



(86) Date de dépôt PCT/PCT Filing Date: 2011/07/28
(87) Date publication PCT/PCT Publication Date: 2012/02/02
(45) Date de délivrance/Issue Date: 2018/05/22
(85) Entrée phase nationale/National Entry: 2013/01/29
(86) N° demande PCT/PCT Application No.: US 2011/045656
(87) N° publication PCT/PCT Publication No.: 2012/016000
(30) Priorité/Priority: 2010/07/29 (US61/368,681)

(51) Cl.Int./Int.Cl. *A61K 9/00* (2006.01),
A61K 45/06 (2006.01)
(72) Inventeurs/Inventors:
LIKITLERSUANG, SUKHON, US;
KELLY, WILLIAM F., US;
PARASHAR, AJAY P., US;
PUJARA, CHETAN P., US
(73) Propriétaire/Owner:
ALLERGAN, INC., US
(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : SOLUTIONS DE BRIMONIDINE ET DE TIMOLOL SANS CONSERVATEUR
(54) Title: PRESERVATIVE FREE BRIMONIDINE AND TIMOLOL SOLUTIONS

(57) **Abrégé/Abstract:**

The present invention is directed to preservative-free solutions of brimonidine and timolol for lowering intra-ocular pressure and treatment of glaucoma.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2012 (02.02.2012)



(10) International Publication Number
WO 2012/016000 A3

(51) International Patent Classification:

A61K 9/00 (2006.01) *A61K 45/06* (2006.01)

(21) International Application Number:

PCT/US2011/045656

(22) International Filing Date:

28 July 2011 (28.07.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/368,681 29 July 2010 (29.07.2010) US

(71) Applicant (for all designated States except US): **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, California 92612 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LIKITLER-SUANG, Sukhon** [TH/US]; 611 Wycliffe, Irvine, California 92602 (US). **KELLY, William F.** [US/US]; 5 Rodaja, Rancho Santa Margarita, California 92688 (US). **PARASHAR, Ajay P.** [IN/US]; 25 Palatine #206, Irvine, California 92616 (US). **PUJARA, Chetan P.** [IN/US]; 6 Wheeler, Irvine, California 92620 (US).

(74) Agents: **WURST, John** et al.; Allergan, Inc., 2525 Dupont Drive, Irvine, California 92612 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,

HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

15 March 2012

(54) Title: PRESERVATIVE FREE BRIMONIDINE AND TIMOLOL SOLUTIONS

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



WO 2012/016000 A3

Preservative Free Brimonidine and Timolol Solutions

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

20 Brimonidine tartrate is a selective and potent alpha-2 adrenergic agonist. Brimonidine lowers intraocular pressure by reducing aqueous humor production and increasing uveoscleral outflow. Timolol maleate is a non-selective beta adrenergic receptor blocking agent. Currently marketed brimonidine and timolol combination ophthalmic solution with preservative is indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately
25 controlled IOP.

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
30 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.

35 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, hyperemia, foreign body sensation, stinging or burning, and dry eye sensation.

40 Patients experiencing hypersensitivity reactions with benzalkonium chloride cannot use a commercial brimonidine and timolol products 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

5

The present invention is directed to a brimonidine and timolol solutions without benzalkonium chloride or other preservatives 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.

10

Brimonidine and timolol ophthalmic solution without preservative is a clear, greenish-yellow, isotonic, sterile solution. The drug product contains brimonidine 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 final solution would be an aqueous solution having a pH value within the range of about 6.5 to about 7.3, preferably 6.9 and osmolality in range of 260-220 mOsmol/kg.

15

20

The compositions of the present invention may be generally made according to the teachings of US Patent No. 7,323,463.

Certain embodiments of the present invention are described below:

25

1) A preservative free brimonidine and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: about 0.2% w/v brimonidine; about 0.5% w/v timolol; about 2.15% w/v sodium phosphate dibasic heptahydrate; water and at a pH of about 6.9.

30

2) A preservative free brimonidine and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: 0.2% w/v brimonidine; 0.5% w/v timolol; about 2.15% w/v sodium phosphate dibasic heptahydrate; hydrochloric acid, sodium hydroxide, and water and at a pH of about 6.9.

3) The preservative free composition of paragraphs 1 – 2 wherein the timolol is timolol maleate at 0.68% w/v and brimonidine is brimonidine tartrate.

35

4) A composition as described in Table 1.

5) The composition of any of paragraphs 1 – 4 wherein the composition is a solution and is useful for treating glaucoma.

- 6) The composition of any of paragraphs 1 – 4 wherein the composition is a solution and is contained in a unit dose kit form.
- 7) The composition of any of paragraphs 1 – 4 wherein the composition is applied at least once a day.
- 5 8) The composition of paragraph 2 wherein the composition is applied twice a day.
- 9) The composition of paragraphs 1 or 2 wherein the composition has greater bioavailability of brimonidine and timolol in the eye of the patient with fewer side-effects than brimonidine and timolol preserved with benzalkonium chloride.
- 10) The composition of paragraphs 1 and 2 wherein the composition is contained in a multi-dose vial
10 which has anti-preservative properties such as metal-ions imbedded in its dispensing tip.
- 11) The composition of paragraph 12 wherein the metal ions are silver ions.

DETAILED DESCRIPTION OF THE INVENTION

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

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

Ingredients	Units	Grade	Amount
Brimonidine Tartarate	% w/v	N/A	0.2
Timolol Maleate	% w/v	USP/Ph Eur	0.68
Sodium Phosphate Dibasic Heptahydrate	% w/v	USP	2.15
Sodium Phosphate Monobasic Monohydrate	% w/v	USP	0.43
Hydrochloric Acid	% w/v	USP/Ph Eur	pH 6.9
Sodium Hydroxide	% w/v	USP/Ph Eur	pH 6.9
Purified Water/ Water for injection	Q.S.	USP/Ph Eur	QS

25 The present invention is directed to formulations of brimonidine and timolol without benzalkonium chloride as a preservative. As a result of the removal of benzalkonium chloride, the present invention results in the same or greater bioavailability of the active ingredients bimatoprost and timolol in the eye without the unwanted side-effects associated with the preservative

benzalkonium chloride which will improve efficacy of the product in lowering IOP per dosage unit, superior patient compliance and with fewer side-effects such as hyperemia. Other side effects which may be avoided include asthenia, 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.

What is claimed is:

1. A preservative free brimonidine and timolol composition for lowering intraocular pressure (IOP) in a human patient comprising the following formulation: about 0.2% w/v brimonidine; about 0.5% w/v timolol; about 2.15% w/v sodium phosphate dibasic heptahydrate; and water and at a pH of about 6.9.
2. A preservative free brimonidine and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: 0.2% w/v brimonidine; 0.5% w/v timolol; about 2.15% w/v sodium phosphate dibasic heptahydrate; hydrochloric acid, sodium hydroxide, and water and at a pH of about 6.9.
3. The preservative free composition of claim 1, wherein the timolol is timolol maleate at 0.68% w/v and brimonidine is brimonidine tartrate.
4. A preservative free brimonidine and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: about 0.2% w/v brimonidine tartrate; about 0.68% w/v timolol maleate; about 2.15% w/v sodium phosphate dibasic heptahydrate; about 0.43% w/v sodium phosphate monobasic monohydrate; and water at a pH of about 6.9.
5. The composition of claim 1, wherein the composition is a solution and is useful for treating glaucoma.
6. The composition of claim 1, wherein the composition is a solution and is contained in a unit dose kit form.
7. The composition of claim 1, wherein the composition is for application at least once a day.
8. The composition of claim 2, wherein the composition is for application twice a day.
9. The composition of claim 1, wherein the composition has greater bioavailability of brimonidine and timolol in the eye of the patient with fewer side-effects than brimonidine and timolol preserved with benzalkonium chloride.

10. The composition as defined in any one of claims 1 to 9 for use in lowering IOP in a patient suffering from elevated IOP.
11. Use of a composition as defined in any one of claims 1 to 9 for lowering IOP in a patient suffering from elevated IOP.
12. Use of a composition as defined in any one of claims 1 to 9 for the manufacture of a medicament for lowering IOP in a patient suffering from elevated IOP.