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(54) Title: NOVEL COMBINATION

(57) Abstract: The present invention relates to a combination of ciclesonide with olopatadine.



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Novel Combination

Technical Field of the Invention

The present invention is related to a novel combination of ciclesonide and olopatadine for use in drug therapy in particular in the treatment of allergic rhinitis. In particular the novel combination is administered in the form of an aqueous pharmaceutical composition that contains ciclesonide and olopatadine and having an osmotic pressure of less than 290 mOsm.

Background Art

Allergic rhinitis is a common disorder and the number of patients is steadily increasing. The disease is caused by ambient airborne allergens, which cause an allergic inflammation within the nasal mucosa and it is often accompanied by conjunctivitis. According to the allergen, the allergic rhinitis is subdivided into seasonal allergic rhinitis (allergens like grass pollen, cedar pollen) and perennial allergic rhinitis (indoor allergens like mould, allergens from animals and house dust mite). Allergic rhinitis has a great impact on the quality of life. The patients suffer from an itchy and running nose, nasal blockage, headache and fatigue. Allergic conjunctivitis is often linked to allergic rhinitis and requires co-treatment. The major symptoms of conjunctivitis are burning and itching eyes and lacrimation. The basic mechanisms involved in this disease are the same as for allergic rhinitis.

The current treatment of allergic rhinitis is mainly focused on symptomatic relief. Oral and to a lesser extent topical antihistamines are the most widely used remedies. Oral antihistamines alleviate the histamine driven symptoms only. Allergen contact causes degranulation of mucosal mast cells and histamine is released. Histamine is responsible for the itching and sneezing and the increase in nasal secretion. Antihistamines block the binding of histamine to the histamine-H1-receptor and thereof the histamine mediated symptoms. Beside this obvious pathway, the allergens cause an eosinophilic inflammation of the nasal mucosa, which is mainly responsible for symptoms like nasal hyperreactivity, nasal blockage and the fear of the so called change of floors, which means that an untreated allergic rhinitis can develop to sinusitis and asthma bronchiale.

Treatment with glucocorticoids is currently the only one therapy, which targets the underlying allergic inflammation. To avoid systemic side effects typically for glucocorticoids, e.g. immunosuppression, reduced protein synthesis, impaired growth in children, topical treatment with glucocorticoids is the preferred way of administration.

A disadvantage of nasal steroids is the slow onset of action and the need for continuous treatment. It takes 4-6 days of continuous treatment before a symptom relief can be observed. Therefore, the pa-

tients are recommended to begin to take glucocorticoids before the pollen season starts. The slow onset of action, the need of consequent treatment and the fear of steroid induced side effects have a negative impact on the use of intranasal steroids and patient's compliance.

Other medications available for the treatment are just for symptomatic relief, for example intranasal muscarinic antagonists (ipratropium to reduce nasal secretion), adrenoreceptor agonists (xylometazoline to reduce nasal congestion).

WO 97/01337 describes a nasal spray or nasal drops formulation comprising beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide in combination with the antihistamines levocabastine, azelastine or azatadine and sterile water.

WO 97/46243 is related to a nasal spray containing an intranasal steroid and an antihistamine.

WO 98/48839 is related to topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuraminidase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent.

WO 01/22955 is related to a novel combination of loteprednol, a so-called soft steroid with antihistamines.

WO 03/049770 discloses compositions and methods for treating rhinitis with H1 antagonists/antiallergics and safe steroids. Inter alia olopatadine is mentioned as useful H1 antagonist/antiallergic.

WO 2004/043470 is related to compositions and methods for treating rhinitis with certain combinations of antiallergic agents and steroids. The anti-allergy agent is selected to be emedastine or olopatadine. The steroid is selected to be fluticasone, mometasone, budesonide or beclomethasone.

US 5164194 is related to nasal formulations for azelastine.

US 2003/0055102 is related to topical formulations of olopatadine for treatment of allergic or inflammatory disorders of the eye and nose.

WO 2004/019955 is related to a combination of ciclesonide with antihistamines.

Detailed Description of the invention

Surprisingly it has now been found that combined administration of ciclesonide and olopatadine results in a very effective and safe treatment of symptoms accompanied with allergic rhinitis and/or allergic conjunctivitis. In particular by combined administration of the ciclesonide and the antihistamine as hypotonic aqueous pharmaceutical formulation a rapid onset of action and quick symptom relief is observed without the fear of glucocorticoid like side effects. By administering such hypotonic aqueous pharmaceutical composition according to the invention to the nasal mucosa the active ingredients rapidly enter the nasal mucosa and have a very long retention time. Therefore very low doses of ciclesonide and a once-daily, maximal twice-daily treatment is necessary to achieve an effective treatment.

In one aspect the present invention therefore relates to the combined administration of ciclesonide and olopatadine for the treatment of allergic rhinitis and/or allergic conjunctivitis. Another subject of the invention therefore is a pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis comprising as active ingredients a combination of olopatadine or a pharmaceutically acceptable salt and/or a solvate or physiologically functional derivative thereof and ciclesonide, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof and a pharmaceutically acceptable carrier and/or one or more excipients.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same pharmaceutical formulation (hereinafter also referred to as fixed combination) or in different pharmaceutical formulations (hereinafter also referred to as free combination) or sequentially in any order. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination. As an example, both drugs may be provided separately as oral formulations, or one may be an oral preparation and the other an inhalant, or both may be provided in a form suitable for application to mucosa (nasal application). Administration may be at the same time. Or they may be administered either close in time or remotely, such as where one drug is administered in the morning and the second drug is administered in the evening.

Accordingly, the present invention also provides a method for the prophylaxis or treatment of allergic rhinitis and/or allergic conjunctivitis in a mammal, such as a human, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising olopatadine or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and ciclesonide or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier and/or one or more excipients. In a preferred aspect, there is provided such a method, which comprises administration of a therapeutically effective amount of a combination comprising olopatadine and ciclesonide, and a pharmaceutically acceptable carrier and/or one or more excipients.

The formulations include those suitable for oral, parenteral including subcutaneous, intradermal, intramuscular, intravenous and intraarticular, intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular administration) although the most suitable route may depend upon for example the condition and disorder of the recipient. In a preferred embodiment according to the invention the formulation is suitable for topical administration. In a preferred embodiment the formulation according to the invention is a formulation suitable for application to mucosa in the case of treatment of allergic rhinitis. In the case of treatment of allergic conjunctivitis a preferred formulation is a formulation suitable for conjunctival administration (application to the conjunctival sac). The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier, which constitutes one or more accessory ingredients/excipients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for nasal administration also include powder compositions, which can contain reducing sugars such as lactose as carriers, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e. g. 1, 1, 1, 2-tetrafluoroethane, 1, 1, 1, 2, 3, 3, 3-heptafluoropropane, carbon dioxide or other suitable gas. A class of propellants, which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrofluorocarbons and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11495, W091/14422, W093/11743, and EP-0553298. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications propose, for example, the addition of one or more of excipients such as polar cosolvents or wetting agents (e.g. alcohols such as ethanol), alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids such as oleic acid, polyethoxylates etc.) or bulking agents such as a sugar (see for example WO02/30394) and amino acids and vehicles such as cromoglicic acid and/or nedocromil which are contained at concentrations, which are not therapeutically and prophylactically active (see WO00/07567). For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a mean particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 0.7 to 10 microns, for example, 1 to 5 microns.

A suitable formulation for ciclesonide based on hydrofluorocarbon propellants is for example known from U.S. Patent 6,120,752. U.S. Patent 6,120,752 discloses and claims, inter alia, pharmaceutical

compositions comprising a therapeutically effective amount of ciclesonide or a related compound and a hydrofluorocarbon propellant, preferably selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof, and cosolvent, preferably ethanol, in an amount effective to solubilize ciclesonide and optionally a surfactant.

In one embodiment the present invention therefore also relates to pharmaceutical compositions for treatment of allergic rhinitis, which comprise a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and mixtures thereof. The pharmaceutical compositions may additionally comprise a surfactant and/or ethanol. The pharmaceutical composition preferably is for nasal administration.

Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant, such as plastic or plastic-coated glass bottle or a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. Canisters may be coated with a fluorocarbon polymer as described in WO 96/32150, for example, a co-polymer of polyethersulphone (PES) and polytetrafluoroethylene (PTFE). Another polymer for coating that may be contemplated is FEP (fluorinated ethylene propylene).

The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Thermoplastic elastomer valves as described in W092/11190 and valves containing EPDM rubber as described in W095/02650 may be suitable. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (eg. DF10, DF30, DF60), Bepak pic, UK (eg. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (eg. Spraymiser).

Valve seals, especially the gasket seal and also the seals around the metering chamber, can be manufactured of a material, which is inert to and resists extraction into the contents of the formulation, especially when the contents include ethanol.

Valve materials, especially the material of manufacture of the metering chamber, can be manufactured of a material which is inert to and resists distortion by contents of the formulation, especially when the contents include ethanol. Particularly suitable materials for use in manufacture of the metering chamber include polyesters eg polybutyleneterephthalate (PBT) and acetals, especially PBT.

Materials of manufacture of the metering chamber and/or the valve stem may desirably be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition.

Valves, which are entirely or substantially composed of metal components (eg Spraymiser, 3M-Neotechnic), are especially preferred for use according to the invention.

For nasal administration the medical product based on aerosol formulations preferably has a nasal actuator.

In a preferred embodiment the present invention relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa, comprising as active ingredients a combination of olopatadine and ciclesonide.

The present invention further relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa comprising as active ingredients a combination of olopatadine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm. Preferably the osmotic pressure is 150 mOsm or lower, more preferably 75 mOsm or lower, more preferably 50 mOsm or lower.

According to the present invention it is not particularly required to add a substance for controlling osmotic pressure (osmotic pressure-controlling agent) but when it is added any substance can be used. In the present invention, a substance for controlling osmotic pressure (osmotic pressure controlling agent) can be added to control osmotic pressure, specific examples of which include salts such as sodium chloride and water-soluble sugars such as glucose, with glucose being a particularly preferable example.

In a preferred embodiment the pharmaceutical composition is a pharmaceutical composition as described for ciclesonide in WO 01/28562 or WO 01/28563.

Thus in one aspect the present invention relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa, comprising as active ingredients a combination of olopatadine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm.

The water-insoluble or water-low soluble substance may be any substance, and preferred examples include celluloses, more preferably crystalline celluloses and particularly preferred microcrystalline celluloses. According to the present invention, the concentration of water-insoluble and/or water-low soluble substance present in form of solid particles in an aqueous medium is preferably 0.3% w/w and above, and particularly preferably 0.5% w/w to 5% w/w, relative to the total amount of the composition.

In addition, an aqueous polymer substance can also be added in the present pharmaceutical composition. Specific examples of such include polyvinylpyrrolidone, propylene glycol alginate, pectin, low methoxyl pectin, gua gum, gum Arabic, carrageenan, methyl cellulose, carboxymethyl cellulose sodium, xanthan gum hydroxypropylmethyl cellulose and hydroxypropyl cellulose, while particularly preferable examples include carboxymethyl cellulose sodium, polyethylene glycol and hydroxypropyl cellulose. Carboxymethyl cellulose sodium blended with microcrystalline cellulose, is an example of a

combination of these water-soluble substance and water-insoluble substance that can be used in the present invention. Furthermore, in the case of adding these water-soluble polymer substances, the concentration of said substance is preferably 1% w/w to 30 % w/w relative to the water-insoluble substance and/or water-low soluble substance.

In a preferred embodiment of the invention hydroxypropylmethyl cellulose is contained in the pharmaceutical compositions according to the invention. The hydroxypropylmethyl cellulose may be any grade, a specific example is hydroxypropylmethyl cellulose 2910. Although said hydroxypropylmethyl cellulose may be present at any concentration, its concentration is preferably from 0.001 % w/w to 30 % w/w, particularly preferably from 0.01 % w/w to 5 % w/w, more particularly preferably from 0.01 % w/w to 1 % w/w, and most preferably from 0.01 % w/w to 0.5 % w/w, relative to the total amount of composition.

A surfactant and/or wetting agent, although not essential in the present invention, can be added, specific examples of which include Polysorbate 80, glycerin monosterate, polyoxyl stearate, lauro-macrogol, sorbitan oleate and sucrose fatty acid esters.

An effective amount of ciclesonide and olopatadine used in the present invention can be determined according to the type and degree of the respective disease, as well as the age and body weight of the patient, and so forth. Preferably the pharmaceutical composition according to the invention is administered as one to four sprays per nostril once or twice a day. The dose of ciclesonide per actuation is expediently from 10 µg to 400 µg, preferably 20 µg to 200 µg. The dose of olopatadine is from 50 µg to 1000 µg, preferably 100 µg to 800 µg per actuation.

Ciclesonide (hereinafter also referred to as active ingredient) is the INN for a compound with the chemical name [11β,16α(R)]-16,17-[(Cyclohexylmethylen)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion. Ciclesonide and its preparation are disclosed in DE 4129535. Ciclesonide as used herein also includes, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide (e.g. [11β,16α(S)]-16,17-[(Cyclohexylmethylen)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1,4-dien-3,20-dion) in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof. By the term "physiologically functional derivative" is meant a chemical derivative of ciclesonide having the same physiological function as ciclesonide, for example, by being convertible in the body thereto or by being an active metabolite of ciclesonide. Physiological functional derivatives of ciclesonide which may be mentioned in connection with the invention are for example the 21-hydroxy derivative of ciclesonide with the chemical name 16α,17-(22R,S)-Cyclohexylmethylenedioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion, 16α,17-(22S)-Cyclohexylmethylenedioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion and in particular 16α,17-(22R)-Cyclohexylmethylenedioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion. This compound and its preparation are disclosed in WO 9422899.

Preferably ciclesonide is dispersed in the aqueous medium in form of solid particles.

The concentration of ciclesonide of the present invention is preferably from 0.01 % w/w to 1 % w/w, and particularly preferably from 0.02 w/w to 0.5 % w/w, relative to the total amount of the composition.

Although the ciclesonide particles that can be used in the present invention may be of any size, they are preferably within the range of 10 nm to 100 μ m, and particularly preferably within the range of 100 nm to 10 μ m.

Olopatadine has the chemical name (Z)-11-(3-dimethylaminopropylidene)-6,11-dihydro-dibenz[b,e]oxepine-2-acetic acid and is disclosed in US 5116863. In accordance with the present invention olopatadine may also be present in form of a pharmaceutically acceptable salt and/or a solvate. Suitable pharmacologically acceptable salts of olopatadine are salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom. By the term "physiologically functional derivative" is meant a chemical derivative of olopatadine having the same physiological function as olopatadine, for example, by being convertible in the body thereto or by being an active metabolite of olopatadine. In a preferred embodiment of the present invention olopatadine is employed as hydrochloride salt of (Z)-11-(3-dimethylaminopropylidene)-6, 11-dihydrodibenz[b,e]oxepine-2-acetic acid.

Preferably olopatadine will be dissolved in the pharmaceutical compositions according to the invention.

The concentration of olopatadine is preferably from 0.1 % w/w to 1.0 % w/w, and particularly preferably from 0.2 % w/w to 0.9 % w/w, relative to the total amount of the composition.

Any method for dispersing a water-insoluble substance and/or water-low soluble substance in an aqueous medium may be used for the production of the aqueous pharmaceutical composition according to the invention, a specific example of which is a method that uses a homomixer.

Known antiseptics, pH controlling agents, preservatives, buffers, colorants, smell corrigents and so forth may be added as necessary to the compositions of the present invention to improve its physical properties, stability, appearance or odor and so forth of the formulation.

Examples of antiseptics include benzalkonium chloride, examples of pH controlling agents include hydrochloric acid and sodium hydroxide, examples of preservatives include potassium sorbate, examples of buffers include phosphoric acid and its salt, examples of colorants include red dye no. 2, and examples of smell corrigents include menthol.

Due to the unique galenic formulation, ciclesonide rapidly enters the nasal mucosa and has a very long retention time. Therefore, very low doses of ciclesonide and the once daily, maximal twice-daily treatment is necessary to achieve an effective treatment. A low dose of ciclesonide in a hypotonic watery suspension in combination with olopatadine results in a very effective and safe treatment of all symptoms accompanied with allergic rhinitis. A clear advantage of this combination is the rapid onset of action and quick symptom relief without the fear of glucocorticoid like side effects.

In another embodiment the present invention relates to a combination of ciclesonide with olopatadine and in which ciclesonide is applied in a pharmaceutical composition as described for ciclesonide in WO 01/28562 or WO 01/28563 and olopatadine is applied in a pharmaceutical formulation according to US 2003/0055102.

The invention furthermore relates to a medical product comprising, together,

- (i) ciclesonide; and
- (ii) olopatadine as combined preparation for administration to the nasal mucosa.

In this case the medical product preferably is for the treatment of allergic rhinitis.

The invention also relates to a medical product comprising; together

- (i) ciclesonide; and
- (ii) olopatadine as combined preparation for conjunctival administration (application to the conjunctival sac).

In this case the medical product preferably is for the treatment of allergic conjunctivitis.

When given to the nasal mucosa the formulation according to the present invention may be filled into plastic squeeze bottles or plastic or glass bottles, which are fitted with a metering atomising pump and a nasal adapter or with a suitable dropper. When given to the eye the formulation according to the present invention may be filled into plastic squeeze bottles or plastic or glass bottles, which are fitted with a suitable dropper.

Examples

Ciclesonide aqueous pharmaceutical compositions containing the components indicated below are prepared by processing with a homomixer. Homomixer processing is performed, e.g., at 6000 rpm for 30 minutes.

Example 1: Combination of Ciclesonide and Olopatadine Hydrochloride

Ciclesonide:	0.05% (w/w)
Olopatadine hydrochloride	0.44% (w/w)
Microcrystalline cellulose and carboxymethyl cellulose sodium	1.70% (w/w)
Hydroxypropylmethyl cellulose 2910	0.10% (w/w)
HCl	q.s. pH 3.5 – 6.5
Purified water	q.s. 100

Each 100 mg spray delivered by a nasal applicator delivers 50 µg of ciclesonide and 444 µg of olopatadine hydrochloride (equivalent to 400 µg olopatadine).

Patent Claims

1. Pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis comprising as active ingredients a combination of olopatadine, a pharmaceutically acceptable salt of olopatadine, a solvate or physiologically functional derivative thereof and ciclesonide, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide optionally in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof and a pharmaceutically acceptable carrier and/or one or more excipients.
2. Pharmaceutical composition according to claim 1 for the treatment of allergic rhinitis for application to the mucosa, which is an aqueous pharmaceutical composition comprising the active ingredients together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm.
3. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 150 mOsm or less.
4. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 75 mOsm or less.
5. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 50 mOsm or less.
6. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising an osmotic pressure-controlling agent.
7. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said water-insoluble and/or water-low soluble substance is a cellulose.
8. The pharmaceutical composition for application to the mucosa according to claim 7, wherein said cellulose is microcrystalline cellulose.
9. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said one or more water-insoluble and/or water-low soluble substance is present as solid particles in an aqueous medium.
10. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising a water-soluble polymer substance.

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11. Pharmaceutical composition for application to the mucosa according to claim 10, wherein a combination of said water-insoluble substance and water-soluble polymer is present which is micro-crystalline cellulose and carboxymethyl cellulose sodium.
12. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising a surfactant and/or a wetting agent.
13. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said mucosa is nasal mucosa.
14. Pharmaceutical composition according to claim 1 for treatment of allergic rhinitis comprising a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and mixtures thereof.
15. Pharmaceutical composition according to claim 14, additionally comprising a surfactant.
16. Pharmaceutical composition according to claim 14, additionally comprising a polar cosolvent.
17. Pharmaceutical composition according to claim 16, which polar cosolvent is ethanol.
18. Pharmaceutical composition according to claims 1 through 17, wherein ciclesonide is a compound selected from the group of [11 β ,16 α (R)]-16,17-[(Cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion, [11 β ,16 α (S)]-16,17-[(Cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion, [11 β ,16 α (R,S)]-16,17-[(Cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion, 16 α ,17-(22R)-Cyclohexylmethylenedioxy-11 β ,21-dihydroxypregna-1,4-dien-3,20-dion, 16 α ,17-(22S)-Cyclohexylmethylenedioxy-11 β ,21-dihydroxypregna-1,4-dien-3,20-dion, 16 α ,17-(22R,S)-Cyclohexylmethylenedioxy-11 β ,21-dihydroxypregna-1,4-dien-3,20-dion and mixtures thereof.
19. Pharmaceutical composition according to claim 18, wherein the compound is [11 β ,16 α (R)]-16,17-[(Cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion.
20. Pharmaceutical composition according to claims 1 through 13, wherein olopatadine is present as olopatadine hydrochloride.
21. Pharmaceutical composition according to claims 1 through 13, comprising a combination of olopatadine hydrochloride with ciclesonide.

22. Use of ciclesonide in combination with olopatadine hydrochloride for the manufacture of a pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis.
23. Use of ciclesonide and olopatadine in the manufacture of a combined preparation for administration to the nasal mucosa for the treatment of allergic rhinitis.
24. Use of ciclesonide and olopatadine in the manufacture of a combined preparation for conjunctival administration for the treatment of allergic conjunctivitis.
25. Method for the prophylaxis or treatment of allergic rhinitis and/or allergic conjunctivitis in a mammal, such as a human, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising olopatadine, a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof and ciclesonide or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutical acceptable carrier and/or one or more excipients.
26. Method according to claim 25, wherein a composition according to claim 14 is administered by nasal inhalation for the treatment of allergic rhinitis.
27. Medical product comprising, together,
 - (i) ciclesonide; and
 - (ii) olopatadine as combined preparation for administration to the nasal mucosa.
28. Medical product comprising, together,
 - (i) ciclesonide; and
 - (ii) olopatadine as combined preparation for conjunctival administration.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/060682

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/335 A61K31/58 A61K47/38 A61K47/30 A61K47/10
 A61K9/14 A61K9/12 A61P37/08 A61P27/14

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 A61P

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

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

EPO-Internal, PAJ, WPI Data, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/019955 A (ALTANA PHARMA AG; MARX, DEGENHARD; MUELLER, HELGERT) 11 March 2004 (2004-03-11) cited in the application page 1, paragraph 1 page 2, paragraph 9 - page 3, paragraphs 2,4 page 4, paragraphs 2-4,7 page 5, paragraphs 1,5 - page 6, paragraphs 2,5	1-28
Y	EP 1 467 762 B (ALCON, INC) 20 October 2004 (2004-10-20) cited in the application page 2, paragraphs 1,3,5-7,11 ----- -/--	1-28

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

& document member of the same patent family

Date of the actual completion of the international search

27 June 2006

Date of mailing of the international search report

06/07/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060682

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/35963 A (ALCON UNIVERSAL LTD; YANNI, JOHN, M) 25 May 2001 (2001-05-25) page 1, lines 5-8 page 2, lines 3-5,16-21,23-26,28-32 -----	1-28
Y	WO 03/002093 A (ALCON, INC; CASTILLO, ERNESTO, J; HAN, WESLEY, WEHSIN; ZHANG, HUIXIANG) 9 January 2003 (2003-01-09) page 1, lines 9-12 page 2, lines 17-24 page 4, lines 10-13 page 6, lines 27-30 -----	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/060682

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/060682

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