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54 **TITULO** COMBINACION DE AZELASTINA Y ESTEROIDES

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- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [ ] Poderes si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen descripción reivindicaciones dibujos)
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- [x] Copia del examen preliminar efectuado por la IPEA
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- [ ] Otros

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FIGURA CARACTERÍSTICA

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(54) Title COMBINATION OF AZELASTINE AND STEROIDS

(57) Abstract A pharmaceutical product or formulation which comprises azelastine or a pharmaceutically acceptable salt solvate or physiologically functional derivative thereof and a steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof preferably the product or formulation being in a form suitable for nasal or ocular administration

COMBINATION OF AZELASTINE AND STEROIDS

The present invention relates to pharmaceutical products and formulations More particularly the present invention relates to pharmaceutical products and formulations useful for preventing or minimising allergic reactions More particularly but not exclusively, the present invention relates to pharmaceutical products and formulations for nasal and ocular use

Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms

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

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 ciclesonide Corticosteroids known for ocular anti inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate for example

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

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 a steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative 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 without any significant interference between the two or adverse reaction in situ.

In one aspect the invention provides a pharmaceutical formulation comprising azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid preferably a corticosteroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, the formulation preferably being in a form suitable for administration nasally or ocularly

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

The preferred forms of formulations of the invention are nasal drops eye drops nasal sprays nasal inhalation solutions or aerosols or insufflation powders

Preferred embodiments of the invention can comprise stable aqueous solutions of azelastine or one or more of its salts in combination with steroids which may be beclomethasone mometasone fluticasone budesonide or ciclesonide, 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 the steroid should be released per individual actuation.

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 p-hydroxybenzoates 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", benzyldimethyl-[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'

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.

In the case of preservatives the following amounts of individual substances can, for example be used thimero sal 0 002-0 02% benzalkonium chloride 0 002 to 0 02% (in combination with thimero sal the amount of thimero sal 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%

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%

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.

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.

It is optionally possible to use additional isotonization agents Isotonization agents which may for example be used are saccharose glucose glycerine, sorbitol, 1,2 propylene

glycol and NaCl

The isotonization 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

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example Glucose $1H_2O$ 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)

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.

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

In the event of the use of hydroxypropyl cellulose 0 1% by weight of the formulation, for example, is used for this purpose.

In the event of the use of Avicel RC 591 or CLll, 0 65-3 0% by weight of the formulation for example is used for the purpose

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

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

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)

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

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

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

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

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) at least one steroid 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 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.

The present invention also provides an aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and (ii) at least one steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a propellant.

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.

Suitable prppellants 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

A pharmaceutical aerosol formulation according to the present invention preferably further comprises a polar cosolvent such as C_{2-6} 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

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

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 10μm. Azelastine or its salts and the steroid 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 dextrins, 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.

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

The use of insufflation powders can represent a preferred embodiment of the present invention and there is provided by the present invention a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, 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.

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.

The present invention also provides an insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

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 / steroid combinations provided by the present invention. By providing a dry insufflation powder formulation of azelastine together with a steroid 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.

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.

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.

The present invention further provides therefore a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt thereof and (ii) at least one steroid selected from the group consisting of beclomethasone fluticasone mometasone and pharmaceutically acceptable esters 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 beclomethasone dipropionate fluticasone propionate fluticasone valerate mometasone furoate and mometasone furoate monohydrate.

The present invention also provides a pharmaceutical formulation comprising (i) azelastine or a pharmaceutically acceptable salt thereof and (ii) at least one steroid selected from the group consisting of beclomethasone fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor Suitably the esters can be selected from beclomethasone dipropionate fluticasone propionate, fluticasone valerate mometasone furoate and mometasone furoate monohydrate

In the case of a nasal spray a particularly preferred formulation as provided by the present invention is a nasal spray comprising azelastine or a pharmaceutically acceptable salt thereof (preferably azelastine hydrochloride) together with mometasone either as the free base or in ester form, preferably as mometasone furoate

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 beclomethasone dipropionate

azelastine hydrochloride and fluticasone propionate

azelastine hydrochloride and fluticasone valerate

azelastine hydrochloride and mometasone furoate and

azelastine hydrochloride and mometasone furoate monohydrate

There is also provided by the present invention 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 which method comprises administration of 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

The present invention also provides 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 which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation substantially as hereinbefore described

There is also provided by the present invention for 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

a pharmaceutical product as a combined preparation for simultaneous separate or sequential use in the treatment of such conditions

There is further provided by the present invention, therefore, a process of preparing a pharmaceutical product substantially as hereinbefore described which process 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) at least one steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof

The present invention also provides a process of preparing a pharmaceutical formulation substantially as hereinbefore described, which process comprises admixing a pharmaceutically acceptable carrier or excipient with (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative 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

The present invention is now illustrated by the following Examples which do not limit the scope of the invention in any way 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

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	

Example 2

Dosage aerosol giving off 0 5 mg of azelastine hydrochloride and 50 micrograms of beclomethasone dipropionate freon solvate per stroke

About 8 0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about -55 degree C in an appropriate cooling vessel A mixture of 0 086 kg of pre-cooled sorbitantrioleate and 0 8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at -55 degrees C 0 0688 kg of micronized azelastine hydrochloride 0 00688 kg of beclomethasone dipropionate freon solvate and 0 0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring The total weight of the suspension thereby obtained is made up to 9 547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1 2-dichlorotetrafluoroethane cooled to about -55 degree C

Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring It is then ready to be filled

Example 3

Nasal spray or nasal drops with Azelastine and steroid*

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0 10

	Fluticasone propionate	0 0357
	Glycerin	2 60
	Avicel RC 591	1 35
	Polysorbate 80	0 025
	Benzalkonium chloride	0 01
	Phenyl ethyl alcohol	0 25
	Purified water	q s

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg)

Example 4

Nasal spray or nasal drops with Azelastine and steroid*

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0 10
	Fluticasone valerate	0 0357
	Glycerin	2 60
	Avicel RC 591	1 20
	Polysorbate 80	0 030
	Benzalkonium chloride	0 01
	Phenyl ethyl alcohol	0 25
	Purified water	q s

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone valerate (50 mcg)

Example 5

Nasal spray or nasal drops with Azelastine and steroid*

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0 10
	Fluticasone propionate	0 0714
	Glycerin	2 60
	Avicel RC 581	1 35
	Polysorbate 80	0 025
	Benzalkonium chloride	0 01
	Phenyl ethyl alcohol	0.25
	Purified water	q s

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg)

Example 6

Nasal spray or nasal drops with Azelastine and steroid

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0 10
	Mometasone Furoate	0 05173
	Glycerin	2 30
	Disodium edetate	0 005
	Polysorbate 80	0 0125
	Avicel RC 581	1 35
	Benzalkonium chloride	0 01
	Citric acid monohydrate	0 20
	Disodium hydrogen phosphate	0 10

	dodecahydrate	
	Purified water	q s

Example 7

Nasal spray or nasal drops with Azelastine and steroid*

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0 10
	Mometasone Furoate monohydrate	0 05173
	Glycerin	2 60
	Avicel CL 611	2 295
	Polysorbate 80	0 0125
	Benzalkonium chloride	0 01
	Phenyl ethyl alcohol	0 25
	Purified water	q s

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Mometasone furoate (50 mcg)

Example 8

Nasal MDI with Azelastine and steroid

Sr No	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Mometasone Furoate monohydrate	50
	HFA 134a	q s
	Lecithin	0 1%
	Alcohol	(up to 5%)

Example 9

Nasal MDI with Azelastine and steroid

Sr No	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	50
	HFA 134a	q s
	Sorbitan trioleate	0 1%
	Alcohol	(up to 5%)

Example 10

Nasal MDI with Azelastine and steroid

Sr No	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	100
	HFA 134a	q s
	Oleic acid	0 1%

Example 11

Nasal MDI with Azelastine and steroid

Sr No	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone Valerate	50
	HFA 134a	q s
	Alcohol	(up to 5%)

Insufflatable powders containing Azelastine and Steroid

Example 12

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	50 mcg
	Lactose	q s (up to 25 mcg)

Example 13

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	100 mcg
	Mannitol	q s (up to 30 mcg)

Example 14

Sr No	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	250 mcg
	Lactose	q s (up to 30 mcg)

CLAIMS

1 A pharmaceutical formulation which comprises azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof preferably the formulation being in a form suitable for nasal or ocular administration

2 A pharmaceutical formulation according to claim 1 wherein said azelastine is present as azelastine hydrochloride

3 A formulation according to claim 1 or 2 wherein the steroid is beclomethasone or a pharmaceutically acceptable ester thereof, mometasone or a pharmaceutically acceptable ester thereof, fluticasone or a pharmaceutically acceptable ester thereof, budesonide or ciclesonide in any chiral form or mixture

4 A formulation according to claim 3 wherein the steroid is beclomethasone propionate mometasone furoate mometasone furoate monohydrate fluticasone propionate or fluticasone valerate

5 A formulation according to any of claims 1 to 4 which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation

6 A formulation according to any of claims 1 to 5 wherein the formulation has a particle size of less than about 10 μm, preferably less than 5 μm

7 A formulation according to any of claims 1 to 6 which is a suspension containing 0 0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine and from 0 5 to 1 5% (weight/weight of the formulation) of said steroid

8 A formulation according to claim 7 which contains from 0 001 to 1% (weight/weight of the formulation) azelastine or salt thereof, and from 0 5% to 1 5% (weight/weight of the

formulation) steroid

9 A formulation according to any of claims 1 to 8 which also contains a surfactant.

10 A formulation according to claim 9 wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11 A formulation according to claim 9 or 10 which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12 A formulation according to any of claims 1 to 11 which also contains an isotonic agent.

13 A formulation according to claim 12 wherein the isotonic agent comprises sodium chloride saccharose, glucose, glycerine sorbitol or 1 2-propylene glycol

14 A formulation according to any of claims 1 to 13 which also contains at least one of a buffer a preservative and a suspending or thickening agent.

15 A formulation according to claim 14 wherein said preservative is selected from edetic acid and its alkali salts lower alkyl p-hydroxybenzoates chlorhexidine phenyl mercury borate or benzoic acid or a salt, a quaternary ammonium compound or sorbic acid or a salt thereof

16 A formulation according to claim 14 or 15 wherein the suspending agent or thickening agent is selected from cellulose derivatives gelatin polyvinylpyrrolidone tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose) alginic acid polyvinyl alcohol, polyacrylic acid, or pectin.

17 A formulation according to any of claims 14 15 or 16 wherein the buffer comprises a citric acid-citrate buffer

18 A formulation according to any of claims 14 15 16 or 17 wherein the buffer maintains the pH of the aqueous phase at from 3 to 7 preferably 4 5 to about 6 5

19 A formulation according to any of claims 1 to 18 which is an aqueous suspension or solution

20 A formulation according to claim 19 which is in the form of an aerosol, an ointment, eye drops nasal drops a nasal spray or an inhalation solution.

21 A formulation according to claim 20 which is in the form of nasal drops or nasal spray

22 A formulation according to claim 20 which is in the form of an aerosol

23 A pressure packing having a dosage or metering valve which contains a formulation according to claim 22

24 A MDI which includes a pressure packing according to claim 23

25 A formulation according to any of claims 1 to 19 which is in the form of an insufflation powder

26 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) at least one steroid 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 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

27 An aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt solvate or physiologically functional derivative thereof, together with a propellant.

28 A pharmaceutical product comprising (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof provided as an insufflation powder 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.

29 An insufflation powder formulation comprising (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a pharmaceutically acceptable carrier or excipient therefor.

30 A pharmaceutical product comprising (i) azelastine or a pharmaceutically acceptable salt thereof and (ii) at least one steroid selected from the group consisting of beclomethasone fluticasone mometasone and pharmaceutically acceptable esters 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.

31 A pharmaceutical formulation comprising (i) azelastine or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

32 A nasal spray comprising azelastine or a pharmaceutically acceptable salt thereof, together with mometasone either as mometasone free base or as mometasone furoate, and a pharmaceutically acceptable carrier or excipient therefor

33 A pharmaceutical product comprising azelastine hydrochloride and beclomethasone dipropionate 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

34 A pharmaceutical formulation comprising azelastine hydrochloride and beclomethasone dipropionate together with a pharmaceutically acceptable carrier or excipient therefor

35 A pharmaceutical product comprising azelastine hydrochloride and fluticasone propionate, 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

36 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor

37 A pharmaceutical product comprising azelastine hydrochloride and fluticasone valerate 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

38 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor

39 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate 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

40 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate together with a pharmaceutically acceptable carrier or excipient therefor

41 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate monohydrate 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

42 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate monohydrate, together with a pharmaceutically acceptable carrier or excipient therefor

43 A pharmaceutical formulation substantially as herein described in any of the Examples

44 A process of preparing a pharmaceutical product according to any of claims 26 28 30 33 35 37 39 or 41 which process comprises providing (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid or a pharmaceutically acceptable salt solvate or physiologically functional derivative 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

45 A process of preparing a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31 32, 34 36, 38 40 42 or 43 which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof

46 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 which method comprises administration of a therapeutically effective amount of a pharmaceutical product according to any of claims 26 28 30 33, 35, 37 39 or 41 as a combined preparation for simultaneous separate or sequential use in the treatment of such conditions

47 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, which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any of claims 1 to 22 27 29 31 32 34, 36 38 40 42 or 43

48 For 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, a pharmaceutical product according to any of claims 26 28, 30 33 35 37 39 or 41 as a combined preparation for simultaneous separate or sequential use in the treatment of such conditions

49 A method of treating irritation or disorders of the nose or eye which comprises applying either directly to nasal tissues or to the conjunctival sac of the eyes as appropriate, a pharmaceutical product according to any of claims 26 28 30 33 35 37 39 or 41 or a pharmaceutical formulation according to any of claims 1 to 22 27 29 31, 32 34 36 38 40 42 or 43

50 A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a product or formulation as defined in the preceding claims

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* CPW/CRT/20632

Box No. I TITLE OF INVENTION

PHARMACEUTICAL PRODUCTS AND FORMULATIONS

Box No. II APPLICANT ☐ This person is also inventor

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CIPLA LIMITED
289 Bellasis Road
Mumbai Central
Mumbai 400 008
India

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LULLA Amar
103 Maker Towers 'L
Cuff Parade
Colaba
Mumbai 400 005
India

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

WAIN Christopher Paul
A A Thornton & Co
235 High Holborn
London WC1V 7LE

Telephone No.
+44 1604 638242

Facsimile No.
+44 1604 638164

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence**: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MALHOTRA Geena
8 Anderson House
Opp Mazgaon Dock P O
Mazgaon
Bombay 400 010
INDIA

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: IN

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WAIN Christopher Paul
A A Thornton & Co
235 High Holborn
London WC1V 7LE

This person is:
- ☒ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address. *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*

- ☒ AE United Arab Emirates
- ☒ AG Antigua and Barbuda
- ☒ AL Albania
- ☒ AM Armenia
- ☒ AT Austria
- ☒ AU Australia
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria
- ☒ BR Brazil
- ☒ BY Belarus
- ☒ BZ Belize
- ☒ CA Canada
- ☒ CH & LI Switzerland and Liechtenstein
- ☒ CN China
- ☒ CO Colombia
- ☒ CR Costa Rica
- ☒ CU Cuba
- ☒ CZ Czech Republic
- ☒ DE Germany
- ☒ DK Denmark
- ☒ DM Dominica
- ☒ DZ Algeria
- ☒ EC Ecuador
- ☒ EE Estonia
- ☒ ES Spain
- ☒ FI Finland
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia
- ☒ GH Ghana
- ☒ GM Gambia
- ☒ HR Croatia
- ☒ HU Hungary
- ☒ ID Indonesia
- ☒ IL Israel
- ☒ IN India
- ☒ IS Iceland
- ☒ JP Japan
- ☒ KE Kenya
- ☒ KG Kyrgyzstan
- ☒ KP Democratic People's Republic of Korea
- ☒ KR Republic of Korea
- ☒ KZ Kazakhstan
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MA Morocco
- ☒ MD Republic of Moldova
- ☒ MG Madagascar
- ☒ MK The former Yugoslav Republic of Macedonia
- ☒ MN Mongolia
- ☒ MW Malawi
- ☒ MX Mexico
- ☒ MZ Mozambique
- ☒ NO Norway
- ☒ NZ New Zealand
- ☒ OM Oman
- ☒ PH Philippines
- ☒ PL Poland
- ☒ PT Portugal
- ☒ RO Romania
- ☒ RU Russian Federation
- ☒ SC Seychelles
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SK Slovakia
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan
- ☒ TM Turkmenistan
- ☒ TN Tunisia
- ☒ TR Turkey
- ☒ TT Trinidad and Tobago
- ☒ TZ United Republic of Tanzania
- ☒ UA Ukraine
- ☒ UG Uganda
- ☒ US United States of America
- ☒ UZ Uzbekistan
- ☒ VC Saint Vincent and the Grenadines
- ☒ VN Viet Nam
- ☒ YU Yugoslavia
- ☒ ZA South Africa
- ☒ ZM Zambia
- ☒ ZW Zimbabwe

Check boxes below reserved for designating States which have become party to the PCT after issuance of this sheet.

☐ ☐ ☐

☐ ☐ ☐

Precautionary Designation Statement In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1 If in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available, in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.

(ii) If in Box No. II or in any of the sub-boxes of Box No. III the indication "the States indicated in the Supplemental Box" is checked, in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant.

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America, in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor.

(iv) If in addition to the agent(s) indicated in Box No. IV there are further agents, in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV.

(v) If in Box No. V the name of any State (or OAPI) is accompanied by the indication "patent of addition" or "certificate of addition", or if in Box No. V the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part", in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI) and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application.

(vi) If in Box No. VI there are more than five earlier applications whose priority is claimed, in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement, in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

CONTINUATION OF BOX III

Mr C P Wain is applicant for Malawi (MW) only

CONTINUATION OF BOX NO IV

Further agents of A A Thornton & Co 235 High Holborn London WC1V 7LE United Kingdom who have been appointed to act on behalf of the applicants before the competent International Authorities are:

CRAWFORD Andrew Birkby
LERWILL John
GOODENOUGH Nigel
CURTIS Philip Anthony
BUTCHER Ian James
GILL Ian Stephen
HEDGES Martin Nicholas

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 14/06/2002	0213739.6	GB		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii))

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used)*

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i) Declaration as to the identity of the inventor

☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent

☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application

☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America)

☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty

Box No. IX CHECK LIST LANGUAGE OF FILING

This international application contains:

(a) in paper form the following number of sheets

request (including declaration sheets)	6
description (excluding sequence listings and/or tables related thereto)	16
claims	7
abstract	1
drawings	
Sub-total number of sheets	30
sequence listings	
tables related thereto	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form, see (c) below)	
Total number of sheets	30

(b) ☐ only in computer readable form (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ also in computer readable form (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings
- ☐ tables related thereto

(additional copies to be indicated under items 9(ii) and/or 10(ii) in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*

		Number of items
1	☒ fee calculation sheet	1
2	☐ original separate power of attorney	
3	☐ original general power of attorney	
4	☒ copy of general power of attorney; reference number if any:	1
5	☐ statement explaining lack of signature	
6	☐ priority document(s) identified in Box No. VI as item(s)	
7	☐ translation of international application into *(language)*	
8	☐ separate indications concerning deposited microorganism or other biological material	
9	☐ sequence listings in computer readable form *(indicate type and number of carriers)*	
	(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	
	(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	
	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column	
10	☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*	
	(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	
	(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	
	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	
11	☐ other *(specify)*	

Figure of the drawings which should accompany the abstract.

Language of filing of the international application. ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

MARTIN HEDGES

For receiving Office use only

1 Date of actual receipt of the purported international application		2 Drawings ☐ received ☐ not received
3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
4 Date of timely receipt of the required corrections under PCT Article 11(2)		
5 International Searching Authority (if two or more are competent) ISA /	6 ☐ Transmittal of search copy delayed until search fee is paid	

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Date of receipt of the record copy by the International Bureau

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB 03/02557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61K31/56 A61K31/57 A61K31/58 A61K9/00
A61P37/08 A61P27/14 A61P11/06 //(A61K31/56 31 55),
(A61K31/57 31 55) (A61K31/58 31 55)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16) page 2 line 8 -page 8, line 25	1-50
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 (1997-06-25) page 2 line 34 -page 5 line 30 example 3	1-50

-/—

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

[X] Patent family members are listed in annex.

Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 September 2003	17/09/2003

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

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/GB 03/02557

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE Online! US NATIONAL LIBRARY OF MEDICINE (NLM) BETHESDA MD US 2000 PORTMANN D ET AL Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)!' Database accession no NLM11233712 XP002252974 abstract & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE FRANCE 2000, vol 121 no 4 2000 pages 273-279 ISSN 0035-1334	1-50
X	BUSSE W W ET AL CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION NEW YORK NY US vol 153 no 1, 1996 pages 122-127 XP000604179 ISSN 1073-449X page 127 column 1 paragraph 2	1-50

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/02557

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9701337	A	16-01-1997	AU 6392496 A WO 9701337 A1		30-01-1997 16-01-1997
EP 0780127	A	25-06-1997	EP 0780127 A1		25-06-1997

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW/20632	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No PCT/GB 03/02557	International filing date (day/month/year) 13 06 2003	Priority date (day/month/year) 14 06 2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/55

Applicant
CIPLA LIMITED et al

1 This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

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

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT)

These annexes consist of a total of sheets.

3 This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 01 2004	26 08 2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vandenbogaerde, A Telephone No. +49 89 2399 7674

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No PCT/GB 03/02557

III Non-establishment of opinion with regard to novelty inventive step and industrial applicability

1 The questions whether the claimed invention appears to be novel to involve an inventive step (to be non obvious) or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos 46 47 49 50 with respect to industrial applicability

because

☒ the said international application or the said claims Nos 46 47 49 50 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify)

see separate sheet

☐ the description claims or drawings *(indicate particular elements below)* or said claims Nos are so unclear that no meaningful opinion could be formed *(specify)*

☐ the claims or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☐ no international search report has been established for the said claims Nos

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions

☐ the written form has not been furnished or does not comply with the Standard

☐ the computer readable form has not been furnished or does not comply with the Standard

V Reasoned statement under Article 35(2) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	/
	No	Claims	1 50
Inventive step (IS)	Yes	Claims	/
	No	Claims	1 50
Industrial applicability (IA)	Yes	Claims	1 45 48 YES / 46 47 49 50 see separate sheet
	No	Claims	

2 Citations and explanations

see separate sheet

spray for the treatment of allergic rhinoconjunctivitis
D3 discloses (cf abstract) a combination of (i) the antihistamine azelastine and (ii) the corticoid beclomethasone as nasal spray for the local treatment of seasonal or aperiodic rhinitis
D4 describes (page 126-127 discussion) that the combined use of (i) azelastine and (ii) corticosteroid medication in patients with asthma allowed patients to achieve a reduction in the use of inhaled corticosteroids while showing improvements in the severity of asthma symptoms and in pulmonary function

V 1 Claims 1-43 - *Composition (for use in medicine)* Novelty - Inventive step

V 1 1 The subject matter of claims 1-43 relates to a composition per se or to a composition for use in medicine comprising (i) azelastine and (ii) a steroid i e beclomethasone mometasone fluticasone budesonide or ciclesonide

V 1 2 The subject matter of independent claim 1 is not novel according to Article 33(2) PCT over the teaching of D1 D2 D3 or D4

V 1 3 Dependent claims 2 22 and 25 do not contain any features which in combination with the features of any claim to which they refer meet the requirements of the PCT in respect of novelty and/or inventive step the reasons being as follows Document D1 which is considered to represent the most relevant state of the art discloses (cf page 2 line 8 page 8 line 25) a combination of (i) a topical nasal antihistaminic i e levocabastine azelastine or azatadine and (ii) a topical nasal steroid i e beclomethasone flunisolide triamcinolone dexamethasone or budesonide as nasal spray or nasal drops for the treatment of allergic rhinitis The problem to be solved by the present invention may therefore be regarded as the provision of alternative formulation comprising (i) azelastine and (ii) a steroid for the treatment of allergic disorders of eye and nose or airway disorders It would be obvious to use an alternative steroid to use alternative carriers or to prepare an alternative formulation (i e inhalation formulation) because no unexpected technical effect can be seen

V 1 4 The same objections also apply to independent claims 23 (and dependent claims 24-25) 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 and 44

V 2 Claims 46-50 - *Therapeutical application* Novelty - Inventive step

V 2 1 The subject matter of claims relates to the therapeutical application of a composition comprising (i) azelastine and (ii) a steroid i e beclomethasone

mometasone fluticasone budesonide or cyclosenide for the treatment of conditions for which administration of one or more anti histamine and/or one or more steroid is indicated i e irritation or disorders of the nose or eye (e g allergic rhinitis, rhinoconjunctivis) or airway disorders (e g asthma)

V 2 2 The subject matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT for the same reasons as given under point V 1

V 3 Claims 44-45 *Process* Novelty - Inventive step

V 3 1 The subject matter of claims 44 45 relates to a process for preparing a pharmaceutical composition comprising (i) azelastine and (ii) a steroid i e beclomethasone mometasone fluticasone budesonide or cyclosenide

V 3 2 The subject matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT since merely standard processes are used for preparing a composition which is already known (cf point V 1)

V 4 Industrial applicability

For the assessment of the present claims 46 47 and 49 50 on the question whether they are industrially applicable no unified criteria exist in the PCT Contracting States The patentability can also be dependent upon the formulation of the claims The EPO for example does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment but may allow however claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

Novelty

- The claims at issue covered secretory leukocyte proteinase inhibitor (SLPI) human seminal inhibitor (HUSI-I) antileukoproteinase the proteinase inhibitor in human tears cervical mucus inhibitor (CUSI) and bronchial mucus inhibitor (BMI) which were different names for the same protein termed mucus proteinase inhibitor (MPI) in post-published document (8) taken as an expert opinion HUSI-I and BMI (documents (1) (3) and (6)) antileukoproteinase (document (2)) CUSI (documents (5) and (6)) had already been obtained in pure form

- According to page 361 of document (1) HUSI-I consisted of a single polypeptide chain of about 100 amino acid residues The fact that an incorrect amino acid sequence might have been assigned to HUSI-I was irrelevant for the purpose of novelty since the statement in a claim of intrinsic parameters such as the correct amino acid sequence for an otherwise known protein did not render it novel

- The subject-matter of claims 15 and 16 for the Contracting State AT lacked novelty over document (2) which disclosed all the steps (a) to (d) stated in these claims

Inventive step

- Document (1) was concerned with early attempts to characterize the inhibitor HUSI-I known to be present in human seminal plasma The problem to be

COMBINACION DE AZELASTINA Y ESTEROIDES

La presente invención se relaciona con productos y formulaciones farmacéuticas Más particularmente la presente invención se relaciona con productos y formulaciones farmacéuticas útiles para la prevención o minimización de reacciones alérgicas Más particularmente pero no exclusivamente la presente invención se relaciona con productos y formulaciones farmacéuticos para uso nasal y ocular

Tales relaciones alérgicas comúnmente comprenden los síntomas relacionados con alergias y relacionados con elementos vasomotores y los síntomas relacionados con rinovirus

Es conocido el uso de antihistamínicos en pulverizadores nasales y gotas para los ojos para tratar las condiciones relacionadas con alergia Así por ejemplo es conocido el uso azelastina antihistamínica (usualmente como la sal de clorhidrato) como un pulverizado nasal contra rinitis estacional o alérgica perenne o como gotas para los ojos contra conjuntivitis estacional y alérgica perenne

Es conocido tratar estas condiciones utilizando un corticosteroide que suprimirá las condiciones inflamatorias nasal y ocular Entre los corticosteroides conocidos para uso nasal están por ejemplo la

beclometasona mometasona fluticasona budesonida y ciclosenida Los corticosteroides conocidos para uso anti-inflamatorio ocular incluyen betametasona sodio dexametasona sodio y prednisolona acetato por ejemplo

Sería altamente deseable sin embargo suministrar un tratamiento que combine los efectos de los tratamientos antihistamínicos y los tratamientos colesteroides en una formulación farmacéuticamente aceptable que sea tolerante in situ sin afectar significativamente la potencia de los farmacéuticos constituyentes

Nosotros hemos encontrado ahora que muy sorprendendentemente la azelastina (4-[(4-clorofenil)metil]-2-(hexahidro-1-metil-1H-azepin-4-il)-(1(2H)-eftalazinona) o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este preferiblemente en forma de sal y aún más preferiblemente en la forma de la sal de clorhidrato pueden ser combinados ventajosamente con un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este Para suministrar un producto o formulación de combinación estable muy efectivo para tratamiento nasal u ocular La combinación puede suministrar en una administración sencilla o en un régimen de dosis las propiedades antihistamínicas de la azelastina y las propiedades anti-inflamatorias (y/u

otras) de los esteroides sin ninguna interferencia significativa entre las dos o reacciones adversas in situ

En un aspecto la invención suministra una formulación farmacéutica que comprende azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y un esteroide preferiblemente un corticosteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este la formulación preferiblemente está en una forma adecuada para administración nasal u ocular

El término derivado fisiológicamente funcional como se utiliza aquí denota un derivado químico de cualquiera de los agentes terapéuticos específicos descritos aquí que tienen la misma o similar función fisiológica que el agente terapéutico de base libre y por ejemplo siendo convertible en el cuerpo a este De acuerdo con la presente invención ejemplos de derivados fisiológicamente funcionales incluyen ésteres

Las formas preferidas de las formulaciones de la invención son gotas nasales gotas para los ojos pulverizadores nasales soluciones de inhalación nasal o aerosoles o polvos de insuflación

Las modalidades preferidas de la invención pueden comprender soluciones acuosas estables de azelastina o una o más de sus sales en

combinación con esteroides que pueden ser beclometasona mometasona fluticasona budesonida o ciclosenida que se pueden utilizar en la forma de solución para inhalación aerosol presurizado gotas para los ojos o gotas nasales y en una modalidad particular preferida en la forma de un pulverizado (preferiblemente un pulverizado nasal) El pulverizado puede por ejemplo estar formado por el uso de una botella apretable para pulverizado convencional o un vaporizador de bomba Además también es posible utilizar aerosoles de gas comprimido En una modalidad preferida 0 03 a 3 mg de base de azelastina y 0 05 a 0 15 mg de esteroide deben ser liberados por accionamiento individual

Las formulaciones preferiblemente contienen un preservativo y/o estabilizador Estos incluyen por ejemplo ácido etileno diamina tetra acético (ácido edético) y sus sales alcalinas (por ejemplo sales de alcalinas tales como sal de disodio sal de calcio sal de calcio-sodio) alquil p-hidroxibenzoatos inferiores clorhexidina (por ejemplo en la forma de acetato o gluconato) y fenil mercurio borato Otros preservativos adecuados son compuestos de amonio cuaternario farmacéuticamente útiles por ejemplo cloruro de cetilpiridio tetradeciltrimetil amonio bromuro generalmente conocido como cetrimida benzildimetil-[2-[2-[p-(1 1 3 3-tetrametil-butil)fenoxi]etoxi]-amonio generalmente conocido es cloruro de benzeconio y cloruro de miristil y picolinio Cada uno de estos compuestos puede ser utilizado en una concentración de 0 002 a 0 05% por ejemplo 0 02%

(peso/volumen en formulaciones líquidas o de otra manera peso/peso) Los preservativos preferidos entre los compuestos de amonio cuaternario son sin embargo cloruro de alquilbenzil dimetil amonio y mezclas de estos por ejemplo los compuestos generalmente conocidos como "cloruro de benzalconio"

La cantidad total de preservativos en las formulaciones (soluciones ungüentos etc) van preferiblemente desde 0 001 a 0 10 g preferiblemente 0 01 g por 100 ml de solución/suspensión o 100 g de formulación

En el caso de los preservativos las siguientes cantidades de sustancias individuales pueden por ejemplo ser utilizados timero sal 0 002-0 02% cloruro de benzalconio 0 002 a 0 02% (en combinación con timero sal la cantidad de timero sal es por ejemplo = 0 002 a 0 005%) acetato de clorhexidina o gluconato 0 01 a 0 02% nitrato borato acetato/fenil mercúrico 0 002-0 004% éster de ácido p-hidroxibenzoico (por ejemplo una mezcla de metil éster y propilester en la proporción 7 3) preferiblemente 0 05-0 15 más preferiblemente 0 1%

El preservativo utilizado es preferiblemente una combinación de ácido edético (por ejemplo como la sal de disodio) y cloruro de benzalconio En esta combinación, el ácido edético es preferiblemente utilizado en una concentración de 0 05 a 0 1% el cloruro de benzalconio preferiblemente es

utilizado en una concentración de 0 005 a 0 05% más preferiblemente 0 01%

En el caso de las soluciones/suspensiones se hace siempre referencias al porcentaje en peso/volumen en el caso de formulaciones sólidas o semisólidas a porcentaje en peso /peso de la formulación

Las sustancias auxiliares adicionales que pueden por ejemplo ser utilizadas por la formulación de la invención son polivinil pirolidona ésteres de ácido graso sorbitan tal como sorbitan trioleato ésteres de ácido graso de sorbitan polietixolado (por ejemplo trioleato de sorbitan polietoxilado) sorbimacrogol oleato anfotensuros sintéticos (tritones) éteres de óxido de etileno de productos de condensación de octilfenolformaldehído fosfaturos tales como lecitina grasas polietoxiladas oleotriglicéridos polietoxilados y alcoholes grasos polietoxilados En este contexto polietoxilado significa que las sustancias relevantes contienen cadenas de polioxietileno el grado de polimerización de las cuales está generalmente entre 2 a 40 en particular entre 10 a 20 Estas sustancias son preferiblemente utilizadas para mejorar la solubilidad del componente azelastina

Es opcionalmente posible utilizar agentes de isotonización adicionales Los agentes de isotonización que pueden por ejemplo ser utilizados son sacarosa glucosa glicerina sorbitol 1 2-propilen glicol y NaCl

Los agentes de isotonización ajustan la presión osmótica de la formulación a la misma presión osmótica de la secreción nasal Para este propósito estas sustancias en cada caso van a ser utilizadas en tal cantidad que por ejemplo en el caso de una solución una reducción del punto de congelamiento de 0 50 a 0 56 grados C se logra en comparación con el agua pura

En el ejemplo 1 es posible utilizar en lugar de NaCl ml de solución por ejemplo glucosa $1H_2O$ 3 81 g sacarosa 6 35 g glicerina 2 2 g 1 2-propilen glicol 1 617 g sorbitol 3 84 g (en el caso de las mezclas de estas sustancias correspondientemente menos podrían opcionalmente ser utilizadas)

Más aún es posible agregar agentes espesantes a las soluciones de acuerdo con la presente invención para evitar que las soluciones fluyan hacia fuera de la nariz demasiado rápido y para darle a la solución una viscosidad de aproximadamente 1 5 a 3 preferiblemente 2 mPa

Tales agentes espesantes pueden por ejemplo ser derivados de celulosa (por ejemplo éter de celulosa) en el cual los grupos hidroxi de celulosa son parcialmente eterificados con alcoholes alifáticos insaturados inferiores y/o a oxialcoholes alifáticos insaturados inferiores (por ejemplo

metil celulosa carboximetil celulosa hidroxipropilmetilcelulosa) gelatina polivinil pirolidona tragacanto etoxosa (agentes ligantes y espesantes solubles en agua sobre la base de etil celulosa) ácido algínico polivinil alcohol ácido poliacrílico pectina y agentes equivalentes Si estas sustancias contienen grupos ácidos las correspondientes sales fisiológicamente aceptables también se pueden utilizar

En el evento del uso de hidroxipropil celulosa 0 1% en peso de la formulación por ejemplo se utiliza para este propósito

En el evento del uso de Avicel RC 591 o CLII 0 65-3 0% en peso de la formulación por ejemplo se utiliza para el propósito

También es posible agregar a las formulaciones sustancias amortiguadoras tales como ácido cítrico/amortiguador de borato hidrogensulfato de sodio fosfatos (hidrogenfosfato de sodio hidrogenfosfato de disodio) trometamol o amortiguadores convencionales equivalentes con el fin por ejemplo de ajustar las formulaciones a un valor de pH de 3 a 7 preferiblemente 4 5 a 6 5

La cantidad de ácido cítrico es por ejemplo 0 01 a 0 14 g preferiblemente 0 04 a 0 05 g la cantidad de hidrogenfosfato de disodio 0 1 a

0 5 g preferiblemente 0 2 a 0 3 g por 100 ml de solución Los pesos dados se relacionan en cada caso con las sustancias ahídras

En este caso de soluciones y suspensiones la concentración máxima total del agente activo y el amortiguador es preferiblemente menor de 5% en particular menor de 2% (peso/volumen)

Para la aplicación nasal una solución o suspensión puede preferiblemente ser utilizada que sea aplicada como un aerosol es decir en la forma de una dispersión fina en aire o en otro gas portador convencional por ejemplo por medio de un vaporizador de bomba convencional

La aplicación como un aerosol de dosis es sin embargo también posible Los aerosoles de dosis son definidos por ser empaques a presión que contienen la azelastina o sus sales en combinación con esteroides en la forma de una solución o suspensión en un así llamado propulsante El propulsante puede ser un líquido presurizado clorinado hidrocarburo florinado o mezclas de varios hidrocarburos clorinados florinados así como también propano butano isobutano o mezclas de estos entre ellos o con hidrocarburos clorinados florinados que son gaseosos a presión atmosférica y a temperatura ambiente Los hidrofluorocarburos (HFC) tales como el HFC 134a y el HFC 227a también se pueden utilizar y son preferidos por razones ambientales El empaque a presión tiene una dosis o válvula de medición la

cual al accionamiento libera una cantidad definida de solución o suspensión del medicamento La subsecuente muy repentina vaporización del propulsante gotea la solución o suspensión de azelastina hacia las gotas más finas o las partículas más diminutas que puedan ser pulverizadas en la nariz o que estén disponibles para inspiración dentro de la nariz Ciertos aplicadores plásticos se pueden utilizar para accionar la válvula y transportar la suspensión pulverizada hacia dentro de la nariz

En el caso de la aplicación de un aerosol también es posible utilizar un adaptador convencional

Las modalidades particularmente preferidas de la presente invención son aquí descritas y se apreciará por supuesto que cualquiera de la descripción previa de los ingredientes adecuados y las formulaciones características puede también ser aplicable a los siguientes productos y formulaciones como se suministran en la presente invención

Se apreciará por lo tanto que la presente invención suministra además un producto farmacéutico que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado en una formulación de aerosol preferiblemente junto con un propulsante típicamente adecuado para suministro MDI y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado

fisiológicamente funcional de este suministrado en una formulación de aerosol preferiblemente junto con un propulsante típicamente adecuado para suministro de MDI como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento de condiciones para lo cual la administración de uno o más antihistamínicos y/o uno o más esteroides es indicada

La presente invención también suministra una formulación de aerosol preferiblemente adecuada para suministro MDI que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este junto con un propulsante

También se apreciará de lo anterior que los agentes terapéuticos respectivos de la preparación combinada se pueden administrar simultáneamente o en la misma o diferentes formulaciones farmacéuticas o separada o secuencialmente Si existe administración separada o secuencial también se apreciará que los agentes terapéuticos subsecuentemente administrados se deben administrar a un paciente dentro de una escala de tiempo con el fin de lograr o más particularmente optimizar lo anteriormente mencionado con el efecto terapéutico sinérgico ventajoso de una preparación

combinada como la presente en un producto farmacéutico de acuerdo con la presente invención

Los propulsantes adecuados para uso en los productos farmacéuticos de las formulaciones como se suministran por medio de la presente invención incluyen 1 1 1 2-tetrafluoroetano (HFA 134a) O 1 1 1 2 3 3 3 - heptafluoropropano (HFA 227) o una combinación de ambos o mono-fluoro triclorometano y dicloro difluorometano en particular 1 1 1 2-tetrafluoroetano (HFA 134a) o 1 1 1 2 3 3 3-heptafluoropropano (HFA 227) siendo el HFA 134a el preferido

Una formulación de aerosol farmacéutica de acuerdo con la presente invención comprende preferiblemente además un cosolvente polar tal como alcoholes alifáticos C_{2-6} y polioles por ejemplo etanol isopropanol y propilenglicol siendo el etanol el preferido Preferiblemente la concentración del cosolvente está en el rango de aproximadamente 2 al 10% en peso típicamente hasta aproximadamente 5% de la formulación total

Una formulación farmacéutica en aerosol de acuerdo con la presente invención puede además comprender uno o más tensoactivos Tales tensoactivos pueden ser incluidos para estabilizar las formulaciones y para lubricación de un sistema de válvula Algunos de los tensoactivos más comúnmente utilizados en las formulaciones de aerosol son aceites

derivados de fuentes naturales tales tales como aceite de maíz aceite de oliva aceite de semilla de algodón y aceite de semilla de girasol y también fosfolípidos Los tensoactivos ademados pueden incluir lecitina ácido oleico u oleato sorbitan

Una modalidad adicional preferida de la presente invención puede ser aquella en que la formulación o producto se suministra en la forma de un polvo insuflable donde preferiblemente el tamaño de partícula máximo de la sustancia adecuadamente no excede 10 µm La azelastina por sus sales y el esteroide se pueden mezclar con sustancias portadoras inertes o dirigirse hacia arriba sobre las sustancias portadoras inertes Las sustancias portadoras que pueden por ejemplo ser utilizadas son azucares tales como glucosa sacarosa lactosa o fluctuosa También los almidones o derivados de almodón oligosacáridos tales como dextrinas ciclodextrinas y sus derivados polivinilpirolidona ácido algínico tilosa ácido silícico celulosa derivados de celulosa (por ejemplo éter de celulosa) alcoholes de azúcar tales como manitol o sorbitol carbonato de calcio fosfato de calcio etc

En una modalidad los agentes terapéuticos empleados tienen un tamaño de partícula de no tan aproximadamente 10µm preferiblemente menos de 5µm

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El uso de polvos de insuflación puede representar una modalidad preferida de la presente invención y se suministra por medio de la presente invención un producto farmacéutico que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado como un polvo de insuflación y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado como un polvo de insuflación como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroide es indicada

Se apreciará de lo anterior que los agentes terapéuticos respectivos de la preparación combinada se pueden administrar simultáneamente o en la misma o diferentes formulaciones de polvo de insuflación o separadamente o secuencialmente Si existe una administración separada o secuencial como se discutió anteriormente también se apreciará que los agentes terapéuticos subsecuentemente administrados deben ser administrados a un paciente dentro de una escala de tiempo con el fin de lograr o más particularmente optimizar lo anteriormente mencionado a un efecto terapéutico sinérgico ventajoso de una preparación combinada como la presente en un producto farmacéutico de acuerdo con la presente invención

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La presente invención también suministra una formulación en polvo de insuflación que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este junto con un portador farmacéuticamente aceptable o excipiente para este

Las formulaciones en polvo de suflación seco como se suministran por medio de la presente invención pueden ser benéficas donde se requiere que los agentes terapéuticos como se emplearon de acuerdo con la presente invención sean retenidas en la cavidad nasal y los efectos colaterales sistémicos se puedan minimizar o eliminar Adicionalmente las formulaciones de polvo de insuflación como se emplean en la presente invención pueden ser benéficas por medio de las cuales la retención de azelastina o la sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este en la mucosa nasal es mejorada y el amargo post sabor asociado con las formulaciones antihistamínicas líquidas significativamente reducida mientras también exhiben el efecto terapéutico sinergístico asociado con las combinaciones de azelastina/esteroide suministradas por la presente invención El suministrar una formulación de polvo de insuflación seco de azelastina junto con un esteroide que tiene un tamaño de partícula promedio de menos de aproximadamente 10µm los

agentes terapéuticos pueden estar restringidos primariamente al órgano objetivo deseado la mucosa nasal

La formulación de insuflación de polvo seco de acuerdo con la presente invención se puede administrar mediante el uso de un insuflador que puede producir una nube finamente dividida del polvo seco El insuflador preferiblemente es suministrado con medios para asegurar la administración de una cantidad sustancialmente predeterminada de una formulación o producto como se suministra por medio de la presente invención El polvo puede ser aplicado directamente con un insuflador que es suministrado con una botella o recipiente para el polvo o el polvo puede ser llenado en una cápsula o cartucho tal como una cápsula de gelatina u otro dispositivo de dosis simple adaptado para administración El insuflador preferiblemente tiene medios para abrir la cápsula u otro dispositivo de dosis

Las combinaciones preferidas de los agentes terapéuticos empleados en los productos farmacéuticos y las combinaciones de acuerdo con la presente invención (en particular pulverizadores nasales o gotas aerosol o productos de insuflación y formulaciones como se describieron anteriormente) comprenden una cualquiera de las siguientes combinaciones

La presente invención suministra además por lo tanto un producto farmacéutico que comprende (i) azelastina o una sal farmacéuticamente

aceptable de esta y (ii) al menos un esteroide seleccionado del grupo que consiste de beclometasona fluticasona mometasona y ésteres farmacéuticamente aceptables de este como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de condiciones para las cuales la administración de una o más antihistaminas y/o uno o más esteroides está indicado Adecuadamente los ésteres se pueden seleccionar de dipropionato de beclometasona propionato de fluticasona valerato de fluticasona fluroato de mometasona y monohidrato furoato de mometasona

La presente invención también suministra una formulación farmacéutica que comprende (i) azelastina o una sal farmacéuticamente aceptable de esta y (ii) al menos un esteroide seleccionado del grupo que consiste de beclometasona fluticasona mometasona y ésteres farmacéuticamente aceptables de este junto con un portador excipiente farmacéuticamente aceptable para este Adecuadamente los ésteres se pueden seleccionar de dipropionato de beclometasona propionato de fluticasona valorato de fluticasona furoato de mometasona y monohidrato furoato de mometasona

En el caso de pulverizadores nasales una formulación particularmente preferida como se suministra por medio de la presente invención es un pulverizado nasal que comprende azelastina o una sal farmacéuticamente aceptable de esta (preferiblemente clorhidrato de azelastina) junto con

mometasona o como la base libre o en forma de éster preferiblemente furoato de mometasona

Las combinaciones específicas de los agentes terapéuticos empleados en los productos farmacéuticos y las formulaciones de acuerdo con la presente invención comprenden una cualquiera de las siguientes combinaciones

Clorhidrato de azelastina y dipropionato de beclometasona

Clorhidrato de azelastina y propionato de fluticasona

Clorhidrato de azelastina y valerato de fluticasona

Clorhidrato de azelastina y valerato de fluticasona

Clorhidrato de azelastina y furoato de mometasona y Clorhidrato de azelastina y monohidrato furoato de mometasona

También se suministra por medio de la presente invención un método para la profilaxis o tratamiento en un mamífero tal como un humano de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es el indicado cuyo método comprende la administración de una cantidad terapéuticamente efectiva de un producto farmacéutico sustancialmente como se describió anteriormente como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de tales condiciones

La presente invención también suministra un método para la profilaxis o tratamiento en un mamífero tal como un humano de condiciones para la cual la administración de uno o más antihistamínicos y/o uno o más esteroides es el indicado cuyo método comprende la administración de una cantidad terapéuticamente efectiva de una formulación farmacéutica sustancialmente como se describió anteriormente

También se suministra por medio de la presente invención para uso en la elaboración de un medicamento para la profilaxis o tratamiento de un mamífero tal como un humano de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es el indicado un producto farmacéutico como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de tales condiciones

Se suministra adicionalmente por medio de la presente invención por lo tanto un proceso para preparar un producto farmacéutico sustancialmente como se describió anteriormente cuyo proceso comprende suministrar como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es el indicado (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente

funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este

La presente invención también suministra un proceso para preparar una formulación farmacéutica sustancialmente como se describió anteriormente cuyo proceso comprende mezclar un portador farmacéuticamente aceptable o excipiente con (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este Preferiblemente las formulaciones farmacéuticas de acuerdo con la presente invención pueden comprender formulaciones de polvo de insuflación pulverizadores nasales soluciones de inhalación nasal o aerosoles sustancialmente como se describió anteriormente

La presente invención se ilustra ahora en los siguientes ejemplos que no limitan el alcance de la invención de ninguna manera En los ejemplos donde solo los ingredientes de las formulaciones de acuerdo con la presente invención están listados estas formulaciones son preparadas mediante técnicas bien conocidas en el arte

Ejemplo 1

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Pulverizado nasal o gotas nasales con 0 1% de clorhidrato de azelastina como ingrediente activo y esteroide 0 1%

Sr No	Ingredientes	Cantidad %p/v
1	Clorhidrato de azelastina	0 1%
2	Esteroides	0 1%
3	Edeato de disodio	0 005%
4	Cloruro de sodio	0 9%
5	Cloruro benzalconio	0 001%
6	Avicel RC 591	1 2%
7	Monohidrato de ácido cítrico	0 2%
8	Dodecahidrato dehidrogen fosfato de disodio	0 1%
9	Agua purificada	

Ejemplo 2

El aerosol en dosis da 0 5 mg de clorhidrato de azelastina y 50 microgramos de solvato freon dipropionato de beclometasona por aplicación

Aproximadamente 8 0 kg de una mezcla de 70 partes en peso de difluorometano y 30 partes en peso de 1 2 de diclorotetrafluoroetano son enfriadas a aproximadamente menos 55 grados C en un recipiente de enfriada apropiada Una mezcla de 0 086 kg de sorbitantrioleato pre enfriado y 0 8600 kg de triclorofluorometano pre enfriado son disueltos con agitación en la mezcla a menos 55 grados C 0 0688 kg de clorhidrato de de azelastina

micronizado 0 0688 kg de solvato freon dipropionato de beclametasona y 0 0688 kg de lactosa micronizada son entonces incorporados en porciones dentro de la solución obtenida de esta manera con agitación intensiva El peso total de la suspensión obtenida de seta manera es hecha hasta de 9 547 kg a través de la adición de más de la mezcla de 70 partes en peso de difluorodiclorometano y 30 partes en peso de 1 2-diclorotetrafluoroetano enfriado a aproximadamente menos 55 grados C

Luego del cierre del recipiente de enfriado la suspensión es de nuevo enfriada a aproximadamente menos 55 grados C bajo agitación intensiva Esta entonces está lista para ser llenada

Ejemplo 3

El rociado nasal o las gotas nasales con azelastina y esteroide

Sr No	Ingredientes	Cantidad %p/p
	Clorhidrato de azelastina	0 10%
	Propianato de fluticasona	0 0357
	Glicerina	2 60
	Avicel RC 591	1 35
	Polisorbato 80	0 025
	Cloruro de benzalconio	0 01
	Fenil etil alcohol	0 25
	Agua purificada	q s

Cada pulverizado suministra Clorhidrato de Azelastina (140 mcg) y Fluticasona y propionato de fluticasona (50 mcg)

Ejemplo 4

Pulverizado nasal y gotas nasales con Azelastina y esteroide*

Sr No	Ingredientes	Cantidad %p/p
	Clorhidrato de azelastina	0 10
	Valerato de fluticasona	0 0357
	Glicerina	2 60
	Avicel RC 591	1 20
	Polisorbato 80	0 030
	Cloruro de benzalconio	0 01
	Fenil etil alcohol	0 25
	Agua purificada	

*Cada pulverizado suministra Clorhidrato de Azelastina (140 mcg) y valerato de Fluticasona (50 mcg)

Ejemplo 5

Pulverizado nasal o gotas nasales con Azelastina y esteroide*

Sr No	Ingredientes	Cantidad %p/p
	Clorhidrato de azelastina	0 10
	Propionato de fluticasona	0 0714
	Glicerina	2 60
	Avicel RC 581	1 35
	Polisorbato 80	0 025

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	Cloruro de benzalconio	0 01
	Fenil etil alcohol	0 25
	Agua purificada	

*Cada pulverizado suministra Clorhidrato de Azelastina (140 mcg) y propionato de de Fluticasona (50 mcg)

Ejemplo 6

Pulverizado nasal y gotas nasales con Azelastina y esteroide

Sr No	Ingredientes	Cantidad %p/p
	Clorhidrato de azelastina	0 10
	Furoato de mometasona	0 05173
	Glicerina	2 30
	Edetato de disodio	0 005
	Polisorbato 80	0 0125
	Avicel RC 581	1 35
	Cloruro de benzalconio	0 01
	Monohidrato de ácido cítrico	0 20
	Hidrogenfosfato de disodio	0 10
	Dodecahidrato	
	Agua purificada	q s

Ejemplo 7

Pulverizado nasal o gotas nasales con Azelastina esteroide*

Sr No	Ingredientes	Cantidad %p/p
	Clorhidrato de azelastina	0 10
	Monohidrato furoato de	0 5173

	mometasona	
	Glicerina	2 60
	Avicel RC 611	1 295
	Polisorbato 80	0 0125
	Cloruro de benzalconio	0 01
	Fenil etil alcohol	0 25
	Agua purificada	q s

*Cada pulverizado suministra Clorhidrato de Azelastina (140 mcg) y furoato de mometasona (50 mcg)

Ejemplo 8

MDI nasal con Azelastina y esteroide

Sr No	Ingredientes	Cantidad en mcg
	Clorhidrato de azelastina	0 10
	Monohidrato furoato de mometasona	0 0357
	HFA 134a	2 60
	Lecitina	1 20
	Alcohol	0 030

Ejemplo 9

MDI nasal con Azelastina y esteroide

Sr No	Ingredientes	Cantidad en mcg
	Clorhidrato de azelastina	140
	Propionato de Fluticasona	50
	HFA 134a	q s
	Trioleato de sorbitan	0 1%

	Alcohol	(Hasta de 5%)

Ejemplo 10

MDI nasal con Azelastina y esteroide

Sr No	Ingredientes	Cantidad en mcg
	Clorhidrato de azelastina	140
	Propionato de fluticasona	100
	HFA 134a	q s
	Acido oleico	0 1%

Ejemplo 11

MDI nasal con Azelastina y esteroide

Sr No	Ingredientes	Cantidad en mcg
	Clorhidrato de azelastina	140
	Valerato de fluticasona	50
	HFA 134a	q s
	Alcohol	(Hasta de 5%)

Los polvos insuflables que contienen azelastina y Esteroide

Ejemplo 12

Sr No	Ingredientes	Cantidad (%p/p)
	Azelastina	140 mcg

	Clorhidrato (Micronizada)	
	Propionato de Fluticasona	50 mcg
	Lactosa	q s (hasta 25 mcg)

Ejemplo 13

Sr No	Ingredientes	Cantidad (%p/p)
	Azelastina Clorhidrato (Micronizada)	140 mcg
	Propionato de Fluticasona	100 mcg
	Manitol	q s (hasta 25 mcg)

Ejemplo 14

Sr No	Ingredientes	Cantidad (%p/p)
	Azelastina Clorhidrato (Micronizada)	140 mcg
	Propionato de Fluticasona	250 mcg
	Lactosa	q s (hasta 30 mcg

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REIVINDICACIONES

1 Una formulación farmacéutica que comprende azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este preferiblemente la formulación está en una forma adecuada para la administración nasal u ocular

2 Una formulación farmacéutica de acuerdo a la reivindicación 1 en donde dicha azelastina está presente como clorhidrato de azelastina

3 Una formulación de acuerdo a la reivindicación 1 o 2 en donde el esteroide es beclometasona o un éster farmacéuticamente aceptable de este mometasona o un éster farmacéuticamente aceptable de este fluticasona o un éster farmacéuticamente aceptable de este budesonida o ciclosenida y cualquier forma quiral o mezcla

4 Una formulación de acuerdo a la reivindicación 3 en donde el esteroide es propionato de beclometasona furoato de mometasona monohidrato furoato de mometasona, propionato de fluticasona o valerato de fluticasona

5 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 4 que contiene el esteroide en una cantidad desde aproximadamente 50 microgramos/ml a aproximadamente 5 mg/ml de la formulación

6 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 5 en donde la formulación tiene un talle de partícula de al menos de aproximadamente 10 µm preferiblemente menos de 5µm

7 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 6 la cual es una suspensión que contiene 0 0005 a 2% (peso/peso) de la formulación) de azelastina o una sal farmacéuticamente aceptable de azelastina y desde 0 5 a 1 5% (peso/peso de la formulación) de dicho esteroide

8 Una formulación de acuerdo a la reivindicación 7 que contiene desde 0 001 a 1% (peso/peso de la formulación) azelastina o sal de esta y desde 0 5% a 1 5% (peso/peso de la formulación) esteroide

9 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 8 que también contiene un tensoactivo

10 Una formulación de acuerdo a la reivindicación 9 en donde el tensoactivo comprende un polisorbato o un tensoactivo poloxamero

11 Una formulación de acuerdo a la reivindicación 9 o 10 que contiene desde aproximadamente 50 microgramos a aproximadamente 1 miligramo de tensoactivo por ml de formulación

12 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 11 que también contiene un agente isotónico

13 Una formulación de acuerdo a la reivindicación 12 en donde el agente isotónico comprende cloruro de sodio sacarosa glucosa glicerina sorbitol o 1 2-propilen glicol

14 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 13 que también contiene al menos una de un amortiguador un preservativo o un agente de suspensión o espesamiento

15 Una formulación de acuerdo a la reivindicación 14 en donde dicho preservativo se selecciona de ácido edético y sus sales alcalinas alquil p-hidroxibenzoatos inferiores clorhexidina borato de fenil mercurio o ácido benzoico o una sal un compuesto de amonio cuaternario o ácido sórbico o una sal de estos

16 Una formulación de acuerdo a la reivindicación 14 o 15 en donde el agente de suspensión o el agente de espesamiento se selecciona de derivados de celulosa gelatina polivinil pirolidona tragacanto etoxosa (agentes ligantes y espesantes solubles en agua sobre la base de etil celulosa) ácido algínico alcohol polivinílico ácido poliacrílico o pectina

17 Una formulación de acuerdo a una cualquiera de las reivindicaciones 14 15 o 16 en donde el amortiguador comprende un amortiguador de ácido cítrico-citrato

18 Una formulación de acuerdo a una cualquiera de las reivindicaciones 14 15 16 o 17 en donde el amortiguador mantiene el pH de la fase acuosa en desde 3 a 7 preferiblemente 4 5 a aproximadamente 6 5

19 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 18 que está en suspensión acuosa de solución

20 Una formulación de acuerdo a la reivindicación 19 que está en la forma de un aerosol un ungüento gotas para los ojos gotas nasales y un pulverizado nasal o una solución para inhalación

21 Una formulación de acuerdo a la reivindicación 20 que está en la forma de gotas nasales o pulverizado nasal

22 Una formulación de acuerdo a la reivindicación 20 que está en la forma de un aerosol

23 Un empaque a presión que tiene una válvula de dosis o medición que contiene una formulación de acuerdo a la reivindicación 22

24 Un MDI que incluye un empaque a presión de acuerdo a la reivindicación 23

25 Una formulación de acuerdo a una cualquiera de las reivindicaciones 1 a 19 que está en la forma de un polvo de insuflación

26 Un producto farmacéutico que comprende (i) azelastina o una sal farmacéutica aceptable solvato o derivado fisiológicamente funcional de este suministrado en una formulación de aerosol preferiblemente junto con un propulzante típicamente adecuado para suministro MDI y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado en una formulación de aerosol preferiblemente junto con un propulzante típicamente adecuado para suministro MDI como una preparación combinada para uso simultáneo separado o secuencial en el

tratamiento de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es la indicada

27 Una formulación de aerosol preferiblemente adecuada para suministro MDI que comprende (i) azelastina o una sal farmaceuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este junto con un propulzante

28 Un producto farmacéutico que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado como un polvo de insuflación y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este suministrado como un polvo de insuflación como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de las condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es la indicada

29 Una formulación en polvo para insuflación que comprende (i) azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente

funcional de este junto con un portador farmacéuticamente aceptable de excipiente para este

30 Un producto farmacéutico que comprende (i) azelastina o una sal farmacéuticamente aceptable de esta y (ii) al menos un esteroide seleccionado del grupo que consiste de beclometasona fluticasona mometasona y ésteres farmacéuticamente aceptables de estos como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es las indicada

31 Una formulación farmacéutica que comprende (i) azelastina o una sal farmacéuticamente aceptable de esta y (ii) al menos un esteroide seleccionado del grupo que consiste de beclometasona fluticasona mometasona y ésteres farmacéuticamente aceptables de estos junto con un portador farmacéuticamente aceptable o excipiente para este

32 Un pulverizado nasal que comprende azelastina o una sal farmacéuticamente aceptable de esta junto con mometasona o como base libre de mometasona o como fureato de mometasona y un portador farmacéuticamente aceptable de excipiente para este

33 Un producto farmacéutico que comprende clorhidrato de azelastina y dipropionato de beclometasona como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento o condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es la indicada

34 Una formulación farmacéutica que comprende clorhidrato de azelastina y dipropionato de beclometasona junto con un portador farmacéuticamente aceptable excipiente para este

35 Un producto farmacéutico que comprende clorhidrato de azelastina y propionato de fluticasona como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de condición para lo cual la administración de uno lo más antihistamínicos y/o uno o más esteroides es la indicada

36 Una formulación farmacéutica que comprende clorhidrato de azelastina y propionato de fluticasona junto con un portador farmacéuticamente aceptable de excipiente para este

37 Un producto farmacéutico que comprende clorhidrato de azelastina y valerato de fluticasona como una preparación combinada para uso simultaneo separado o secuencial en el tratamiento de condiciones

para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es la indicada

38 Una formulación farmacéutica que comprende clorhidrato de azelastina y valerato de fluticasona junto con un portador farmaceuticamente aceptable de excipiente para esta parte

39 Un producto farmacéutico que comprende clorhidrato de azelastina y furoato de mometasona como una combinación combinada para uso simultaneo separado o secuencial en el tratamiento de condiciones para lo cual la administración de uno o más antihistamínico y/o uno o más esteroides es indicada

40 Una formulación farmacéutica que comprende clorhidrato de azelastina y furoato de mometasona junto con un portador farmacéuticamente aceptable o excipiente para este

41 Un producto farmacéutico que comprende clorurato de azelastina y monohidrato furoato de mometasona como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento de condiciones para las cuales la administración de una o más antihistamínicos y/o uno o más esteroides es indicada

42 Una formulación farmacéutica que comprende clorhidrato de azilastina y monohidrato furoato de mometasona junto con un portador excipiente farmacéuticamente aceptable para este

43 Una formulación farmacéutica sustancialmente como se describe aquí en cualquiera de los ejemplos

44 Un proceso para preparar un producto farmacéutico de acuerdo a una cualquiera de las reivindicaciones 26 28 30 33 35 37 39 o 41 cuyo proceso comprende suministrar (i) la azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este y (ii) al menos un esteroide una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este como una preparación combinada para uso simultáneo separado de secuencial en el tratamiento de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es indicada

45 Un proceso para preparar una formulación farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 22 27 29 31 32 34 36 38 40 42 o 43 cuyo proceso comprende mezclar un portador farmacéuticamente aceptable de excipiente con la azelastina o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente

funcional de este y al menos un esteroide o una sal farmacéuticamente aceptable solvato o derivado fisiológicamente funcional de este

46 Un método para al profilaxis o tratamiento en un mamífero tal como un humano de condiciones para las cuales las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es indicado cuyo método comprende la administración de una cantidad terapéuticamente efectiva de un producto farmacéutico de acuerdo a cualquiera de las reivindicaciones 26 28 30 33 35 37 39 41 como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento de tales condiciones

47 Un método para profilaxis o tratamiento en un mamífero tal como un humano de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es indicada cuyo método comprende la administración de una cantidad terapéuticamente efectiva de una formulación farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 22 27 29 31 32 34 36 38 40 42 o 43

48 Para uso en la elaboración de un medicamento para la profilaxis o tratamiento de un mamífero tal como un humano de condiciones para las cuales la administración de uno o más antihistamínicos y/o uno o más esteroides es indicado un producto farmacéutico de acuerdo a una

cualquiera de las reivindicaciones 26 28 30 33 35 37 39 a 41 como una preparación combinada para uso simultáneo separado o secuencial en el tratamiento de tales condiciones

49 Un método para tratar la irritación o desordenes de la nariz u ojo que comprende aplicar bien sea directamente a los tejidos de la nariz o al saco conjuntivo de los ojos según sea apropiado un producto farmacéutico de acuerdo a una cualquiera de las reivindicaciones 26 28 30 33 35 37 39 o 41 o una formulación farmacéutica de acuerdo a una cualquiera de las reivindicaciones 1 a 22 27 29 31 32 34 36 38 40 42 o 43

50 Un método para tratar desordenes de las vías aéreas que comprende administrar mediante nebulización a las superficies de las vías aéreas una cantidad de tratamiento efectiva de un producto o formulación como se definió en las reivindicaciones precedentes

80

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA 05 - 104
FECHA : ENERO 3 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacion 05000035 00000000 Folios 88
Fecha (AMD): 2005-01-06 16:41:38
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758703	03/01/2005	45,625,400 00

C O N C E P T O

CANT	REMTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN	443,000
		TOTAL : $	443,000 00

SON CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

Cdo 12092-841-001-9

81

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05000835 00000000 Folios 60
Fecha (AMD) 2005-01-06 16 41 38
Tramite 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **MODELO DE UTILIDAD**	( )	(✓)
Indicación de que se solicita la concesión de una patente	( )	(✓)
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	(✓)
Descripción de la invención.	( )	(✓)
Dibujos de ser estos pertinentes. ✗	( )	(✓)
Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud		
- *Representación gráfica o fotografica del Diseno Industrial o muestra del* Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable Claudia M Neva

Fecha

8/A 82

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a)
EMILIO FERRERO
Apoderado(a)
CIPLA LIMITED

Oficio N°
12708

ASUNTO

Radicación N°	05 - 00895
Solicitud internacional	PCT/GB2003/02557
Fecha inicio fase nacional	14/01/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT) regla 51 bis del Reglamento y Circular Unica de la Superintendencia de Industria y Comercio se le comunica que

- El solicitante deberá anexar la traducción del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante establecido de acuerdo con la regla 4 17 51 bis PCT (Art 26-k) Decisión 486) Folios 51-53
- La solicitud no contiene el poder debidamente otorgado con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante cuando éste fuere una persona jurídica

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486 se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2 literal e) del capítulo quinto del título primero de la Circular Unica N° 10 de 2001

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

El anterior requerimiento fue notificado por fijación en lista de fecha

04 FEB 2005

202044

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