US 20080249065A1

(19) **United States**

(12) **Patent Application Publication**

Conti

(10) **Pub. No.: US 2008/0249065 A1**

(43) **Pub. Date: Oct. 9, 2008**

(54) **OPHTHALMIC PHARMACEUTICAL COMPOSITIONS BASED ON AMINO ACIDS AND SODIUM HYALURONATE**

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(21) Appl. No.: **12/091,481**

(22) PCT Filed: **Oct. 16, 2006**

(86) PCT No.: **PCT/EP06/09967**

§ 371 (c)(1),
(2), (4) Date: **Apr. 24, 2008**

(30) **Foreign Application Priority Data**

Oct. 26, 2005 (IT) MI2005A002036

Publication Classification

(51) **Int. Cl.**
A61K 31/728 (2006.01)
A61P 27/04 (2006.01)

(52) **U.S. Cl.** **514/54**

(57) **ABSTRACT**

This invention relates to ophthalmic wound-healing pharmaceutical compositions based on amino acids and sodium hyaluronate.

OPHTHALMIC PHARMACEUTICAL COMPOSITIONS BASED ON AMINO ACIDS AND SODIUM HYALURONATE

FIELD OF INVENTION

[0001] The present invention relates to ophthalmic pharmaceutical compositions, based on amino acids and sodium hyaluronate, with a protective and regenerating action on the corneal epithelial cells.

PRIOR ART

[0002] No cure for hypolacrimation (dry eye) has yet been found. Dry eye syndrome is treated with eyedrops or gels (artificial tears) having a cleansing, lubricant and disinfecting action, which possess the chemico-physical characteristics of natural tears.

[0003] Artificial tears are fairly dense preparations, designed to remain in the eye at length and prevent rapid dilation.

[0004] These products considerably reduce the quality of vision after administration, and do not perform any wound-healing action.

[0005] Eye surgery designed to correct visual defects and remove cataracts is becoming increasingly common. These operations do not usually require stitches, but the wounds take some time to heal.

[0006] No wound-healing agents exist which promote rapid healing of corneal ulcerations, wounds and lesions of post-operative, pathological, traumatic or parasurgical origin.

[0007] Consequently, treatment usually involves administering topical preparations (eyedrops, ointments or artificial tears) with an antibiotic and anti-inflammatory activity.

[0008] There is therefore a need for new preparations which perform a regenerating action at epithelial level, and promote corneal re-epithelialisation and rapid healing.

DESCRIPTION OF THE INVENTION

[0009] It has now been found that the combination of some amino acids with sodium hyaluronate is particularly effective in promoting the process of reconstitution of the corneal epithelium and the stromal tissue in the case of pathological, traumatic, surgical or parasurgical corneal lesions.

[0010] The invention therefore relates to ophthalmic pharmaceutical compositions containing, as active ingredient, a combination of:

[0011] a) glycine and proline;

[0012] b) sodium hyaluronate; and possibly

[0013] c) lysine and leucine.

[0014] More particularly, the compositions according to the invention contain glycine, L-proline and sodium hyaluronate, and possibly L-lysine in the form of hydrochloride and L-leucine.

[0015] The compositions according to the invention have a surprising effect as adjuvants: they aid regeneration of the epithelial microvilli and induce and accelerate corneal re-epithelialisation after eye surgery.

[0016] The compositions according to the invention will therefore be used to treat:

[0017] slight, moderate or serious alterations of the tear film: the regeneration effect on the epithelial microvilli, which represent the fundamental substrate for effective restoration of the glycocalyx and consequently the tear film, drastically reduces the typical symptoms of dry eye.

[0018] patients who undergo laser treatments (PRK): the reduction in post-operative re-epithelialisation time prevents the appearance of haze and dry eye syndrome which are typical of the first few months after surgery;

[0019] relapsing and/or persistent corneal ulcers: the lasting re-epithelialisation effect prevents relapses and allows complete re-epithelialisation;

[0020] cataract removal surgery, phacoemulsification: the rapid healing effect on the corneal tunnel significantly reduces the discomfort felt by the patient.

[0021] The compositions according to the invention will be applied to the eye 4-6 times a day, for a maximum of 3 months.

[0022] The compositions according to the invention will contain the various active ingredients within the following percentage ranges by weight:

[0023] glycine 0.01 to 0.5%;

[0024] L-proline: 0.09 to 0.06%;

[0025] sodium hyaluronate: 0.5 to 0.1% and possibly

[0026] L-lysine hydrochloride: 0.01 to 0.02%;

[0027] L-leucine: 0.02 to 0.005%.

[0028] According to a preferred aspect, the compositions according to the invention will contain the various active ingredients in the following percentages by weight:

[0029] glycine: 0.1%

[0030] L-proline: 0.075%;

[0031] sodium hyaluronate: 0.3%;

[0032] and possibly

[0033] L-lysine hydrochloride: 0.014;

[0034] L-leucine: 0.011%.

[0035] The following is an example of a formulation according to the invention.

EXAMPLE

[0036]

Eyedrop formulation

INGREDIENTS	Grams per unit dose
Sodium hyaluronate	0.3000
L-Proline	0.0752
Glycine	0.1000
L-Lysine HCl	0.0140
L-Leucine	0.0108
Sodium chloride	0.9000
Distilled water	to 100.0 mL

[0037] Preparation

[0038] 30 kg of purified water is mixed with L-proline, glycine, lysine HCl, L-leucine and sodium chloride, and stirred until all the components have completely dissolved.

[0039] Sodium hyaluronate is added separately to **100** kg of purified water, and stirred until the component has completely dissolved.

[0040] The two solutions are combined and made up to the final volume of 144 litres with purified water, checking that the pH value is between 6 and 7, and adjusting with citric acid or sodium bicarbonate if necessary.

[0041] Finally, the solution is filtered through an 0.22 μm filter under sterile conditions and placed in a container.

[0042] Pharmacological Trial

[0043] The protective and regenerative efficacy of the artificial tears according to the invention in reconstituting the corneal epithelium and stromal tissue in the case of pathological, traumatic, surgical, or parasurgical corneal lesions was investigated.

[0044] 300 eyes of 200 patients were examined:

[0045] 100 eyes of 50 patients suffering from slight, moderate or serious alterations of the tear film (Group A);

[0046] 80 eyes of 40 patients who underwent laser surgery (PRK) (Group B);

[0047] 20 eyes of 20 patients suffering from relapsing and/or persistent corneal ulcers (Group C);

[0048] 84 eyes of 84 patients who underwent cataract removal surgery, namely phacoemulsification with IOL implantation (Group D).

[0049] Cytomorphological study of the eye surface with confocal scanning electron microscopy (SEM) made it possible to analyse the histological modifications of the epithelial cells, and especially the microvilli. The Schimer test and BUT were used for the staging of the tear deficiency.

[0050] Regeneration of the epithelial microvilli, the fundamental substrate for effective restoration of the glycocalyx, and consequently the tear film, was observed in Group A. The patients already perceived a noticeable benefit after 10 days of treatment, with a drastic reduction in the typical symptoms of dry eye.

[0051] In Group B, the post-operative re-epithelialisation time was shortened from the usual 4-6 days to 2-3 days, and the administration of artificial tears, even after re-epithelialisation was complete, proved to prevent the appearance of haze and the dry eye syndrome typical of the first few months after surgery.

[0052] In Group C, re-epithelialisation and stability of the epithelium were obtained, without relapses, and where the ulcer had been already present for several weeks, complete re-epithelialisation was achieved.

[0053] Early healing of the corneal tunnel, with a definite reduction in the typical discomfort felt by the patient, was observed in Group D only a few days after the cataract operation.

1-5. (canceled)

6. An ophthalmic pharmaceutical composition comprising as active ingredient a combination of:

a) glycine and proline; and

b) sodium hyaluronate.

7. The ophthalmic pharmaceutical composition of claim **6**, the composition further comprising as active ingredient:

c) lysine and leucine.

8. The ophthalmic pharmaceutical composition of claim **6**, wherein proline is L-proline, and wherein glycine, L-proline and sodium hyaluronate are comprised within the following percentage ranges by weight:

glycine 0.01 to 0.5%;

L-proline: 0.09 to 0.06%, and

sodium hyaluronate; 0.5 to 0.1%.

9. The ophthalmic pharmaceutical composition of claim **7**, wherein lysine is L-lysine, leucine is L-leucine and wherein L-lysine and L-leucine are comprised within the following percentage ranges by weight:

L-lysine hydrochloride: 0.01 to 0.02%; and

L-leucine: 0.02 to 0.005%.

10. The ophthalmic pharmaceutical composition of claim **6**, wherein proline is L-proline, and wherein glycine, L-proline and sodium hyaluronate have the following percentage ranges by weight:

glycine: 0.1%

L-proline: 0.075%; and

sodium hyaluronate: 0.3%.

11. The ophthalmic pharmaceutical composition of claim **7**, wherein lysine is L-lysine, leucine is L-leucine and wherein L-lysine and L-leucine have the following percentage ranges by weight:

L-lysine hydrochloride: 0.014%, and

L-leucine: 0.011%

12. The ophthalmic pharmaceutical composition of claim **6**, wherein the composition is in form of eyedrops, artificial tears, ointment or gel.

13. The ophthalmic pharmaceutical composition of claim **7**, wherein the composition is in form of eyedrops, artificial tears, ointment or gel.

14. The ophthalmic pharmaceutical composition of claim **8**, wherein the composition is in form of eyedrops, artificial tears, ointment or gel.

15. The ophthalmic pharmaceutical composition of claim **9**, wherein the composition is in form of eyedrops, artificial tears, ointment or gel

16. The ophthalmic pharmaceutical composition of claim **10** wherein the composition is in form of eyedrops, artificial tears, ointment or gel.

17. The ophthalmic pharmaceutical composition of claim **11** wherein the composition is in form of eyedrops, artificial tears, ointment or gel.

18. A method to treat a corneal ulceration in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **6**.

19. A method to treat a corneal ulceration in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **7**.

20. A method to treat a lesion of pathological, traumatic, surgical, or parasurgical origin in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **6**.

21. A method to treat a lesion of pathological, traumatic, surgical, or parasurgical origin in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **7**.

22. A method to treat symptoms of dry eye in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **6**.

23. A method to treat symptoms of dry eye in a patient, the method comprising

administering to the patient the ophthalmic pharmaceutical composition of claim **7**.

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