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(54) **COMBINATION OF AZELASTINE AND FLUTICASONE**
KOMBINATION VON AZELASTINE UND FLUTICASONE
ASSOCIATION D'AZELASTINE ET DE FLUTICASONE

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Description

5 [0001] The present invention relates to pharmaceutical products according to claim 20 and formulations according to claim 1. More particularly the present invention relates to said pharmaceutical products and formulations useful for preventing or minimising allergic reactions. More particularly, but not exclusively, the present invention relates to said pharmaceutical products and formulations for nasal and ocular use.

[0002] Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

10 [0003] It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

[0004] It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosporine. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

[0005] It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable formulation, which is tolerated in situ, without significantly disrupting the potency of the constituent pharmaceuticals.

20 [0006] We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably in salt form and even more preferably in the form of the hydrochloride salt, can advantageously be combined with the steroid fluticasone, or a pharmaceutically acceptable ester thereof, to provide a stable, very effective combination product or formulation preferably for nasal or ocular treatment. The combination can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and the anti-inflammatory (and/or other) properties of the steroid fluticasone, without any significant interference between the two, or adverse reaction in situ.

25 [0007] In one aspect the invention provides a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof.

[0008] The term "physiologically functional derivative" as used herein denotes a chemical derivative of any of the specific therapeutic agents described herein having the same or similar physiological function as the free base therapeutic agent and, for example, being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

[0009] The preferred forms of formulations of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

35 [0010] Preferred embodiments of the invention can comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with Fluticasone, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of fluticasone or ester thereof should be released per individual actuation.

40 [0011] The formulations preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl phydroxybenzoates, chlorhexidine (for example in the form of the acetate or gluconate) and phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide" benzyltrimethyl-2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

50 [0012] The total amount of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0.10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

[0013] In the case of preservatives, the following amounts of individual substances can, for example, be used: thimerosal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimerosal the amount of thimerosal is, for example =0.002 to 0.005%); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1 %.

[0014] The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and

benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

[0015] In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

[0016] Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides and polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component

[0017] It is optionally possible to use additional isotonicization agents. Isotonicization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol and NaCl.

[0018] The isotonicization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

[0019] In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose 1H₂O 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

[0020] Moreover, it is possible to add thickening agents to solutions according to the present invention to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

[0021] Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

[0022] In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

[0023] In the event of the use of Avicel RC 591 or CL11, 0.65-3.0% by weight of the formulation, for example, is used for the purpose.

[0024] It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

[0025] The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

[0026] In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

[0027] For the nasal application, a solution or suspension can preferably be used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

[0028] Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant. The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, and HFC 227a can also be used, and are preferred for environmental reasons. The pressure packing has a dosage or metering valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

[0029] In the case of application as an aerosol, it is also possible to use a conventional adapter.

[0030] Particularly preferred embodiments of the present invention are hereinafter described and it will of course be appreciated that any of the previous description of suitable ingredients and formulation characteristics can also be applicable to the following products and formulations as provided by the present invention.

[0031] It will be appreciated, therefore, that the present invention further provides a pharmaceutical product comprising

(i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) the steroid fluticasone, or a pharmaceutically acceptable ester thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

[0032] It will also be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

[0033] Suitable propellants for use in pharmaceutical products of formulations as provided by the present invention include 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), or a combination of both, or mono-fluoro trichloromethane and dichloro difluoromethane, in particular 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), with HFA 134a being preferred.

[0034] A pharmaceutical aerosol formulation according to the present invention preferably further comprises a polar cosolvent such as C₂₋₆ aliphatic alcohols and polyols, for example ethanol, isopropanol and propylene glycol, with ethanol often being preferred. Preferably, the concentration of the cosolvent is in the range of about 2 to 10% by weight, typically up to about 5%, of the total formulation.

[0035] A pharmaceutical aerosol formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilise the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids. Suitable surfactants can include lecithin, oleic acid or sorbitan oleate.

[0036] A further preferred embodiment of the present invention can be where a formulation or product is provided in the form of insufflatable powder, where preferably the maximum particle size of the substance suitably does not exceed 10 μm. Azelastine or its salts and the fluticasone or its esters may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrans, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

[0037] In one embodiment, the therapeutic agents employed have a particle size of less than about 10 μm, preferably less than 5 μm.

[0038] It will be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different insufflation powder formulations, or separately or sequentially. If there is separate or sequential administration as discussed above, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

[0039] Dry insufflation powder formulations as provided by the present invention can be beneficial where it is required that therapeutic agents as employed according to the present invention are retained in the nasal cavity, and systemic side effects can be minimised or eliminated. Furthermore, insufflation powder formulations as employed in the present invention can be beneficial whereby retention of azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, at the nasal mucosa is improved, and the bitter aftertaste associated with liquid antihistamine formulations significantly reduced, whilst also exhibiting the synergistic therapeutic effect associated with the azelastine/fluticasone combinations provided by the present invention. By providing a dry insufflation powder formulation of azelastine, together with fluticasone, having an average particle size of less than about 10 μm, the therapeutic agents can be restricted primarily to the desired target organ, the nasal mucosa.

[0040] A dry powder insufflation formulation according to the present invention can be administered by the use of an insufflator, which can produce a finely divided cloud of the dry powder. The insufflator preferably is provided with means to ensure administration of a substantially pre-determined amount of a formulation or product as provided by the present invention. The powder may be used directly with an insufflator which is provided with a bottle or container for the powder, or the powder may be filled into a capsule or cartridge, such as a gelatin capsule, or other single dose device adapted for administration. The insufflator preferably has means to open the capsule or other dose device.

[0041] Preferred combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention (in particular nasal sprays or drops, aerosol or insufflation products and formulations as described above) comprise any one of the following combinations.

[0042] Thus, in another aspect of the present invention, there is provided a pharmaceutical product comprising (i)

azelastine, or a pharmaceutically acceptable salt thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated. Suitably the esters can be selected from fluticasone propionate and fluticasone valerate.

5 **[0043]** Specific combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention comprise any one of the following combinations:

azelastine hydrochloride and fluticasone propionate; and
 azelastine hydrochloride and fluticasone valerate.

10 **[0044]** The pharmaceutical products herein described may be used in methods for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, the methods comprising administering a therapeutically effective amount of a pharmaceutical product substantially as hereinbefore described, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

15 **[0045]** The pharmaceutical formulations of the present invention may also be used in a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, the methods comprising administering a therapeutically effective amount of a pharmaceutical formulation substantially as hereinbefore described.

20 **[0046]** In another aspect of the present invention, there is provided the use, in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, of a pharmaceutical product, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

25 **[0047]** The pharmaceutical products substantially as hereinbefore described, may be prepared by a process which comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone, or a pharmaceutically acceptable ester thereof.

30 **[0048]** The pharmaceutical formulations substantially as hereinbefore described, may be prepared by a process which comprises admixing a pharmaceutically acceptable carrier or excipient with: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and (ii) fluticasone or a pharmaceutically acceptable ester thereof Preferably pharmaceutical formulations according to the present invention can comprise insufflation powder formulations, nasal sprays, nasal inhalation solutions or aerosols substantially as hereinbefore described.

35 **[0049]** The present invention is now illustrated by the following Examples, which do not limit the scope of the invention in any way. Examples 2, 6, 7 and 8 are comparative examples. In Examples where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art.

Example 1

40 **[0050]** Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

Sr. No	Ingredients	Quantity %w/v
1.	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%
4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

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