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Solutions containing epinastin

The invention relates to topically administered aqueous solutions containing epinastin, optionally in the form of its racemates, its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof.

Background of the Invention

Allergic reactions of the eye (hereinafter referred to as ocular allergic reactions) signifies a series of differently defined syndromes. The following are examples of ocular allergic reactions, e.g.: seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant cell conjunctivitis, vernal keratoconjunctivitis or atopic keratoconjunctivitis. Examples of allergic reactions of the nose (hereinafter referred to as nasal allergic reactions) include seasonal allergic rhinitis and perennial allergic rhinitis, for example.

The immunological mechanism on which ocular and nasal allergic reactions are based comprises *inter alia* inflammatory processes caused by histamine. The allergic reactions produced by the release of histamine occur at an early stage of the ocular and nasal allergic reactions mentioned above.
Moreover, ocular and nasal allergic reactions may be due to the release of other mast cell mediators as well as toxic eosinophilic granule proteins and enzymes. The influx of neutrophils and eosinophils into the tissue of the ocular conjunctiva and the nasal mucous membrane leads to a late phase reaction, hereinafter referred to as LPR.

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LPR normally occurs within a period of 3-6 hours after the initial histamine-mediated allergic reaction. LPR is also characterised by the occurrence of vasodilation and chemosis and by the swelling of the conjunctiva and the nasal mucous membrane.

Whereas histamine-produced allergic reactions can be counteracted by administering antihistamines, the influx of neurophils and eosinophils into the tissue of the ocular conjunctiva and the nasal mucous membrane remains unaffected by administering pure antihistamines.

Problem of the Invention

The problem of the present invention is therefore to provide topically administerable solutions which inhibit the influx of neutrophils and eosinophils into the tissue of the ocular conjunctiva and the nasal mucous membrane, thereby reducing or preventing the occurrence of LPR and are therefore characterised by a longer lasting duration of activity.

More Detailed Description of the Invention

It has been found, surprisingly, that topically administerable aqueous solutions containing epinastin, optionally in the form of its racemate, its enantiomers and possibly in the form of the pharmacologically acceptable acid addition salts thereof, may be used to solve the problem on which the invention is based, since they inhibit the influx of neutrophils and eosinophils into the tissue of the ocular conjunctiva and nasal mucous membrane, thereby reducing or preventing the occurrence of LPR and are accordingly characterised by a longer lasting duration of activity.

The compound epinastin (3-amino-9,13b-dihydro-1H-dibenz-[c,f]imidazol[1,5-a]azepine) and the acid addition salts

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thereof are described for the first time in German Patent Application P 30 08 944.2.

The effect of the topically administered solutions containing epinastin as inhibitors of the influx of eosinophils and neutrophils was demonstrated using the so-called passive ocular anaphylaxis model in rats.

Description of Experiment:

72 hours after the rats have been sensitised by injecting antiserum into the eyelids of the test animals, a fresh provocation was induced in them by intravenous administration of ovalbumin. Some of the experimental animals were pretreated by the administration of solution containing epinastin according to the invention into the conjunctival sac 15 minutes before the ovalbumin is administered. Two hours after the administration of ovalbumin the experimental animals were killed and the conjunctiva was investigated for its content of eosinophils and neutrophils and the mast cell granulation was determined.

Results:

The animals pretreated with epinastin solution according to the invention (0.05-0.5%) had a significantly lower content of eosinophils in their conjunctiva. The animals pretreated with epinastin solution according to the invention had a significantly lower content of lymphocytes in their conjunctiva ($p<0.01$). In the animals pretreated with epinastin solution according to the invention, a roughly 35% inhibition of mast cell degranulation was determined ($p<0.01$).

Consequently, the invention relates to topically administered aqueous solutions containing epinastin, optionally in the form of its racemate, its enantiomers

and optionally in the form of the pharmacologically acceptable addition salts thereof, in a concentration of 0.005 to 0.5, preferably 0.02 to 0.1, most preferably 0.03 to 0.07 mg/ml of solution.

The above-mentioned topically administered aqueous solutions containing epinastin hydrochloride are preferred according to the invention.

Suitable aqueous solvents are physiologically acceptable aqueous solvents, physiologically acceptable saline solutions being particularly preferred.

According to the invention, topically administered solutions are preferably prepared which typically contain 0.005 to 0.5, preferably 0.02 to 0.1, most preferably 0.03 to 0.07 mg/ml of epinastin, optionally in the form of its racemate, its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof, as well as physiological saline solutions as the main carriers. The pH of the solutions according to the invention should preferably be maintained within the range from 6.5 - 7.2 by means of a suitable buffer system. The preparations may also contain conventional, pharmaceutically acceptable excipients, preservatives, stabilisers and/or penetration promoters.

According to a first aspect, there is provided, the use of an aqueous solution comprising epinastine, optionally in the form of its racemate or its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof, in the manufacture of a medicament for the treatment of late phase allergic reactions of the eye or nose by topical administration.

According to a second aspect, there is provided,

a pharmaceutical composition in the form of an aqueous solution suitable for topical administration and consisting essentially of:

Epinastine as sole active ingredient, optionally in the form of its racemate or its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof;

water or physiologically acceptable saline;

a buffer to maintain the pH within the range 6.5-7.2; and

a preservative;

and optionally one or more entity selected from:

a chelating agent;

a viscosity agent;

a penetration promoter;

an antioxidant;

a substance to adjust the tonicity of the solution.

The preferred carrier which may be used in the solutions according to the invention is purified water and preferably a physiological saline solution.

Without restricting the subject matter of the invention to the following, the excipients which may be used according to the invention include viscosity agents such as polyvinyl alcohol, povidone, hydroxypropylmethylcellulose,

poloxamers, carboxymethylcellulose, carbomers and hydroxyethylcellulose.

Without restricting the subject matter of the invention to the following, the preferred preservatives which may be used in the solutions according to the invention include benzalkonium chloride, chlorobutanol, thimerosal, phenyl mercury acetate and phenyl mercury nitrate.

The penetration promoters may be, for example, surfactants, specific organic solvents such as dimethylsulphoxide and other sulphoxides, dimethylacetamide and pyrrolidone, specific amides of heterocyclic amines, glycols such as propyleneglycol, propylene carbonate, oleic acid, alkylamines and derivatives thereof, various cationic, anionic, non-ionogenic and amphoteric surfactants and the like.

Substances may be added as necessary or as desired in order to adjust the tonicity of the solution. Such substances include salts and especially sodium chloride, potassium chloride, mannitol and glycerol or other suitable physiologically acceptable agents for adjusting tonicity, without restricting the invention to the above.

Various buffers and substances may be used to adjust the pH, provided that the preparation obtained is physiologically acceptable. These buffers might include acetate buffer, citrate buffer, phosphate buffer and borate buffer.

Similarly, physiologically acceptable antioxidants which may be used according to the invention include sodium metabisulphite, sodium thiosulphate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene, without restricting the invention to this list.

Other carrier components which may be incorporated in the solutions according to the invention are chelating agents. The preferrred chelating agent is disodium edetate (Na-EDTA), although other chelating agents may also be used instead of or in conjunction with disodium edetate.

The above-mentioned topically administered aqueous solutions according to the invention may be applied either to the conjunctiva or to the nasal mucous membrane. Solutions for ophthalmic use are of equal importance to solutions for nasal application for the purposes of the present invention.

The invention relates not only to the solutions according to the invention mentioned hereinbefore but also to the use of the above-mentioned topically administered aqueous solutions for inhibiting the influx of neutrophils and eosinophils into the tissue of the ocular conjunctiva or the tissue of the nasal mucous membrane.

The present invention also relates to the use of epinastin, optionally in the form of its racemate, its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof, for producing the topically administered aqueous solutions according to the invention for treating disorders of the ocular conjunctiva or the nasal mucous membranes in which there is therapeutic value in inhibiting the influx of neutrophils and eosinophils into the tissue of the ocular conjunctiva or the nasal mucous membrane in allergic reactions.

The above-mentioned use for inhibiting LPR is preferred, whilst it is particularly preferable to use the preparation to treat the diseases listed at the beginning.

The Examples shown in Table 1 illustrate the invention without restricting it.

Table 1:	Solution 1 0.05% [g/100ml]	Solution 2 0.01% [g/100ml]	Solution 3 0.05% [g/100mgl]	Solution 4 0.10% [g/100ml]	Solution 5 0.01% [g/100ml]	Solution 6 0.05% [g/100ml]	Solution 7 0.10% [g/100ml]
Epinastin-hydrochloride	0.0500	0.0100	0.0500	0.1000	0.0100	0.0500	0.1000
Na-EDTA	0.0500	0.0500	0.0500	0.0500	-	-	-
Sodium chloride	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
Sodium dihydrogen phosphate dihydrate	0.7800	0.7800	0.7800	0.7800	0.4100	0.4100	0.4100
Benzalkonium chloride	0.0101	0.0101	0.0101	0.0101	0.0101	0.0101	0.0101
Sodium hydroxide	0.0001	0.0001	0.0001	0.0001	-	-	-
Sodium dihydrogen phosphate dihydrate	-	-	-	-	0.6500	0.6500	0.6500
Hydroxyethylcellulose	-	-	-	-	0.1000	0.1000	0.1000
Water	99.4198	99.4598	99.4198	99.3698	99.0749	99.0349	99.9849
	100.8100	100.8100	100.8100	100.8100	100.7550	100.7550	100.7550

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What is claimed is:

1. Use of an aqueous solution comprising epinastine, optionally in the form of its racemate or its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof, in the manufacture of a medicament for the treatment of late phase allergic reactions of the eye or nose by topical administration.

2. Use as claimed in claim 1 wherein the aqueous solution comprises water or physiologically acceptable saline, and the concentration of epinastine is 0.0005 to 0.1% w/w of solution.

3. Use as claimed in any preceding claim whereby epinastine is in the form of epinastine-hydrochloride.

4. Use as claimed in any preceding claim wherein the aqueous solution also comprises a buffer to maintain the pH within the range 6.5-7.2.

5. Use as claimed in any preceding claim wherein the aqueous solution also comprises a preservative.

6. Use as claimed in any preceding claim wherein the aqueous solution also comprises one or more entity selected from:

   a chelating agent;

   a viscosity agent;

   a penetration promoter;

   an antioxidant;

   a substance to adjust the tonicity of the solution.

7. Use as claimed in any preceding claim wherein the aqueous solution comprises a viscosity agent selected from polyvinyl alcohol, povidone, hydroxypropylmethyl-cellulose, poloxamers, carboxymethylcellulose, carbomers and hydroxyethylcellulose.

8. Use as claimed in any preceding claim wherein the aqueous solution comprises a preservative selected from benzalkonium chloride, chlorobutanol, thimerosal, phenyl mercury acetate and phenyl mercury nitrate.

9. Use as claimed in any preceding claim wherein the aqueous solution comprises a penetration promoter selected from dimethylsulphoxide, dimethylacetamide, pyrrolidone, propylene glycol, propylene carbonate and oleic acid.

10. Use as claimed in any preceding claim wherein the aqueous solution comprises a substance to adjust the tonicity of the solution selected from sodium chloride, potassium chloride, mannitol and glycerol.

11. Use as claimed in any preceding claim wherein the aqueous solution comprises a buffer selected from acetate buffer, citrate buffer, phosphate buffer and borate buffer.

12. Use as claimed in any preceding claim wherein the aqueous solution comprises an antioxidant selected from sodium metabisulphite, sodium thiosulphate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

13. Use as claimed in any preceding claim wherein the aqueous solution comprises a chelating agent being disodium edetate.

14. Use as claimed in any preceding claim wherein the aqueous solution comprises water, epinastine hydrochloride, sodium chloride, sodium dihydrogen phosphate dihydrate, benzalkorxium chloride, hydroxyethylcellulose and optionally sodium-EDTA and sodium hydroxide.

15. A pharmaceutical composition in the form of an aqueous solution suitable for topical administration and consisting essentially of:

Epinastine as sole active ingredient, optionally in the form of its racemate or its enantiomers and optionally in the form of the pharmacologically acceptable acid addition salts thereof;

water or physiologically acceptable saline;

a buffer to maintain the pH within the range 6.5-7.2; and

a preservative;

and optionally one or more entity selected from:

a chelating agent;

a viscosity agent;

a penetration promoter;

an antioxidant;

a substance to adjust the tonicity of the solution.

16. A pharmaceutical composition as claimed in claim 15 wherein the concentration of epinastine is 0.0005 to 0.1% w/w of solution.

17. A pharmaceutical composition as claimed in claim 15 or claim 16 wherein epinastine is present as epinastine-hydrochloride.

18. A pharmaceutical composition as claimed in any of claims 15 to 17 wherein each of the preservative and, if present, the chelating agent, viscosity agent, penetration promoter, antioxidant and/or substance to adjust the tonicity of the solution may be as described in claims 7 to 14.

19. Use as claimed in any one of claims 1 to 14 substantially as herein described.

20. A pharmaceutical composition as claimed in any one of claims 15 to 18 substantially as herein described.