



(51) International Patent Classification:

A61K 45/06 (2006.01) A61K 31/535 (2006.01)
A61K 9/08 (2006.01) A61K 31/5575 (2006.01)
A61K 47/12 (2006.01)

(21) International Application Number:

PCT/US2014/020210

(22) International Filing Date:

4 March 2014 (04.03.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13/785,911 5 March 2013 (05.03.2013) US

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(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, BN, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, KM, 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))

(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.



WO 2014/138018 A1

PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS

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CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims priority to U.S. Patent Application Serial No. 13/785,911, filed March 5, 2013 which is a continuation-in-part of U.S. Patent Application Serial No. 13/812,597, filed January 28, 2013, which claims priority to Provisional Patent Application Serial No. 61/368,685, filed July 29, 2010, both of which are hereby incorporated by reference in their 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 and tolerability standpoint while at least 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.

- 5 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
- 10 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:

- 15 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 and having no preservative.
- 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;
- 20 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 and 2, wherein the timolol is timolol maleate at 0.68% w/v.
- 25 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.
- 30 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 less ocular irritation than bimatoprost and timolol preserved with benzalkonium chloride .
- 35 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-microbial properties such as metal-ions imbedded in its dispensing tip.
 13) The composition of paragraph 12, wherein the metal ions are silver ions.
 5 14) The bimatoprost and timolol composition of paragraph 1, wherein the composition has better intraocular lowering ability and fewer side-effects than the same composition preserved with benzalkonium chloride.

DETAILED DESCRIPTION OF THE INVENTION

10 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

15 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, 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, hypermia, allergic conjunctivitis, eyelid edema, eyelid erythema,
 20 eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

Example 1

Ganfort® is a fixed combination of bimatoprost 0.03%/timolol 0.5% with 50 ppm benzalkonium chloride (BAK, as preservative) used in a number of countries worldwide as an effective treatment for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT). A preservative-free (PF) formulation of Ganfort®, hereafter referred to as Ganfort® PF, has been developed to cater to diverse patients needs. Ganfort® PF is the same formulation as that of Ganfort®, except for the removal of 50 ppm BAK. The use of a preservative-free formulation is preferred for patients who have a known sensitivity to preservatives or where preservative use is a concern particularly in patients with dry eyes or other ocular surface disorders.

The IOP lowering efficacy of a PF formulation of the bimatoprost component of Ganfort® was studied: In a 5-day, 30 patient, randomized, masked, paired-eye comparison study of bimatoprost 0.03 PF with bimatoprost 0.03% (preserved with 50 ppm BAK), the treatment difference (i.e. bimatoprost PF minus bimatoprost preserved) in IOP lowering efficacy on Days 2 - 5 ranged from -0.25 mmHg to +0.53 mmHg, mostly (9 out of 10 time points) favoring the preserved formulation (Clinical Study Report on file); In a 12 week, 597 patient, multi-center, randomized, masked, parallel group study, the a-priori defined primary efficacy analysis of IOP change from baseline in worse eye IOP at week 12 (per protocol population), showed a treatment difference of +0.02 to +0.32 mmHg favoring bimatoprost preserved (Clinical Study Report on file). Based on the results of these studies, and the known penetration enhancing effects of BAK, it was anticipated that the removal of BAK from Ganfort® PF would result in a reduction in its IOP lowering effect, though this may not be statistically significant.

For development of Ganfort® PF, a 12 week, multi-center, randomized, masked study was conducted in 561 patients with glaucoma or ocular hypertension, comparing the efficacy and safety of Ganfort® PF with Ganfort®. IOP was measured at 3 time points (hour 0, hour 2 and hour 8), at each of the study visits (baseline, weeks 2, 6 and 12). The study was designed to test for statistical non-inferiority as well as statistical equivalence of PF formulation with preserved formulation, based on pre-established criteria using IOP margins of 1.5 mmHg. Differences in the IOP lowering effects of the two formulations (Ganfort® PF minus Ganfort®) were evaluated, where a negative difference is indicative of greater IOP lowering by Ganfort® PF.

At baseline, no statistically or clinically significant differences in worse eye IOP (identified as the eye with higher baseline IOP) or average eye IOP (average IOP of both eyes) were observed between the Ganfort® PF and Ganfort® groups. While Ganfort® PF met the criteria for statistical non-inferiority and equivalence with Ganfort® based on the a priori established statistical criteria, the differences in treatments (Ganfort® PF – Ganfort®) in IOP lowering from baseline at all of the 9 follow-up time points (hours 0, 2 and 8, at weeks 2, 6 and 12), favored Ganfort® PF:

1) In a-priori defined primary analysis at week 12 (per protocol population), the treatment difference in change from baseline in worse eye IOP was -0.30 to -0.37 mmHg;

2) Across the 12 week study (ITT population), the treatment difference in change from baseline for worse eye IOP ranged from -0.12 to -0.54 mmHg, favoring Ganfort® PF at all follow up time points; and,

3) The treatment difference in change from baseline for average eye IOP ranged from -0.19 to -0.49 mmHg during weeks 2 to 12, favoring Ganfort® PF at all follow up time points.

Table I: Baseline and Change From Baseline in IOP (mm Hg) in Study of Example I

Worse Eye IOP ^a (PP)						Worse Eye IOP ^a (ITT)			Average Eye IOP ^b (ITT)		
Visit	Hour	Statistic	GANFORT® PF (N = 256)	GANFORT® (N = 260)	Difference (95% CI) ^c	GANFORT® PF (N = 278)	GANFORT® (N = 283)	Difference (95% CI) ^d	GANFORT® PF (N = 278)	GANFORT® (N = 283)	Difference (95% CI) ^e
Baseline	0	Mean	25.41	25.38	0.01	25.34	25.30	0.08	24.94	24.86	0.11
		SD	2.232	2.209	(-0.35, 0.37)	2.233	2.244	(-0.27, 0.42)	2.116	2.131	(-0.21, 0.43)
	2	Mean	24.79	24.72	0.04	24.71	24.61	0.14	24.29	24.23	0.09
		SD	2.676	2.470	(-0.38, 0.47)	2.700	2.536	(-0.27, 0.54)	2.515	2.426	(-0.29, 0.46)
	8	Mean	23.88	23.82	0.06	23.81	23.80	0.06	23.42	23.36	0.10
		SD	3.008	2.747	(-0.39, 0.50)	2.989	2.795	(-0.36, 0.49)	2.904	2.703	(-0.30, 0.51)
Week 2	0	Mean	-9.16	-8.94	-0.27	-9.01	-8.65	-0.36	-8.72	-8.37	-0.40
		SD	3.280	3.162	(-0.75, 0.21)	3.245	3.327	(-0.81, 0.09)	3.065	3.196	(-0.88, 0.08)
	2	Mean	-8.66	-8.46	-0.26	-8.53	-8.17	-0.37	-8.24	-8.00	-0.33
		SD	3.593	3.188	(-0.73, 0.20)	3.688	3.368	(-0.82, 0.07)	3.466	3.232	(-0.82, 0.16)
	8	Mean	-8.45	-8.14	-0.29	-8.22	-7.85	-0.43	-7.94	-7.53	-0.49
		SD	3.377	3.062	(-0.73, 0.16)	3.507	3.290	(-0.85, 0.00)	3.368	3.203	(-0.97, -0.01)
Week 6	0	Mean	-8.93	-9.03	-0.01	-8.89	-8.79	-0.12	-8.66	-8.55	-0.19
		SD	3.170	3.148	(-0.47, 0.45)	3.246	3.312	(-0.57, 0.33)	3.052	3.153	(-0.67, 0.29)
	2	Mean	-8.71	-8.60	-0.38	-8.69	-8.22	-0.54	-8.39	-8.05	-0.48
		SD	3.601	3.442	(-0.84, 0.08)	3.695	3.619	(-0.98, -0.09)	3.467	3.424	(-0.97, 0.02)
	8	Mean	-7.99	-8.05	-0.09	-7.94	-7.80	-0.23	-7.71	-7.54	-0.26
		SD	3.412	3.272	(-0.54, 0.37)	3.454	3.473	(-0.67, 0.21)	3.324	3.340	(-0.75, 0.22)
Week 12	0	Mean	-9.06	-8.72	-0.37	-8.94	-8.51	-0.46	-8.65	-8.30	-0.45
		SD	3.216	3.088	(-0.83, 0.10)	3.290	3.253	(-0.91, -0.01)	3.109	3.009	(-0.92, 0.02)
	2	Mean	-8.53	-8.38	-0.30	-8.44	-8.08	-0.40	-8.11	-7.86	-0.38
		SD	3.520	3.297	(-0.73, 0.14)	3.646	3.504	(-0.83, 0.03)	3.392	3.413	(-0.87, 0.11)
	8	Mean	-7.98	-7.72	-0.36	-7.87	-7.52	-0.45	-7.57	-7.27	-0.43
		SD	3.435	3.172	(-0.78, 0.07)	3.496	3.362	(-0.86, -0.03)	3.395	3.226	(-0.92, 0.05)

GANFORT® PF = bimatoprost 0.3 mg/mL + timolol 5 mg/mL preservative-free; IOP = intraocular pressure; ITT = intent-to-treat; PP = per protocol

In the ITT population, missing values were imputed using the last observation carried forward (LOCF) method.

^a Worse eye refers to the eye with the worse baseline IOP, which was determined as the eye with the higher mean diurnal IOP at baseline. If both eyes had the same mean diurnal IOP at baseline, the right eye was designated as the worse eye.

^b Average eye IOP refers to the average IOP of both eyes. ^cConfidence intervals (CI) are based on the analysis of covariance (ANCOVA) model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT®) is based on the least-squares means from the ANCOVA model. If patients had baseline IOP value excluded due to protocol deviations then they were not included in the change from baseline analyses.

^d CIs are based on the ANCOVA model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT®) is based on the least-squares means from the ANCOVA model.

^e CIs are based on the analysis of variance (ANOVA) model with treatment and investigator as fixed effects. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT®) is based on the least-squares means from the ANOVA model.

Source: Clinical Study Report on file

Other analysis of efficacy produced similar results. Hence Ganfort® PF, showed consistently numerically greater IOP reduction than Ganfort®.

5 Treatment in patients with glaucoma or OHT is aimed at lowering IOP in order to preserve visual function and hence quality of life. The impact of IOP reduction on disease progression have been well established (Kass et al, 2002; AGIS, 2000; Heijl et al, 2002), with data indicating that for each 1 mmHg of IOP reduction, the risk of progression is reduced by approximately 10% (Litchter, 2002; Leske et al, 2007). Preservative free formulations offer an alternative treatment for patients
10 who are sensitive to preservatives or who have susceptibility to preservative-related ocular surface adverse events. However, with the known penetration enhancing effects of BAK, it is anticipated that a loss in efficacy will be seen, in which case the treating physician has to balance treatment tolerability for a particular patient versus the undesired loss of IOP lowering efficacy. The results of the above – described study, showing an increased IOP lowering effect of removal of BAK in the
15 Ganfort® PF formulation is an unexpected finding that can benefit patients with glaucoma and OHT who often require efficacious, long term treatment.

BAK Effect

Given the known penetration enhancing effect of benzalkonium chloride (BAK), which is a preservative used in many marketed ophthalmic products, it was expected that Ganfort® Preservative
20 Free (PF), which does not contain the 50 ppm BAK present in Ganfort®, would result in lower ocular bioavailability of both bimatoprost and timolol, and consequently be less effective in lowering IOP than Ganfort®. Therefore, data from the above described study contradicted conventional wisdom.

What is claimed is:

- 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 and about 0.5% timolol
5 and having no preservative.
- 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
10 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.
- 15 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.
- 20 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.
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- 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 better
30 intraocular lowering ability and fewer side-effects than the same composition 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.
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/020210

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K45/06 A61K9/08 A61K47/12 A61K31/535 A61K31/5575
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/015998 A2 (ALLERGAN INC [US]; LIKITLERSUANG SUKHON [US]; PARASHAR AJAY P [US]; PU) 2 February 2012 (2012-02-02) claims; table 1	1-10
X	US 2010/210720 A1 (PILOTAZ FREDERIC [FR] ET AL) 19 August 2010 (2010-08-19) paragraphs [0024] - [0030] ----- -/-	1-3,5-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

14 April 2014

Date of mailing of the international search report

23/04/2014

Name and mailing address of the ISA/

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Giménez Miralles, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/020210

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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