613107

FORM 1 SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

ASTA-Pharma Aktiengesellschaft, of Weissmullerstrasse 45, D-6000 Frankfurt am Main 1, FEDERAL REPUBLIC OF GERMANY, hereby apply for the grant of a standard patent for an invention entitled:

Azelastine-containing Medicaments for Application in the Nose and/or at the Eye

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
P 37 38 681.6	DE	13 November 1987

The address for service is:-

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DATED this ELEVENTH day of NOVEMBER 1988

ASTA-Pharma Aktiengesellschaft

By: [signature]

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 75628
S&F CODE: 53300

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SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Azelastine-containing Medicaments for Application in the Nose and/or at the Eye

I/We, Dr. Günter Steinmetz and Dr. Hubert Bopp
[full name of declarant(s)]

of Wildenbruchstraße 41, D-6000 Frankfurt am Main and
[full address of declarant(s) - not post office box]
Am Heiligenstock 4, D-6456 Langenselbold respectively

do solemnly and sincerely declare as follows:-

1. I am/We are authorised by ASTA-Pharma Aktiengesellschaft, the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in Federal Republic of Germany on 13 November 1987 by ASTA Pharma Aktiengesellschaft.

3. Helmut Hettche, of Martinstrasse 23, D-6057 Dietzenbach, Federal Republic of Germany, is the actual inventor of the invention and the facts upon which the applicant is entitled to make the application are as follows:
ASTA-Pharma Aktiengesellschaft is entitled by Contract of Employment between the inventor as employee and ASTA-Pharma Aktiengesellschaft as employer; as a person who would be entitled to have the patent assigned to it if a patent were granted upon an application made by the inventor.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt this 30th day of November 1988

ASTA-PHARMA Aktiengesellschaft
i.V. Steinmetz i.A. Bopp
Dr. Steinmetz Dr. Bopp
Signature of Declarant

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

JTA:62U

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(54) Title
AZELASTINE-CONTAINING MEDICAMENTS FOR APPLICATION IN THE NOSE AND/OR AT THE EYE

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(57) Claim

1. A medicament for nasal application or for application to the eye and/or the nose which contains 0.0005 to 2% (weight/weight) of azelastine or a physiologically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent and/or adjuvant.

6. A process for the preparation of sterile azelastine-containing medicaments according to any one of claims 1 to 5 for application in the nose and/or at the eye, characterized in that 1 to 1000 mg of azelastine or a physiologically acceptable salt thereof is added to 50 to 200 ml at temperatures between -55 to 80°C of water with simultaneous or subsequent addition of

1 to 400 mg of preservatives,
50 to 4000 mg of stabilizers
or solubility-enhancing substances.

17. A method for the treatment states of irritation or disorders of the nose and/or eye in a patient requiring such treatment comprising the application of a medicament which contains
azelastine or its physiologically acceptable salts thereof in the nose and/or to the conjunctival sac of the eye.

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S&F Ref: 75628

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

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Complete Specification Lodged:
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Priority:

Related Art:

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Complete Specification for the invention entitled:

Azelastine-containing Medicaments for Application in the Nose and/or at the Eye

The following statement is a full description of this invention, including the best method of performing it known to me/us

Azelastine-containing medicaments for application in the nose and/or at the eye

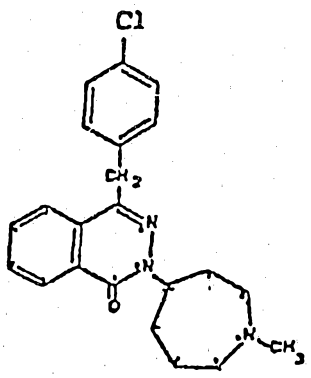
Summary:

Medicament for nasal use or for use at the eye which contains azelastine as active ingredient, whereby the azelastine may also be present in the form of a physiologically acceptable salt.

Azelastine-containing medicaments for application in the nose and/or at the eye

Description:

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular in asthma prophylaxis. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favourable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore azelastine has an exceptionally penetrating, bitter taste which has hitherto prevented every oral application of azelastine solutions since patients refuse to take such azelastine solutions or suspensions.

The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of $1:10^6$. It was surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose with the result that it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

The object of the invention is therefore the preparation of a well tolerated and improved remedy on the basis of azelastine or its salts for the treatment both of the allergy-related and vasomotor-related as well as the rhino virus-related cold and its accompanying symptoms.

According to a first embodiment of the present invention there is provided a medicament for nasal application or for application to the eye and/or the nose which contains 0.0005 to 2% (weight/weight) of azelastine or a physiologically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent and/or adjuvant.

According to a second embodiment of the present invention there is provided a process for the preparation of sterile azelastine-containing formulations for application in the nose and/or at the eye, characterized in that 1 to 1000 mg of azelastine or a physiologically acceptable salt thereof is added to 50 to 200 ml at temperatures between -55 to 80°C of water with simultaneous or subsequent addition of

1 to 400 mg of preservatives,

50 to 4000 mg of stabilizers

or solubility-enhancing substances.

According to a third embodiment of the present invention there is provided a process for the preparation of sterile azelastine-containing formulations for application in the nose and/or at the eye, characterized in that 7.5 mg to 10 g of azelastine or a physiologically acceptable salt thereof is dissolved in 400 to 900 ml of water with simultaneous or subsequent addition of 10 - 200 mg of conserving substances, at temperatures between room temperature and 80°C, emulsifying the solution in 100 - 600 g of a melt of hydrocarbon mixtures, silicons, or other fatty components (fats, fatty alcohols) or mixtures of two or more thereof, as well as emulsifiers and homogenizes and cooling to room temperature to obtain an emulsion.

According to a fourth embodiment of the present invention there is provided a process for the preparation of sterile azelastine-containing formulations for application in the nose and/or at the eye, characterized in that 0.05 to 100 g of azelastine or a physiologically acceptable salt thereof is dispersed at temperatures of between -55 and 80°C, in 5 to 10 kg of a mixture of chlorinated, fluorinated hydrocarbons and/or hydrocarbons, 25 to 150 g of sorbitanetrioleate is added and the obtained suspension is filled into tins which are or will be closed with dosage valves which release 0.025 to 0.1 ml of the suspension per actuation.

According to a fifth embodiment of the present invention there is provided a process for the preparation of sterile azelastine-containing formulations for application in the nose and/or at the eye, characterized in that 5 mg to 10 g of azelastine or a physiologically acceptable salt thereof is mixed with 500 to 1000 g of a physiologically inert carrier substance at temperatures between -55 and 80°C.

According to a sixth embodiment of the present invention there is provided a process for the preparation of a medicament for nasal application and/or for application at the eye, said process comprising mixing 0.0005 to 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

According to a seventh embodiment of the present invention there is provided a method for the treatment states of irritation or disorders of the nose and eye through application or a medicament which contains azelastine or its physiologically acceptable salts in the nose and/or to the conjunctival sac of the eye.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or in a particularly preferred embodiment in the form of a spray (preferably a nasal spray) whereby the spray can be created by the use of a conventional spray-squeeze bottle or of a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

Through the use of nasal drops or a nasal spray the dosage of azelastine required for the treatment of the cold is lowered by about the power of ten and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or juices which flood the entire body with the active substance. In the treatment of a banal illness such as a cold a low incidence of side effects is particularly important and thus represents a considerable medical advance.

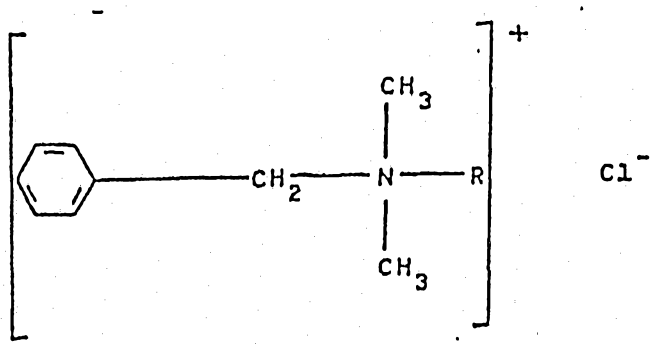
Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols with 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above) whereby the amount of the latter in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates,

chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore it is for example possible to use sodium-(2-ethylmercurithio)-benzoate generally known as "thiomer sal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). 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-γ-picolinium chloride, whereby 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 amongst the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which R = $C_{12}H_{25}$. "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 -2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present as a salt, these amounts should be recalculated as appropriate. In the case of the eye drops the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml, whereby such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alcyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:
thiomer sal 0.002 - 0.02%

benzalkonium chloride 0.002 to 0.02% (in combination with thiomer sal the amount of thiomer sal is, for example = 0.002 to 0.005%;);
chlorhexidine acetate or gluconate 0.01 to 0.02%;
phenyl mercury silver nitrate, borate, acetate 0.002 - 0.004%;
p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05 - 0.15, preferably 0.1%.
The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride, whereby the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, 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, sorbitane fatty acid esters such as sorbitane trioleate, polyethoxylated sorbitane fatty acid esters (for example polyethoxylated sorbitane trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this

context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization 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 components.

In the case of formulation forms containing water, 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, NaCl.

The isotonization agents effect the adjustment of the formulations to the same osmotic pressure as the 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°C is attained in comparison to pure water. In Example 1, for example, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1 it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

It is moreover possible to add thickening agents to the solutions which prevent the solution from flowing out of the nose too quickly and which give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. 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, hydroxypropylmethyl-cellulose), gelatine, 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 weight% are, for example, used for this 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), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g 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 medicament and buffer should be less than 5%, in particular less than 2% (weight/volume).

For the nasal application a solution or suspension is preferably 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 the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these amongst themselves or with chlorinated, fluorinated hydrocarbons which are gaseous under normal pressure and room temperature. The pressure packing has a dosage valve which, on actuation,

releases a defined amount of the solution or suspension of the icament. 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 into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide, compressed air.

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

When suspensions are used, the maximum particle size of the solid substances (azelastine + auxiliary substances) should not exceed 30 µm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 µm.

What occurs here is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, 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, 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. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200 000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

Example 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved in the following order into 9.00 kg of water:
10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkylbenzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogenphosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]
The solution obtained is filled up to 10.05 kg = 10 litres with water and filtered through a membrane filter of pore size 0.2 µm after careful mixing, 500 ml of first runnings being discarded. The filtrate has a pH value of 6.8 +/- 0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

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[1] Commercially available product, for example methocel E4M premium

If the above obtained filtrate is filled into the bottles with dropper pipette conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

Example 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate* , 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-Hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80°C). Subsequently, a solution heated to 70°C of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester are emulsified into 51.021 kg of purified water with the aid of a highspeed stirrer and the emulsion obtained stirred until cold and repeatedly homogenized at regular time intervals.

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* Polyoxyethylene-40-stearate, solid, white to cream-coloured mass, $D.^{25}$ ca. 1.1, F. 40 - 44°C. Solidification point ca. 41°C

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particular suitable for applying the ointment into the nose.

Example 3:

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane are cooled to about - 55°C in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitanetrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at - 55°C. 0.0688 kg of micronized azelastine hydrochloride 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°C.

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

With continued stirring the suspension is filled into the conventional suitable aluminium monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

Example 4:

Eye drops with 0.05% of azelastine hydrochloride.

140 g of polyvinylalcohol (trade name for example: Mowiol 26 - 88 / Hoechst AG, Frankfurt 80) are stirred into 4 litres of cold water for injection purposes, the suspension is heated to 90°C and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:
5 g of azelastine hydrochloride in 1 litre of water for injection purposes, 0.2 g of phenyl mercury silver nitrate in 2 litres of water for injection purposes, 70 g of sodium chloride in 1 litre of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium hydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 litre of water for injection purposes and filled up to 10 litres with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 µm with glass fibre pre-filter and filled into sterile eye drop bottles umder aseptic conditions after discarding a first running of 500 ml.

The claims defining the invention are as follows:

1. A medicament for nasal application or for application to the eye and/or the nose which contains 0.0005 to 2% (weight/weight) of azelastine or a physiologically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent and/or adjuvant.

2. A medicament according to claim 1 characterized in that it is used for the treatment of allergy-related, or vasomotor or rhino virus-related colds or symptoms.

3. A medicament according to any one of the preceding claims, characterized in that it further contains a pharmaceutically acceptable preservative in an amount of 0.001 to 0.1% (in solutions - weight per volume of the solution; in the case of solid formulations weight by weight of the formulation).

4. A medicament according to any one of the preceding claims, characterized in that it constitutes an aqueous solution.

5. A medicament according to any one of the preceding claims, characterized in that it further contains 0.001 to 0.05% (weight/volume) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume) of alkylbenzyldimethyl ammonium chloride.

6. A process for the preparation of sterile azelastine-containing medicaments according to any one of claims 1 to 5 for application in the nose and/or at the eye, characterized in that 1 to 1000 mg of azelastine or a physiologically acceptable salt thereof is added to 50 to 200 ml at temperatures between -55 to 80°C of water with simultaneous or subsequent addition of

1 to 400 mg of preservatives,

50 to 4000 mg of stabilizers

or solubility-enhancing substances.

7. A process according to claim 6 wherein 0.5 to 10 g of thickening agent is further added to form a gel.

8. A process according to claim 6 or 7 wherein up to 15 weight % of one or more water miscible solvents are further added.

9. A process according to any one of claims 6 to 8 wherein buffers are further added to adjust the pH to between 6.5 and 7.1.

10. A process according to any one of claims 6 to 9 wherein isotonization agents are further added.

11. A process for the preparation of sterile azelastine-containing medicaments according to any one of claims 1 to 5 for application in the

nose and/or at the eye, characterized in that 7.5 mg to 10 g of azelastine or a physiologically acceptable salt thereof is dissolved in 400 to 900 ml of water with simultaneous or subsequent addition of 10 - 200 mg of conserving substances, at temperatures between room temperature and 80°C, emulsifying the solution in 100 - 600 g of a melt of hydrocarbon mixtures, silicons, or other fatty components (fats, fatty alcohols) or mixtures of two or more thereof, as well as emulsifiers and homogenizes and cooling to room temperature to obtain an emulsion.

12. A process for the preparation of sterile azelastine-containing medicaments according to claim 1 for application in the nose and/or at the eye, characterized in that 0.05 to 100 g of azelastine or a physiologically acceptable salt thereof is dispersed at temperatures between -55 and 80°C, in 5 to 10 [illegible] a mixture of chlorinated, fluorinated hydrocarbons and/or hydrocarbons, 25 to 150 g of sorbitanetrioleate is added and the obtained suspension is filled into tins which are or will be closed with dosage valves which release 0.025 to 0.1 ml of the suspension per actuation.

13. A process for the preparation of sterile azelastine-containing medicaments according to claim 1 for application in the nose and/or at the eye, characterized in that 5 mg to 10 g of azelastine or a physiologically acceptable salt thereof is mixed with 500 to 1000 g of a physiologically inert carrier substance at temperatures between -55 and 80°C.

14. A process according to claim 13 wherein a solution comprising azelastine or a physiologically acceptable salt thereof is mixed with the stated amount of inert carrier substance and the solvent is subsequently evaporated off and the obtained mixture is filled in amounts of 20 to 1000 mg into hard gelatine capsules or small packages.

15. A process for the preparation of a medicament according to claim 1 for nasal application and/or for application at the eye, said process comprising mixing 0.0005 to 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

16. A process for the preparation of a medicament according to claim 1 for nasal application and/or for application at the eye substantially as hereinbefore defined with reference to any one of the Examples.

17. A method for the treatment states of irritation or disorders of the nose and/or eye in a patient requiring such treatment comprising the application of a medicament which contains

azelastine or its physiologically acceptable salts thereof in the nose and/or to the conjunctival sac of the eye.

18. A medicament for nasal application or for application at the eye which contains 0.0005 to 2% (weight/weight) of azelastine substantially as hereinbefore described with reference to any one of the Examples.

19. The product of the process of any one of claims 6 to 16.

20. A method of treating irritation or disorders of the nose and/or eye in a patient requiring such treatment comprising administering to the nose and/or to the conjunctival sac of the eye of said patient an effective amount of a medicament according to any one of claims 1 to 5 or 18 or 19.

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