller: Birkner, Justizangestellte,
Urkundsbeamter/Urkundsbeamtin der Geschäftsstelle

Partnerschaftsregister des Amtsgerichts München	Wiedergabe des aktuellen Registerinhalts Abruf vom 10.02.2016 07:38	Nummer der Partnerschaft: **PR 1262**
	Seite 1 von 1	

1. **Anzahl der bisherigen Eintragungen:**

   3

2. **a) Name:**

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   b) Sitz, Zweigniederlassungen:

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   c) Gegenstand:

   Patent- und rechtsanwaltliche Dienstleistungen, insbesondere Rechtsberatung im Bereich gewerblicher Rechtsschutz.

3. **a) Allgemeine Vertretungsregelung:**

   Jeder Partner vertritt einzeln.

   b) Partner, Vertretungsberechtigte und besondere Vertretungsbefugnis:

   Partner: Dr. Barth, Stephan Manuel, Patentanwalt, Gröbenzell, *13.02.1959
   Partner: Dr. Behnisch, Werner Wilhelm Friedrich, Patentanwalt, München, *29.06.1955
   Partner: Charles, Peter Cecil Glyndwr, Patentanwalt, München, *23.06.1964
   Partner: Gehrig, Philip Walter, Patentanwalt, München, *10.05.1968
   Partner: Hassa, Oliver Michael, Patentanwalt, Gröbenzell, *27.09.1967
   Partner: Dr. Hecht, Christoph Joachim, Patentanwalt, Maisach-Gernlinden, *06.07.1977
   Partner: Peckmann, Ralf, Patentanwalt, München, *27.11.1970
   Partner: Sandmann, Wolfgang, Patentanwalt, München, *18.10.1968
   Partner: Stangl, Franz Christoph, Rechtsanwalt, Germering, *17.01.1976

4. **a) Rechtsform:**

   Partnerschaft

   b) Sonstige Rechtsverhältnisse:

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5. **a) Tag der letzen Eintragung:**

   08.02.2016

Amtsgericht München -Registergericht-
Infanteriestr. 5, 80325 München
Telefon: 089/5597-06
Fax: 089/5597-3560

Amtsgericht München, 80325 München

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80801 München

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Einsicht Mo-Mi, Fr 8.30-12.00 Uhr
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Bei Antwort bitte angeben:
Unser Geschäftszeichen
PR 1262 (Fall 3)

Datum
10.02.2016

Mitteilung über die Eintragung im Partnerschaftsregister München
isarpatent - Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB, Sitz: München, PR 1262
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3.
b) Partner, Vertretungsberechtigte und besondere Vertretungsbefugnis:

Eingetreten:
Partner:
Stangl, Franz Christoph, Rechtsanwalt, Germering, *17.01.1976
Personendaten ergänzt, nun:
Partner:
Gehrig, Philip Walter, Patentanwalt, München, *10.05.1968

5.
a) Tag der Eintragung:
08.02.2016
Sammer

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Beschwerdekammern
Boards of Appeal
Chambres de recours

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Appeal number T0371/12-3.3.07

Patent No.: 1768649
Patent Proprietor: UCB FARCHIM S.A.
Opponent: Zentiva k.s.

Minutes of the oral proceedings

of 11 March 2016

Composition of the Board:

Chairman: J. Riolo
Members: A. Usuelli
D. T. Keeling

Start of oral proceedings:	09:00 hours
End of oral proceedings:	11:05 hours

Present on behalf of the appellant (patent proprietor):
Mr W. Sandmann, professional representative, identified by EPO ID-card, accompanied by Ms M. Lechien.

Present on behalf of the respondent (opponent):
Ms J. Sahlin, professional representative, identified by EPO ID-card, accompanied by Mr J. Öri.

The Chairman declared the oral proceedings open. He summarised the relevant facts as appearing from the file and invited the parties to state their requests.

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent maintained as granted (Main Request) or on the basis of the claims of one of the four Auxiliary Requests filed by letter of 11 February 2016. The appellant further

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Appeal number T0371/12-3.3.07

requested that documents D16 and D16A not be admitted into the proceedings.

The respondent (opponent) requested that the Third and Fourth Auxiliary Requests not be admitted into the proceedings and that the appeal be dismissed.

The parties addressed the Board concerning the question whether the subject-matter of the claims of the Main Request involved an inventive step starting from D1 as the closest prior art. Both parties stated that the arguments put forward with regard to the Main Request also applied to the First and Second Auxiliary Requests.

The Chairman closed the debate as regards the question whether the subject-matter of the claims of the Main Request or of the First or Second Auxiliary Request involved an inventive step starting from D1 as the closest prior art.

The parties presented arguments on the question whether the Third and Fourth Auxiliary Requests should be admitted into the proceedings.

The parties stated that they maintained their requests as set out above.

After deliberation the Chairman announced the Board's finding that the claims of the Main Request and of the First and Second Auxiliary Requests did not involve an inventive step and that the Third and Fourth Auxiliary Requests should not be admitted into the proceedings.

The following decision was announced:

The appeal is dismissed.

The Chairman closed the oral proceedings.

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Appeal number T0371/12-3.3.07

The Minute Writer: D. T. Keeling

The Chairman: J. Riolo

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FINLANDE

Datum/Date
08.04.16

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: T0371/12-3.3.07

Please find enclosed a copy of the minutes of the oral proceedings of 11.03.16.

The Registrar M. Kiehl
Tel.: 089 / 2399 - 3371

Annex(es):

Registered letter

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The Registrar S. Fabiani
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Annex(es): ☑ Acknowledgement of receipt - EPO Form 3936
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Registered letter with advice of delivery

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(B) [-] To Chairmen and Members
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Datasheet for the decision of 11 March 2016

Case Number: T 0371/12 - 3.3.07

Application Number: 05758582.0

Publication Number: 1768649

IPC: A61K9/08, A61K31/495

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Patent Proprietor:
UCB FARCHIM S.A.

Opponent:
Zentiva k.s.

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:
Inventive step - main request, auxiliary request 1 and auxiliary request 2 (no)
Late-filed auxiliary requests 3 and 4 - admitted (no)

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Case Number: T 0371/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 March 2016

Appellant: (Patent Proprietor)	UCB FARCHIM S.A. Z.I. de Planchy, Chemin de Croix Blanche 10 1630 Bulle (CH)
Representative:	Isarpatent Patentanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Respondent: (Opponent)	Zentiva k.s. U kabelovny 130 10237 Praha 10 (CZ)
Representative:	Boco IP Oy Ab Itämerenkatu 5 00180 Helsinki (FI)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 December 2011 revoking European patent No. 1768649 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
D. T. Keeling

Summary of Facts and Submissions

I. European patent No. 1 768 649, based on European application 05758582.0, was granted on the basis of seven claims.

Claim 1 as granted read as follows:

"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, the preservative being 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".

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC). The following documents were among those cited during the first-instance proceedings:

D1: EP 605203 A2
D3: Handbook of Pharmaceutical Excipients, 3rd Ed. 2000, pages 340-342 and 450-453
D4: Allergy 2001, 56:339-343

III. By decision posted on 22 December 2011, the opposition division revoked the patent. The decision was based on the patent as granted as main request and on two

auxiliary requests filed on 19 October 2010 (auxiliary request 1) and 29 September 2011 (auxiliary request 2).

IV. With regard to the requirement of inventive step, the opposition division came to the following conclusions:

a) Document D1, representing the closest prior art, disclosed in example 5 a composition comprising *inter alia* cetirizine hydrochloride and 3 mg/ml of a mixture of parahydroxybenzoates (parabens). The composition defined in claim 1 of the patent in suit differed from this composition in that it contained a lower concentration of parabens, i.e. more than 0 and less than 1.5 mg/ml.

The patent did not contain any data supporting the alleged effect of reducing the risk of allergic reactions. Furthermore, it was not convincingly shown that the problem of providing compositions having the recommended efficacy of antimicrobial preservation, was actually solved over the whole scope of the claim. Hence, the technical problem was to be defined as the provision of further liquid "compositions of cetirizine, levocetirizin or efletirizine comprising parabens showing (some degree of) antimicrobial effectiveness".

Document D3 disclosed the standard concentrations of methylparaben and propylparaben when used in the antimicrobial preservation of ophthalmic, nasal and oral solutions. The ranges of concentrations disclosed in this document overlapped with the range recited in claim 1 of the patent in suit. The skilled person faced with the technical problem would have modified the amount of parabens of the composition of D1 in the

light of the teaching of D3 thereby obtaining compositions falling in claim 1 of the patent in suit. Hence, the main request did not comply with the requirements of Article 56 EPC.

b) The limitations introduced in the auxiliary requests did not change the assessment of inventive step. In particular, the use of levocetirizine instead of racemic cetirizine was obvious in view D4, which indicated that the pure enantiomer had more therapeutic activity than the racemic mixture and hence it could be used in lower amount. Thus, auxiliary requests 1 and 2 were not inventive either.

V. The patent proprietor (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal filed on 23 April 2012 the appellant maintained the main request (i.e. maintenance of the patent as granted) and submitted two auxiliary requests. Additionally, with the same letter it submitted the following document:

D17: Supplementary examples

VI. The Board issued a communication pursuant to Article 15(1) RPBA on 4 November 2015. In relation to inventive step, the Board agreed with the appealed decision that document D1 represented the closest prior art and that the pharmaceutical composition claimed in the patent differed from the composition of example 5 of D1 in the lower concentration of parabens. Furthermore, the Board observed that according to document D3, the parabens could be used in concentrations which were below the concentration in which these substances were present in

the composition of D1 and within the range of claim 1 of the patent.

As to the auxiliary requests the Board indicated that these appeared to extend the protection conferred by the patent.

VII. By letter dated 11 February 2016, the appellant withdrew the auxiliary requests submitted on 23 April 2012 and filed four new auxiliary requests.

Claim 1 of auxiliary request 1 read as follows:

"1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy benzoate esters are methyl p-hydroxybenzoate/ propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight".

Claim 1 of auxiliary request 2 differed from claim 1 of auxiliary request 1 in that the lowest concentration of parabens was set at 0.1 mg/ml instead of 0.01 mg/ml.

Claim 1 of auxiliary requests 3 and 4 were based on the corresponding claims of respectively auxiliary request 1 and auxiliary request 2 but differed therefrom in the indication that the composition was in the form of an oral solution.

VIII. Oral proceedings were held on 11 March 2016.

IX. As far as relevant for the present decision, the arguments of the appellant can be summarized as follows:

a) Inventive activity - Main request and auxiliary requests 1 and 2

Document D1 was the closest prior art. This document disclosed in example 5 an ophthalmic composition comprising cetirizine and a mixture of methyl- and propylparaben. The composition claimed in the patent in suit differed from this composition of D1 in that it contained a lower amount of parabens. Starting from the closest prior art the technical problem was to be seen in the provision of a composition comprising cetirizine, levocetirizine or efletirizine as active ingredient, presenting a reduced risk of allergic reactions and at the same time maintaining a sufficient capacity to resist antimicrobial contamination. Examples 1 and 2 of the patent demonstrated the antimicrobial effect of cetirizine and levocitirizine compositions which did not contain parabens. It was clear from comparative examples 1 and 2 of D17 that this effect was not due to the presence of sodium acetate, which was not active against some microorgansims. Hence, the antimicrobial properties of the compositions of examples 1 and 2 of the patent in suit were due to the active ingredients. Thanks to these antimicrobial properties it was possible to reduce the amount of parabens in the composition. None of the prior art documents suggested that cetirizine and the other active ingredients had antimicrobial properties.

Document D1 did not address problems concerning the preservation of the compositions. Moreover, in the most part of the examples of this document the preservative agent used was not a paraben and some examples did not contain any preservative agent at all. Thus, the skilled person had no reason to consider in particular the composition of example 5. As to document D3, the lower

amounts of parabens suggested in the table of section 7 were purely theoretical. It was clear from Table 1 that these amounts were not sufficient to provide an adequate protection against microbial contamination. Document D3 appeared therefore to provide inconsistent information. Furthermore, this document suggested to use a combination of different parabens. Hence, the amounts reported in section 7 for methylparaben were to be considered in combination with additional amounts of other parabens. Therefore, the compositions of the patent in suit were not suggested by the combined teaching of D1 and D3.

The compositions of the auxiliary requests were more restricted in terms of active ingredient and amounts of parabens used. The arguments submitted in respect to the main request applied also to the auxiliary requests.

b) Admittance of auxiliary requests 3 and 4

The subject-matter of these requests was restricted to compositions in the form of oral solution. This limitation was included also in granted claim 7. These requests were therefore to be admitted into the appeal proceedings.

X. As far as relevant for the present decision, the arguments of the respondent can be summarized as follows:

a) Inventive activity - Main request and auxiliary requests 1 and 2

The compositions of the patent in suit differed from the composition disclosed in example 5 of D1 on account of the lower concentration of parabens. There was no

evidence supporting the claim that the compositions of the patent in suit caused less adverse reactions. There were also no tests showing the antimicrobial activity of the active ingredients because the compositions tested in the patent and in D17 contained not only cetirizine or levocetirizine but also some preservative agents. The technical problem formulated by the opposition division was therefore correct. The skilled person studying the ophthalmic composition of example 5 of D1 would have considered the information disclosed in section 7 of D3 as to the suitable amounts of parabens in compositions for ophthalmic use. These amounts overlapped with the concentration range defined in claim 1 of the patent in suit. Accordingly, the composition of the patent in suit was obvious in view of the teaching of D1 in combination with D3. Concerning the data disclosed in Table 1 of D3, these referred to the activity of solutions containing only methyl (or propyl) paraben. However, the antimicrobial properties of a pharmaceutical composition were influenced by all the components present in the compositions. Hence, the skilled person would have attributed more weight to the data in section 7 of D3 rather than the data in Table I.

The same arguments applied to the subject-matter of auxiliary requests 1 and 2.

b) Admittance of auxiliary requests 3 and 4

The restriction to compositions in the form of oral solution represented an inadmissible shift of the invention. The appellant had never submitted arguments on inventive step based on the relevance of this specific pharmaceutical form. Accordingly, auxiliary requests 3 and 4 were not to be admitted into the appeal proceedings.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained according to the main request submitted on 23 April 2012, corresponding to the patent as granted, or that the patent be maintained according to one of the four auxiliary requests submitted on 11 February 2016.

XII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (granted patent)

1. Inventive step

The patent in suit relates to pharmaceutical compositions capable of resisting microbial contamination, which contain as active ingredient a substance selected from cetirizine, levocetirzine and efletirizine ([0006] to [0009]).

1.1 Closest prior art

1.1.1 In agreement with the appealed decision, the Board considers that document D1 represents the closest prior art.

This document relates to antiallergic compositions for ophthalmic and nasal use containing citirizine as active ingredient. Although the main problem addressed in D1 concerns the stability of the composition, this document discusses on page 3 (lines 51 to 57) also the need of adding preservative agents, such as parabens, to the citirizine compositions.

1.1.2 Among the compositions disclosed in the eight examples of D1, the composition of example 5 is the one with the most features in common with the subject-matter of claim 1 in that it is the only one containing parabens. Thus, within the disclosure of the closest prior art, example 5 is the most promising starting point to be considered for assessing whether the subject-matter of claim 1 involves an inventive step.

1.1.3 The composition of the patent in suit differs from the composition of example 5 of D1 in the amount of parabens, which is "more than 0 and less than 1.5 mg/ml", whereas in the composition of D1 the parabens concentration is 3 mg/ml.

1.2 Technical problem

1.2.1 In paragraph [0007] of the description it is explained that the invention underlying the patent in suit is based on the recognition that the antihistaminic agents belonging to the family of substituted benzhydryl piperazines, such as cetirizine, levocetirzine and efletirizine, possess antimicrobial properties in aqueous solutions. This makes it possible to reduce the amount of preservative agents in the liquid formulations of these active ingredients. When the preservative agents are parabens, the reduction of concentration leads to a decrease of the risk of allergic reactions in sensitive patients.

Hence, the pharmaceutical compositions claimed in the patent in suit should be safer than the composition of D1 on account of a reduced amount of parabens but at the same time they should maintain an adequate capacity to resist microbial contamination.

1.2.2 The patent does not contain any experimental data supporting the effect of a reduction of the risk of allergic reactions in sensitive patients.

It is however noted that D3 reports that methylparaben and propylparaben may be irritant to the skin, eye and mucous membranes. It is furthermore stated that hypersensitivity reactions to parabens, appearing as contact dermatitis, have been reported (sections "Safety" and "Handling precautions" on pages 342 and 452).

In the light of this general knowledge as to the potential side-effects associated with the use of parabens, the Board considers credible, even in the absence of any experimental evidence, that the composition of the patent in suit causes fewer allergic reactions than the composition of example 5 of D1 because it contains a reduced amount of parabens.

1.2.3 As to the antimicrobial properties of the compositions, the following is observed.

Examples 1 and 2 of the patent show the antimicrobial properties of cetirizine and levocetirizine compositions which do not contain any paraben. The objective of the experiments described in these examples is to demonstrate that the active ingredients have themselves a preservative effect.

The efficacy of antimicrobial preservation of compositions according to claim 1 of the patent in suit comprising variable amounts of parabens is illustrated in examples 3 to 9 of the patent and in example 3 of D17.

Based on this evidence the Board accepts that the composition of the patent in suit maintains an adequate capacity of resisting microbial contamination.

1.2.4 The technical problem is therefore formulated as the provision of a liquid pharmaceutical composition comprising cetirizine, levocetirizine or efletirizine as active ingredient and parabens as preservative agents, which composition presents a reduced risk of allergic reactions and is capable of resisting microbial contamination.

1.3 Obviousness

1.3.1 Document D3 is an extract of an handbook relating to pharmaceutical excipients. It is divided in two parts which concern the products methylparaben and propylparaben.

In section 7 of the part concerning methylparaben it is reported that this substance is widely used as an antimicrobial preservative. In the same section it is indicated that in ophthalmic preparations and in oral solutions methylparaben is used in a concentration of 0.015 to 0.2 %, which corresponds to 0.15 to 2 mg/ml.

Similar information is disclosed in section 7 of the second part of D3, in relation to propylparaben. It is indicated that as an antimicrobial preservative, propylparaben is used in ophthalmic preparations in a concentration of 0.005 to 0.01 % (corresponding to 0.05 to 0.1 mg/ml) and in oral solutions in concentrations of 0.01 to 0.02 % (corresponding to 0.1 to 0.2 mg/ml).

1.3.2 The concentrations reported above for ophthalmic and oral solutions, i.e. liquid compositions, overlap with

the range of more than 0 and less than 1.5 mg/ml recited in claim 1 of the patent in suit. Furthermore, it is also possible to combine methyl and propylparaben in amounts within the ranges disclosed for each of these substances in D3 whilst still respecting the maximum amount allowed by claim 1 (i.e. 1.5 mg/ml).

1.3.3 Document D3 also includes in each of its two parts a table, named in both parts "Table 1", disclosing the minimum inhibitory concentrations (MIC) of methylparaben and propylparaben in aqueous solutions. The tables provide the antimicrobial activity of the two preservative agents against various microorganisms, including bacteria and fungi. As remarked by the appellant, the MICs in respect of some specific microorganisms are sometimes higher than 2 mg/ml. In the appellant's opinion, the skilled person considering these data would conclude that the ranges of concentrations reported for ophthalmic and oral solution in sections 7 of D3 (see point 1.3.1 above) may not be sufficient for an effective protection against microbial contamination.

1.3.4 The Board does not share the appellant's view for the following reasons.

Document D3 indicates that the antimicrobial activity of parabens can be improved by using them in combination since synergistic effects occur (see pages 341 and 450). The activity can be enhanced also by the addition of propylene glycol, a substance which is present also in most of the compositions exemplified in the patent in suit. Other excipients reported to enhance the antimicrobial activity of parabens are phenylethyl alcohol and edetic acid. Finally, D3 indicates that the

preservative effect of the parabens is also affected by the pH.

Thus, D3 does not indicate that the parabens need necessarily to be used in concentrations equal to, or above, the MICs values reported in Table 1. As pointed out by the opposition division in its decision (point 4.2), the MICs are a measure of the antimicrobial properties of a substance which are determined under specific conditions. As such, they can be regarded as parameters that make possible an objective comparison of the antimicrobial activities of different preservative agents. No other meaning can be attributed to the MICs values.

The MICs values of parabens cannot be easily correlated to the overall antimicrobial properties of a composition comprising various substances in addition to parabens, because, as explained above, the antimicrobial properties of parabens can be enhanced in various ways, for instance by combining them and thereby obtaining a synergistic effect or by adding propylene glycol. Thus, whether a composition is sufficiently protected against microbial contamination depends on various factors such as the type of preservative agents used, their amounts and the presence of excipients such as propylene glycol. An adequate protection of a composition can therefore be obtained also using a paraben in a concentration below the MICs values reported in D3.

For these reasons, the Board considers that the skilled person reading document D3, would not see any inconsistency between the ranges of concentrations disclosed in sections 7 and the MICs data. Hence, he would have no reason for disregarding the information disclosed in sections 7 as to the usual concentration of

methylparaben and propylparaben in ophthalmic preparations and oral solutions.

1.3.5 As already discussed in point 1.2.2 above, document D3 also provides information concerning the safety of parabens. On pages 342 and 452 it is reported that parabens may cause hypersensitivity reactions and that they may be irritant to the skin, eyes and mucous membranes.

Hence, the skilled person concerned with the problem of improving the safety profile of the ophthalmic composition of example 5 of D1, would learn from D3 that the parabens may cause various adverse reactions. At the same time however, he would observe that the amount of parabens in the composition of D1 is much higher than the amount suggested in D3 for ophthalmic compositions. In the Board's opinion, this would prompt the skilled person to modify the composition of D1 by reducing the concentration of parabens according to the indications disclosed in sections 7 of D3, and verify whether the new composition has an improved safety profile but is still capable of resisting microbial contamination.

He would therefore arrive at the subject-matter of claim 1 without applying any inventive activity.

1.3.6 The appellant underlined in its submissions that the experimental data of the patent in suit and of D17 demonstrated the antimicrobial properties of the active ingredients of the composition of claim 1. These properties were neither disclosed nor suggested in the prior art.

The interpretation of these data was contested by the respondent with the argument that the compositions

tested contained additional antimicrobial agents, such as sodium acetate. It was therefore not possible to establish whether the antimicrobial activity of the composition was due to the active ingredients or to the additional antimicrobial agents.

In the Board's opinion, establishing whether, and possibly to what extent, cetirizine and the other active ingredients possess an antimicrobial effect, is not a decisive issue in the circumstances of the present case because this effect does not in any case translate into any inventive feature of claim 1.

Indeed, regardless of whether the active ingredients contribute or not to the overall antimicrobial effect of the compositions, the reduction of the amount of parabens, which represents the distinguishing feature over the closest prior art, is suggested by D3 for the reasons discussed above. Furthermore, D3 also suggests the possible advantages that can derive from a reduction of the concentration of parabens, namely an improvement of the safety profile of the composition.

Thus, the conclusion that the subject-matter of claim 1 is obvious in view of the combined teachings of D1 and D3 holds good even if it is acknowledged that the active ingredients possess antimicrobial properties and even if it is acknowledged that these properties were hitherto unobserved.

1.4 It follows from the above that the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary request 1

2. Inventive Step

2.1 Claim 1 of this request differs from claim 1 of the granted patent in that the active ingredient is limited to levocetirizine and the parabens are present as a mixture of methyl- and propylparaben in a ratio of 9:1 and in an amount comprised between 0.1 and 1.125 mg/ml (see point VII above).

2.2 As explained in paragraph [0015] of the patent, levocetirizine is the levorotatory enantiomer of cetirizine. Document D4 reports that both compounds possess antihistaminic activity (see abstract).

The opposition division considered in its decision that the use of levocetirizine instead of racemic cetirizine was obvious in view of D4 which indicates that the levorotatory enantiomer has more therapeutic activity than the racemic form.

This conclusion was not disputed by the appellant during the appeal proceedings. Nor did it submit any argument on inventive step based on the use of levocetirizine as active ingredient.

The Board sees no reason therefore to deviate from the conclusions of the opposition division. Hence, the limitation introduced in claim 1 with regard to the active ingredient does not provide any inventive contribution to the subject-matter of the claim.

2.3 As to the limitation concerning the composition of the parabens mixture and its total amount, the Board observes that also document D3 suggests using

methylparaben together with propylparaben in a ratio of 9:1 (page 340, first paragraph of right column). Furthermore, as already observed in respect of the main request, the ranges of concentration disclosed in sections 7 of D3 for ophthalmic and oral solutions allow combining methyl- and propylparaben in a ratio 9:1 and in a total amount which is comprised in the range of concentration recited in claim 1 in suit.

It follows from the above that also the features introduced in claim 1 concerning the parabens mixture do not provide any inventive contribution to the subject-matter of the claim.

Accordingly, the subject-matter of auxiliary request 1 does not meet the requirements of inventive step.

Auxiliary request 2

3. Inventive step

3.1 Claim 1 of this request is based on claim 1 of auxiliary request 1 and it differs therefrom in that the lowest concentration of parabens is set at 0.1 mg/ml instead of 0.01 mg/ml.

This modification has no effect on the validity of the considerations set out in point 2 above, in respect of auxiliary request 1.

Thus, auxiliary request 2 fails to comply with Article 56 EPC.

Auxiliary requests 3 and 4

4. Admittance into the appeal proceedings

4.1 Auxiliary requests 3 and 4 were submitted on 11 February 2016, i.e one month before the oral proceedings.

According to Article 13(1) RPBA, the discretion of the Board to admit amendments to a party's case is to be exercised in view of *inter alia* the complexity of the new subject-matter, the current state of the proceedings and the need for procedural economy. Furthermore, Article 13(3) RPBA provides that amendments made after oral proceedings have been arranged, as in the present case, shall not be admitted if they raise issues which the Board or the other parties cannot be expected to deal with without adjournment of oral proceedings.

4.2 The subject-matter of claim 1 of auxiliary requests 3 and 4 has been limited to compositions in the form of an oral solution.

The appellant observed that compositions in the form of oral solutions were explicitly foreseen in claim 7 of the patent.

The Board notes in this respect that in the claim referred to by the appellant, also other pharmaceutical forms, such as eye drops, were explicitly mentioned. Auxiliary requests 3 and 4 are therefore the first requests which are limited to oral solutions.

4.3 Before the filing of these requests, the appellant never submitted arguments on inventive step based on the relevance of providing compositions in the form of oral

solutions. Indeed, as is evident from the considerations set out in points 1 to 3 above, the pharmaceutical form of the composition did not play any particular role in the assessment of inventive step.

In the Board's view, the filing of new requests which are focused on a technical feature which was never regarded as a critical aspect of the claimed subject-matter, amounts to a substantial shift of the focus of the invention. Admitting these requests would require a different approach to inventive step, possibly starting from a different prior art in view of the fact that D1 relates only to ophthalmic and nasal compositions. That goes against the requirement of procedural economy and could potentially open new issues which the Board and the respondent cannot reasonably be expected to deal with without adjournment of the oral proceedings.

Thus, the Board, in the exercise of its discretion under Article 13(1) and (3) RPBA, decides not to admit auxiliary Requests 3 and 4 into the appeal proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated

Tracking Information

EP/ECT/PCT No.:	**05758582.0**
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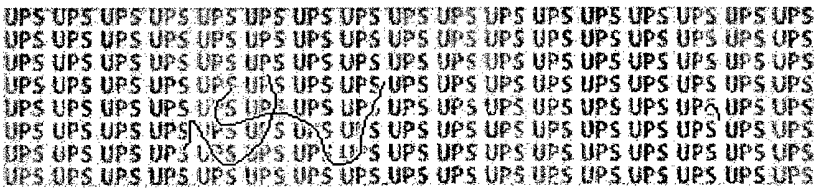
Deposited at:	RECEPTION
Signed by (Name):	SCHLUETTER
Signature:	

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80801 München
ALLEMAGNE

Boards of Appeal

The Registry

Name: S. Fabiani

Tel.: 089 / 2399 - 3371

Date: 19.04.16

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
P30048-EPOP WB APPR	05758582.0 / 1768649
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
UCB FARCHIM S.A.	

Appeal number: T0371/12-3.3.07

EPA/EPO/OEB Formblatt/Form/Formulaire: 3032

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Récépissé du document spécifié ci-dessus

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Sonera Sähköpostifaksi

To: FAX EPO Munich
Fax: *498923994465

From:Boco IP Oy Ab
Date: 26.4.2016

Subject:Our ref: B0199PI-EP / mp, application no 05758582.0

Dear Sirs,

Please find attached the signed EPA form 3936

Yours faithfully,

Merja Pynnönen
IP Specialist,
administration and formalities
Boco IP Oy Ab
Direct: +358 9 6866 8474
www.BocoIP.com

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26 -04- 2016

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Itämerenkatu 5
00180 Helsinki
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Boards of Appeal

The Registry

Name: S. Fabiani

Tel.: 089 / 2399 - 3371

Date: 19.04.16

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
B0199PI-EP OPPO01	05758582.0 / 1768649
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26. April 2016

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Termination of opposition proceedings of patent no. 05758582.0 - 1460/ 1768649 with revocation of the patent 27.04.16

I. Findings

1. The opposition proceedings are terminated for the following reason:
   The patent was revoked

   REVO 22.12.11 ✓

   The time limit pursuant to Article 108 EPC has expired.
   No appeal or application pursuant to Article 122 EPC has been filed.

   REVO 2 and DEAD coded and Form 2365 despatched. ✓

2. Fees situation:

OPPO04	010	00723487	23.06.10	EUR	705,00
NOAP04	011	00574472	20.02.12	EUR	1 180,00
NOAP04	011	00573526	20.02.12	EUR	1 180,00
NOAP04	011	00057633	21.02.12	EUR	1 180,00-
CLMS(2)	015	00307392	16.04.07	EUR	90,00

   Checked for correct fee payment. Refund(s) made on . . . . . .

3. Any models still to hand were returned on . . . . . .

4. Enter "DEAD" and dispose of paper file

27.04.2016 Ullrich, Chantal
Date Formalities officer