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(57) Abrégé/Abstract:
The present invention is directed to preservative-free solutions of bimatoprost and timolol for lowering intra-ocular pressure and treatment of glaucoma.

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(54) Title: PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS

(57) Abstract: The present invention is directed to preservative-free solutions of bimatoprost and timolol for lowering intra-ocular pressure and treatment of glaucoma.

PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS

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CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims the benefit of US Provisional Patent Application Serial No. 61/368,685 which was filed on July 29, 2010 and is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present application is directed to preservative-free formulations of bimatoprost and timolol.

BACKGROUND OF THE INVENTION

Bimatoprost is a prostamide, a synthetic analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) with potent ocular hypotensive activity. Bimatoprost lowers intraocular pressure (IOP) in patients with glaucoma or ocular hypertension by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Timolol is a non-selective beta-adrenergic receptor blocker and functions by reducing aqueous humor production through blockage of the beta receptors on ciliary epithelium.

Use of preservative containing eye drops has been implicated in the development or worsening of ocular surface disease. Management of open angle glaucoma and ocular hypertension require long term treatment with eye drops containing preservatives. Symptoms and signs of ocular surface disease such as ocular surface breakdown, irritation, burning, foreign body sensation, dryness, inadequate quantity of tears, etc. are prevalent in a large proportion of patients with open angle glaucoma and ocular hypertension.

Compared to eye drops preserved with benzalkonium chloride, preservative-free eye drops induce significantly fewer ocular symptoms and signs of irritation in patients, such as pain or discomfort, foreign body sensation, stinging or burning, and dry eye sensation.

Patients experiencing hypersensitivity reactions with benzalkonium chloride cannot use a commercial bimatoprost product containing benzalkonium chloride which is preserved even with 0.005% w/v benzalkonium chloride. Benzalkonium chloride also may be absorbed by the

soft contact lenses therefore patients wearing soft contact lenses are advised to remove lenses prior to administration and wait at least 15 minutes before reinserting them.

SUMMARY OF THE INVENTION

The present invention is directed to a bimatoprost and timolol solutions without benzalkonium chloride or any other preservative which will be superior from a safety & tolerability standpoint while maintaining and/or improving its efficacy of IOP lowering and be available for use by patients hypersensitive to benzalkonium chloride and be convenient for patients wearing soft contact lenses.

Bimatoprost and timolol ophthalmic solution without preservative is a clear to slightly yellow, isotonic, sterile solution. The drug product contains bimatoprost and timolol as the active ingredients. The inactive ingredients are tonicity and buffer agents, and purified water. Suitable buffers such as sodium phosphate dibasic heptahydrate and citric acid monohydrate and suitable tonicity agents such as sodium chloride may be included. The solution is an aqueous solution having a pH value within the range of about 7 to about 8, and preferably about 7.3. Suitable buffers may be included, such as sodium phosphate dibasic heptahydrate, citric acid monohydrate. Preferably, the tonicity agent such as sodium chloride will be employed in an amount to provide a final osmotic value of at least about 200 mOsm/kg, preferably from about 280 to about 370 mOsm/kg.

The present invention can be made generally according to the teachings of US Patent Application Serial No. 10/153,043 which is hereby incorporated by reference in its entirety.

Some embodiments of the invention include the following:

1) A preservative free bimatoprost and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: about 0.03% w/v bimatoprost; about 0.5% timolol; about 0.268% w/v sodium phosphate dibasic heptahydrate; about 0.014% citric Acid monohydrate; about 0.68% sodium chloride, water, hydrochloric acid, sodium hydroxide and and having a pH of about 7.3.

2) The preservative free bimatoprost and timolol solution of paragraph 1 for lowering intraocular pressure in a human patient comprising the following formulation: 0.03% w/v bimatoprost; 0.5% timolol; 0.268% w/v Sodium Phosphate Dibasic Heptahydrate; 0.014% Citric Acid

Monohydrate; about 0.68% sodium chloride, hydrochloric acid, water, sodium hydroxide and having a pH of about 7.3.

3) The preservative free bimatoprost and timolol solution of paragraphs 1 - 2 wherein the timolol is timolol maleate at 0.68% w/v.

4) A composition as described in Table 1.

5) The bimatoprost and timolol solution of paragraphs 1- 4 wherein the solution is useful for treating glaucoma.

6) The bimatoprost and timolol composition of paragraphs 1 – 4 wherein the composition is a solution wherein the solution is contained in a unit dose kit form.

7) The bimatoprost and timolol composition of any of paragraphs 1 – 6 wherein the composition is applied once a day to each eye.

8) The bimatoprost and timolol composition of any of paragraphs 1 - 6 wherein the composition is applied twice a day to each eye.

9) The bimatoprost and timolol compositions of paragraphs 1 – 4 wherein the composition has greater bioavailability of bimatoprost and timolol in the eye of the patient with fewer side-effects than bimatoprost and timolol preserved with benzalkonium chloride or another preservative.

10) The composition of paragraph 1 wherein the composition may be a solution, emulsion, dispersion, suspension, reverse emulsion and microemulsion.

11) The composition of paragraph 1 wherein the composition is contained in a unit-dose vial.

12) The composition of paragraph 1 wherein the composition is contained in a multi-dose vial which has anti-preservative properties such as metal-ions imbedded in its dispensing tip.

13) The composition of paragraph 12 wherein the metal ions are silver ions.

DETAILED DESCRIPTION OF THE INVENTION

A bimatoprost and timolol ophthalmic formulation of the present invention without preservative is shown in Table-1.

Table 1: Example of bimatoprost and timolol ophthalmic solution without preservative according to the present invention:

Ingredients	Units	Grade	Amount
Bimatoprost	% w/v	N/A	0.03
Timolol Maleate	% w/v	USP/Ph Eur	0.68
Sodium Phosphate Dibasic Heptahydrate	% w/v	USP	0.268
Citric Acid Monohydrate	% w/v	USP/Ph Eur	0.014
Sodium Chloride	% w/v	USP/Ph Eur	0.68
Hydrochloric Acid	% w/v	USP/Ph Eur	pH7.3
Sodium Hydroxide	% w/v	USP/Ph Eur	pH7.3
Purified Water/WFI	Q.S.	USP/Ph Eur	QS

The present invention is directed to formulations of bimatoprost and timolol without benzalkonium chloride as a preservative and may be marketed in unit dose form. As a result of the removal of benzalkonium chloride, the present invention results in the same as or greater bioavailability of the active ingredients bimatoprost and timolol in the eye without the unwanted side-effects associated with the preservative benzalkonium chloride such as hyperemia, which will improve efficacy of the product in lowering IOP per dosage unit, with superior patient compliance and fewer side-effects. Other side effects which may be avoided with the preservative free compositions of the present invention include , blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

Claims:

1) A preservative free bimatoprost and timolol composition for lowering intraocular pressure in a patient comprising the following formulation: about 0.03% w/v bimatoprost; about 0.5% timolol; about 0.268% w/v Sodium Phosphate Dibasic Heptahydrate; about 0.014% Citric Acid Monohydrate; about 0.68% sodium chloride; water and having a pH of about 7.3.

2) The preservative free bimatoprost and timolol composition of claim 1 for lowering intraocular pressure in a patient comprising the following formulation: 0.03% w/v bimatoprost; 0.5% timolol; 0.268% w/v Sodium Phosphate Dibasic Heptahydrate; 0.014% Citric Acid Monohydrate; about 0.68% sodium chloride; water and having a pH of about 7.3.

3) The preservative free bimatoprost and timolol solution of claim 2 wherein the timolol is timolol maleate at 0.68% w/v.

4) A composition as described in Table 1.

5) The bimatoprost and timolol composition of claim 1 wherein the composition is a solution and is useful for treating glaucoma.

6) The bimatoprost and timolol composition of claim 1 wherein the composition is contained in a unit dose kit form.

7) The bimatoprost and timolol composition of claim 1 wherein the composition is applied once a day to each eye.

8) The bimatoprost and timolol composition of claim 1 wherein the composition is applied twice a day to each eye.

9) The bimatoprost and timolol composition of claim 1 wherein the composition has greater bioavailability of bimatoprost and timolol in the eye of the patient with fewer side-effects than bimatoprost and timolol preserved with benzalkonium chloride.

10) The bimatoprost and timolol composition of claim 1 wherein the composition is a solution contained in a unit dose vial.