FIXED DOSE COMBINATION OF BIMATOPROST AND BRIMONIDINE

By Inventors: Richard S. Graham, Chetan P Pujara, Sesha Neervannan, Anuradha V. Gore, and Kevin S. Warner

Related Application

This application claims the benefit of U.S. Provisional Application Serial No. 61/509,666, filed July 20, 2011, the disclosure of which is hereby incorporated in its entirety herein by reference.

Field of the Invention:

The present application is directed to composition comprising combinations of brimonidine and bimatoprost useful for lowering intraocular pressure in a patient and the treatment of glaucoma.

Background of the Invention:

Topically applied formulations (defined as formulations applied to the cornea, conjunctiva, etc.) are frequently used in ophthalmology to treat acute and chronic conditions because they are considered to be safer relative to systemically delivered formulations. While topically applied formulations may not produce a high systemic exposure of the active pharmaceutical ingredient, there is still the potential for adverse events (e.g., conjunctival hyperemia) due to topical exposure. Improving the side effect profile while still maintaining and possibly improving efficacy can be accomplished via the following: 1) reduce the concentration of the API to the lowest effective dose; 2) include a second API with a mechanism of action known to minimize the adverse event of the first API; 3) Include a second API which will provide a synergistic effect thereby improving the overall efficacy; and 4) improve patient compliance by reducing the number of different medications that need to be delivered. Specifically, this invention discloses the fixed dose combination of bimatoprost and brimonidine in an appropriate formulation vehicle.

Summary of the Invention:

Formulation development approaches to meet the above criteria for bimatoprost/brimonidine are described as follows:

1. Optimize the pH of the formulation to maximize the unionized fraction of brimonidine in aqueous formulations;
2. Incorporation of viscosity agents in the formulation to increase solution viscosity;

3. Incorporation of ocularly acceptable permeability enhancers to improve tissue bioavailability; and,
4. Non-aqueous based formulations.

The present invention is intended for use in patients who require more than one intraocular pressure lowering agent and/or to improve patient compliance for patients undergoing concurrent bimatoprost and brimoindine monotherapy.

"About" is defined as variations in amounts in either active compounds or excipients that would be considered bioequivalent by a regulatory agency such as the FDA or the EMEA.

"Effective amount" An "effective amount" of a compound is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. Where recited in reference to a disease treatment, an "effective amount" may also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s).

A "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

"Na-CMC" means sodium carboxymethyl cellulose and can be either low density, medium density or high density CMC and mixtures thereof.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein.

"Soluplus®" refers to the solubilizer sold by BASF known as polyvinyl capralactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCA-PVA-PEG).

The term "topical" in the context of methods described herein relates in the customary sense to the administration of a compound or pharmaceutical composition which is incorporated into a suitable pharmaceutical carrier and administered at a topical treatment site of a subject. Accordingly, the term "topical pharmaceutical composition" includes those

pharmaceutical forms in which the compound is administered externally by direct contact with a topical treatment site, e.g., the eye or the skin. The term "topical ocular pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directly to the eye.

The terms "treating" or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being.

Some embodiments of the invention include:

1) A topical composition for use in lowering IOP in a patient comprising an effective amount of bimatoprost and brimonidine and a pharmaceutically acceptable carrier.
2) The composition of embodiment 1 wherein the bimatoprost is present in the concentration range of 0.001 – 0.03 % w/w and the brimonidine is brimonidine tartrate and is present in the concentration range of 0.005 – 0.2% w/w.
3) The composition of embodiments 1 – 2 wherein the bimatoprost is present in the concentration of about 0.01% w/w and the brimonidine is present in the amount of about 0.1% w/w.
4) The composition of embodiments 1 – 3 wherein the composition further comprises excipients selected from the group of excipients listed in Table 1, Table 2 and Table 3.
5) The compositions of embodiment 4 wherein the excipients are present in concentrations at about the concentrations listed in Tables I, II and III.
6) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering the composition of embodiment 3.
7) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering a composition of embodiments 1 - 6.
8) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering one of the compositions listed in Table 1.
9) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering one of the compositions listed in Table 2 or Table 3.
10) The method of embodiments 1 – 9 wherein the composition is administered once a day.

11) The method of embodiments 1 – 9 wherein the composition is administered twice a day or more.

12) A topical composition for ophthalmic application for use in lowering intraocular pressure in a patient comprising about 0.01 % w/w bimatoprost and about 0.1% w/w brimonidine.

13) The composition of embodiment 12 wherein the bimatoprost is present in the concentration of 0.01% w/w and brimonidine is brimonidine tartrate and is present in the amount of 0.1% w/w in an aqueous vehicle.

14) The composition of embodiment 12 further comprising a solubulizer selected from the group consisting of Na-CMC and Soluplus®.

15) The composition of embodiment 12 further comprising buffers selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

16) The compositions of embodiment 12 further comprising tonicity agents wherein the tonicity agents are selected from the group consisting of NaCl and glycerin.

17) The composition of embodiment 12 further comprising preservatives wherein the preservatives are selected from the group consisting of benzalkoniun chloride and Purite.

18) The topical composition of embodiment 12 wherein the composition is a solution and is administered at least once a day.

19) The topical composition of embodiment 12 wherein the composition is administered twice a day.

20) The topical composition of embodiments 12 – 17 wherein the composition is useful in treating glaucoma wherein the glaucoma is selected from the group consisting of open-angle glaucoma, closed-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, and congenital glaucoma.

21) The composition of embodiment 12 wherein the composition of embodiment 12 lowers intraocular pressure more than either bimatoprost or brimonidine administered alone and with fewer side-effects.

22) A method of treating elevated intraocular pressure the method comprising administering a composition to a patient suffering elevated intraocular pressure wherein the composition comprises about 0.01% w/w bimatoprost and about 0.1% w/w brimonidine tartrate.

23) The method of embodiment 22 wherein the composition comprises 0.01% w/w bimatoprost and 0.1% w/w brimonidine.

24) The method of embodiment 22 wherein the composition further comprises a solubulizer selected from the group consisting of Na-CMC and Soluplus® and a buffer selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

25) The method of embodiments 22 - 24 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy (0.2%, 0.15%, or 0.1%) or bimatoprost monotherapy (0.03% or 0.01%).

26) The method of embodiments 22- 24 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy or bimatoprost monotherapy and with fewer overall ocular side effects than either brimonidine and bimatoprost monotherapy.

27) The method of embodiments 22 - 24 wherein the method is effective in treating glaucoma.

28) The method of embodiments 22 – 24 wherein the method is effective in lower ocular hypertension.

29) The method of embodiments 22 - 24 wherein the composition further comprises a preservative.

30) The method of embodiments 22 - 24 wherein the composition is administered at least once a day.

31) The method of embodiment 22 wherein the composition is applied topically to the eye.

Detailed Description of the Invention:

Table 1. Formulation Examples:

Example #	1	2	3	4	5	6	7	8	9	10	11
Active Ingredients	% (w/w)										
Bimatoprost	0.01										
Brimonidine	0.1										
Excipients	% (w/w)										
Hydroxyethyl cellulose										0.3-1	
Sodium phosphate dibasic	0.268	0.268	1.5		0.268	0.268	0.268	0.268	0.268	0.268	0.268
Citric acid	0.014	0.014	0.025		0.014	0.014	0.014	0.014	0.014	0.014	0.014
Glycerin	QS Osm 270-320				QS Osm 270-320			QS Osm 270-320	QS Osm 270-320	QS Osm 270-320	QS Osm 270-320
NaCl		QS Osm 270-320	QS Osm 270-320	QS Osm 270-320		QS Osm 270-320	QS Osm 270-320				
EDTA					0.01	0.01					0.01
Select one or more from the following: Solutol; Tween 20, 40, 60, or 80; Poloxamer, POE 40 Stearate;					0.001-1	0.001-1					0.5
Castor Oil											0.1
Sodium borate				0.045							
Boric acid				0.6							
pH	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8
BAK	0.005	0.005	0.005		0.005	0.005		0.003	0.02	0.005	0.005
Purite				0.01			0.01	0.005			
Water	QS 100%	QS 100%	QS 100%		QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%

Table 1. Formulation Examples Continued:

Example #	12	13	14	15
Active Ingredients	% (w/w)			
Bimatoprost	0.01			
Brimonidine	0.1			
Excipients	% (w/w)			
White petrolatum	QS 100			
Mineral Oil	30-40			5-10
Lanolin	5-15	5-15		
Beeswax		10-20		10-30
ST-Wax 30		8-12		5-10
Cetyl Alcohol		5-10		
Castor Oil		QS 100		QS 100
Jojoba Seed Oil				5-10
Silky Wax 10			5-15	
Cyclomethicone 5-NF			QS 100	
Caprylic/ capric triglyceride			5-15	
Isopropyl myristate			5-15	

Table 2. Further Formulation Examples:

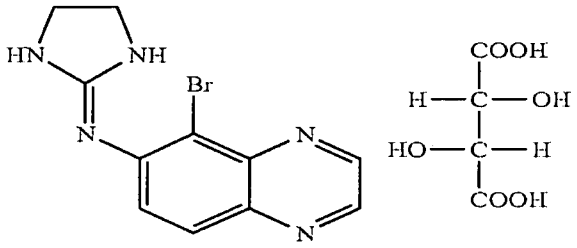
	Lipid Nanoparticle	Silicone with dispersed lipid nanoparticle
Active Ingredients	w/w%	
Bimatoprost	0.01	
Brimonidine	0.1	
Excipients	% (w/w)	
Silicone fluid		QS 100%
Dimethiconol blend 20		0-20
Crodamol MM	10-40	
Water	QS 100%	
Castor Oil		0-5
Solutol HS	0.01-5	
Glycerin	QS to 270-320 mOsm	
BAK	0.01	

The formulations of the present invention can be topically administered once, twice or three times a day in order to lower intraocular pressure in a patient.

The present formulations may be preserved or preservative free. Although the concentrations of actives in Tables 1 and 2 are preferred, bimatoprost may be present in

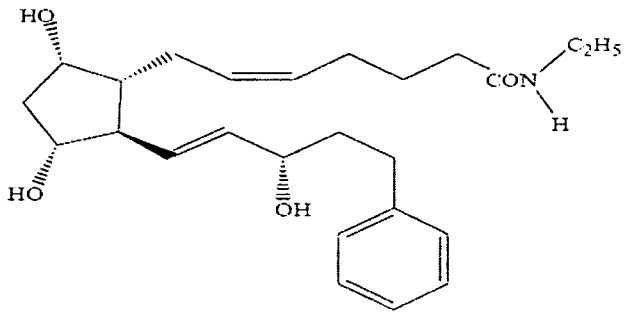
concentration ranges of 0.001 – 0.03 w/w and brimonidine may be present in 0.005 – 0.2% w/w. Concentrations of actives and excipients may be present in about the concentrations listed herein, wherein "about" refers to variations of the concentrations considered to be bioequivalent by the FDA or EMEA in making similar or generic compositions.

Brimonidine includes pharmaceutically acceptable salts of brimonidone such as brimonidine tartrate. Brimonidine tartrate is an alpha adrenergic agonist represented by the following formula:



The chemical name for brimonidine is 5-Bromo-6-(2-imizazolidinylideeneamno) quinoxaline L-tartrate.

Bimatoprost is represented by the following chemical structure:



Bimatoprost's chemical name is (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-

phenyl-1-pentenyl]cyclopentyl]-5-*N*-ethylheptenamide, and its molecular weight is 415.58. Its molecular and its formula is $C_{25}H_{37}NO_4$.

Table 3. Brimonidine/Bimatoprost Fixed Dose Combination Formulations for Stability Evaluation

Formulation#		1	2	3	4	5	6	7	8
Active Ingredients (% w/w)	Bimatoprost	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	Brimonidine (190342-LF)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Solubilizers (% w/w)	Na-CMC (Low viscosity 7LFPH)			0.5	0.5				
	Soluplus®	1	1						1
Buffers (% w/w)	Sodium phosphate dibasic heptahydrate	0.268		0.268		0.268	0.268	0.268	0.268
	Citric acid monohydrate	0.014		0.014		0.014	0.014	0.014	0.014
	Sodium borate decahydrate		0.095		0.095				
	Boric acid		0.229		0.229				
	Target pH	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.0 (6.7-7.3)	7.0 (6.7-7.3)	7.0 (6.7-7.3)	7.7 (7.4-8.0)
	1N Sodium Hydroxide/ 1N Hydrochloric Acid	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH
Tonicity Modifiers (% w/w)	NaCl			0.8	0.8	0.8	0.8	0.8	0.8
	Glycerin	2.3	2.3						
Preservatives (% w/w)	BAK	0.005				0.02	0.01	0.003	0.01
	Purite		0.01					0.01	
Vehicle (% w/w)	Purified Water	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100

Formulation stability for the formulation shown in Table 3 was as follows:

Formulation Stability

Table 4: Potency of Brimonidine in B2 Formulations (expressed as percent of label strength) over 3 months:

Stability		Time Zero	1 Month		3 Month	
			25C/40%RH	40C/25%RH	25C/40%RH	40C/25%RH
Soluplus ® containing formulation, pH 7.7	Formulation 1	100.3	102.1	101.7	99.7	100.2
	Formulation 2	99.4	101.4	102.2	N/A	N/A
	Formulation 8	100.9	101.9	104.1	101.8	102.6
Na CMC containing formulation, pH 7.7	Formulation 3	99.7	101.7	103.3	101.4	101.3
	Formulation 4	99.5	102.1	102.6	100.4	102.1
pH 7.0 formulation	Formulation 5	101.6	102.5	104.1	101.5	103.5
	Formulation 6	102.4	N/A	N/A	102.1	101.6
	Formulation 7	101.6	101.9	104.1	N/A	N/A

Table 5: Potency of Bimatoprost in B2 Formulations (expressed as percent of label strength) over 3 months

Stability		Time Zero	1 Month		3 Month	
			25C/40%RH	40C/25%RH	25C/40%RH	40C/25%RH
Soluplus ® containing formulation, pH 7.7	Formulation 1	101.6	99.8	100.5	99.0	100.4
	Formulation 2	88.6	82.1	81.8	N/A	N/A
	Formulation 8	100.1	97.1	98.6	96.6	97.3
Na CMC containing formulation, pH 7.7	Formulation 3	100.5	102.4	101.4	98.6	100.6
	Formulation 4	101.5	100.7	102.0	99.1	99.7
pH 7.0 formulation	Formulation 5	100.9	99.2	96.9	99.6	100.8
	Formulation 6	100.0	N/A	N/A	97.9	99.8
	Formulation 7	98.6	96.1	98.6	N/A	N/A

Note: Formulation 2 and 7 that contain purite were discontinued after 1 month pull due to drug degradation .

Table 6: Brimonidine/Bimatoprost Fixed Dose Combination Formulations for Rabbit PK Assessments

Formulation		Soluplus® Containing Formulation (pH 7.7)				NaCMC (pH 7.7)	pH 7.0 Formulation		Control	
		SP 0	SP 50	SP 100	SP 100 NaCl	NaCMC 0	LP 50	LP 100	Alphagan 0.2%	Lumigan 0.03%
Active Ingredients (% w/w)	Bimatoprost	0.01	0.01	0.01	0.01	0.01	0.01	0.01		0.03
	Brimonidine Tartrate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	
Solubilizers (% w/w)	**Na-CMC**					**0.5**				
	Soluplus®	**1**	**1**	**1**	**1**					
Buffers (% w/w)	Sodium phosphate dibasic heptahydrate	0.268	0.268	0.268	0.268	0.268	0.268	0.268		0.268
	Citric acid monohydrate	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.050	0.014
	Sodium Citrate Dihydrate								0.45	
	Target pH	**7.7**	**7.7**	**7.7**	**7.7**	**7.7**	**7.0**	**7.0**	**6.3**	**7.3**
Tonicity Modifiers (% w/w)	NaCl				0.8	0.80	0.80	0.8	0.70	0.83
	Glycerin	2.3	2.3	2.3						
Preservatives (ppm)	**BAK**		**50**	**100**	**100**		**50**	**100**	**50**	**50**
Vehicle (% w/w)	Purified Water	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100		

Table 7: Brimonidine and Bimatoprost in Aqueous Humor

Matrix	Treatment		Brimonidine			Bimatoprost		
			Tmax (hr)	Cmax (ng/mL)	AUClast (ng.hr/mL)	Tmax (hr)	Cmax (ng/mL)	AUClast (ng.hr/mL)
Aqueous Humor	Control	Alphagan 0.2% BID	1	472	927			
	pH 7.0 Formulation	LP 50 BID	0.5	295	494	1	9.46	35.1
		LP 100 BID	0.5	296	628	2	23.4	63.6
	Control	Lumigan 0.03% QD				1	39.9	140
	NaCMC pH 7.7	NaCMC 0 BID	0.5	463	758	1	9.44	34.3
	Soluplus® Containing Formulation, pH 7.7	SP 0 BID	0.5	349	611	2	5.16	16.7
		SP 50 BID	0.5	304	662	2	7.95	24.1
		SP 100 BID	0.5	445	677	2	6.35	23.9
		SP 100 NaCl BID	0.5	428	688	1	7.80	26.0
	LLOQ (AQH) = 0.1 ng/mL							

Examples

Example 1 - A 58 year old Caucasian male with elevated intraocular pressure ("IOP") is unresponsive to both brimonidine (0.15% w/v and 0.01% w/v) and bimatoprost monotherapy (both 0.03% w/v and 0.01% w/v) and unable to adequately control his elevated IOP. The 58 year old male administers Formulation 6, in Table 3 twice a day, once in the morning and once in the evening. Administration is 12 hours apart and every day. Within three days of use, the patient's IOP falls to clinically acceptable levels and remains at clinically acceptable levels as long as the patient applies Formula 6 twice a day.

Example 2 - a 71 year old African American female with ocular hypertension is unresponsive to both brimonidine and bimatoprost monotherapy and unable to control her IOP through the use of conventional glaucoma medications. The 71 year old patient administers Formulation 8, in Table 3, once each day. Within seven days of use, the patient's IOP falls to clinically acceptable levels and remains at clinically acceptable levels for over 120 days of daily administration of Formulation 8.

Example 3 – A 68 year old Caucasian male with elevated intraocular pressure, open-angle glaucoma and with sensitivity to ophthalmic preservatives is administered Formulation 3 in Table 3 on a once daily basis. After several days of use, the patients intraocular pressure drops to therapeutically acceptable levels and stays at therapeutically acceptable levels so long as daily administration of Formulation 3 is continued. After 6 months of daily use of Formulation 3, there is no further worsening of the patient's glaucoma and no further detectable damage to the optic nerve.

Example 4 – A 73 Hispanic female suffering ocular hypertension ranging from 17 – 20 mm Hg is unresponsive to commercially available brimonidine and bimatoprost monotherapy. The patient is administered Formulation 5 of Table 3 once a day and after two days the patient's intraocular pressure lowers to acceptable levels. The patient continues administering Formulation 5 every day and intraocular pressure levels remained at therapeutically acceptable levels.

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Related Application

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Field of the Invention:

The present application is directed to composition comprising combinations of brimonidine and bimatoprost useful for lowering intraocular pressure in a patient and the treatment of glaucoma.

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Topically applied formulations (defined as formulations applied to the cornea, conjunctiva, etc.) are frequently used in ophthalmology to treat acute and chronic conditions because they are considered to be safer relative to systemically delivered formulations. While topically applied formulations may not produce a high systemic exposure of the active pharmaceutical ingredient, there is still the potential for adverse events (e.g., conjunctival hyperemia) due to topical exposure. Improving the side effect profile while still maintaining and possibly improving efficacy can be accomplished via the following: 1) reduce the concentration of the API to the lowest effective dose; 2) include a second API with a mechanism of action known to minimize the adverse event of the first API; 3) Include a second API which will provide a synergistic effect thereby improving the overall efficacy; and 4) improve patient compliance by reducing the number of different medications that need to be delivered. Specifically, this invention discloses the fixed dose combination of bimatoprost and brimonidine in an appropriate formulation vehicle.

Summary of the Invention:

Formulation development approaches to meet the above criteria for bimatoprost/brimonidine are described as follows:

1. Optimize the pH of the formulation to maximize the unionized fraction of brimonidine in aqueous formulations;
2. Incorporation of viscosity agents in the formulation to increase solution viscosity;

bioavailability; and,

4. Non-aqueous based formulations.

The present invention is intended for use in patients who require more than one intraocular pressure lowering agent and/or to improve patient compliance for patients undergoing concurrent bimatoprost and brimoindine monotherapy.

"About" is defined as variations in amounts in either active compounds or excipients that would be considered bioequivalent by a regulatory agency such as the FDA or the EMEA.

"Effective amount" An "effective amount" of a compound is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. Where recited in reference to a disease treatment, an "effective amount" may also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s).

A "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

"Na-CMC" means sodium carboxymethyl cellulose and can be either low density, medium density or high density CMC and mixtures thereof.

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein.

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The term "topical" in the context of methods described herein relates in the customary sense to the administration of a compound or pharmaceutical composition which is incorporated into a suitable pharmaceutical carrier and administered at a topical treatment site of a subject. Accordingly, the term "topical pharmaceutical composition" includes those

with a topical treatment site, e.g., the eye or the skin. The term "topical ocular pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directly to the eye.

The terms "treating" or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being.

Some embodiments of the invention include:

1) A topical composition for use in lowering IOP in a patient comprising an effective amount of bimatoprost and brimonidine and a pharmaceutically acceptable carrier.
2) The composition of embodiment 1 wherein the bimatoprost is present in the concentration range of 0.001 – 0.03 % w/w and the brimonidine is brimonidine tartrate and is present in the concentration range of 0.005 – 0.2% w/w.
3) The composition of embodiments 1 – 2 wherein the bimatoprost is present in the concentration of about 0.01% w/w and the brimonidine is present in the amount of about 0.1% w/w.
4) The composition of embodiments 1 – 3 wherein the composition further comprises excipients selected from the group of excipients listed in Table 1, Table 2 and Table 3.
5) The compositions of embodiment 4 wherein the excipients are present in concentrations at about the concentrations listed in Tables I, II and III.
6) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering the composition of embodiment 3.
7) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering a composition of embodiments 1 - 6.
8) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering one of the compositions listed in Table 1.
9) A method of lowering intraocular pressure or treating glaucoma in a human patient comprising administering one of the compositions listed in Table 2 or Table 3.
10) The method of embodiments 1 – 9 wherein the composition is administered once a day.

day or more.

12) A topical composition for ophthalmic application for use in lowering intraocular pressure in a patient comprising about 0.01 % w/w bimatoprost and about 0.1% w/w brimonidine.

13) The composition of embodiment 12 wherein the bimatoprost is present in the concentration of 0.01% w/w and brimonidine is brimonidine tartrate and is present in the amount of 0.1% w/w in an aqueous vehicle.

14) The composition of embodiment 12 further comprising a solubulizer selected from the group consisting of Na-CMC and Soluplus®.

15) The composition of embodiment 12 further comprising buffers selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

16) The compositions of embodiment 12 further comprising tonicity agents wherein the tonicity agents are selected from the group consisting of NaCl and glycerin.

17) The composition of embodiment 12 further comprising preservatives wherein the preservatives are selected from the group consisting of benzalkoniun chloride and Purite.

18) The topical composition of embodiment 12 wherein the composition is a solution and is administered at least once a day.

19) The topical composition of embodiment 12 wherein the composition is administered twice a day.

20) The topical composition of embodiments 12 – 17 wherein the composition is useful in treating glaucoma wherein the glaucoma is selected from the group consisting of open-angle glaucoma, closed-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, and congenital glaucoma.

21) The composition of embodiment 12 wherein the composition of embodiment 12 lowers intraocular pressure more than either bimatoprost or brimonidine administered alone and with fewer side-effects.

22) A method of treating elevated intraocular pressure the method comprising administering a composition to a patient suffering elevated intraocular pressure wherein the composition comprises about 0.01% w/w bimatoprost and about 0.1% w/w brimonidine tartrate.

bimatoprost and 0.1% w/w brimonidine.

24) The method of embodiment 22 wherein the composition further comprises a solubulizer selected from the group consisting of Na-CMC and Soluplus® and a buffer selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

25) The method of embodiments 22 - 24 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy (0.2%, 0.15%, or 0.1%) or bimatoprost monotherapy (0.03% or 0.01%).

26) The method of embodiments 22- 24 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy or bimatoprost monotherapy and with fewer overall ocular side effects than either brimonidine and bimatoprost monotherapy.

27) The method of embodiments 22 - 24 wherein the method is effective in treating glaucoma.

28) The method of embodiments 22 – 24 wherein the method is effective in lower ocular hypertension.

29) The method of embodiments 22 - 24 wherein the composition further comprises a preservative.

30) The method of embodiments 22 - 24 wherein the composition is administered at least once a day.

31) The method of embodiment 22 wherein the composition is applied topically to the eye.

Table 1. Formulation Examples:

Example #	1	2	3	4	5	6	7	8	9	10	11
Active Ingredients	% (w/w)										
Bimatoprost	0.01										
Brimonidine	0.1										
Excipients	% (w/w)										
Hydroxyethyl cellulose										0.3-1	
Sodium phosphate dibasic	0.268	0.268	1.5		0.268	0.268	0.268	0.268	0.268	0.268	0.268
Citric acid	0.014	0.014	0.025		0.014	0.014	0.014	0.014	0.014	0.014	0.014
Glycerin	QS Osm 270-320				QS Osm 270-320			QS Osm 270-320	QS Osm 270-320	QS Osm 270-320	QS Osm 270-320
NaCl		QS Osm 270-320	QS Osm 270-320	QS Osm 270-320		QS Osm 270-320	QS Osm 270-320				
EDTA					0.01	0.01					0.01
Select one or more from the following: Solutol; Tween 20, 40, 60, or 80; Poloxamer, POE 40 Stearate;					0.001-1	0.001-1					0.5
Castor Oil											0.1
Sodium borate				0.045							
Boric acid				0.6							
pH	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8	7.0-7.8
BAK	0.005	0.005	0.005		0.005	0.005		0.003	0.02	0.005	0.005
Purite				0.01			0.01	0.005			
Water	QS 100%	QS 100%	QS 100%		QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%	QS 100%

Example #	12	13	14	15
Active Ingredients	% (w/w)			
Bimatoprost	0.01			
Brimonidine	0.1			
Excipients	% (w/w)			
White petrolatum	QS 100			
Mineral Oil	30-40			5-10
Lanolin	5-15	5-15		
Beeswax		10-20		10-30
ST-Wax 30		8-12		5-10
Cetyl Alcohol		5-10		
Castor Oil		QS 100		QS 100
Jojoba Seed Oil				5-10
Silky Wax 10			5-15	
Cyclomethicone 5-NF			QS 100	
Caprylic/ capric triglyceride			5-15	
Isopropyl myristate			5-15	

Table 2. Further Formulation Examples:

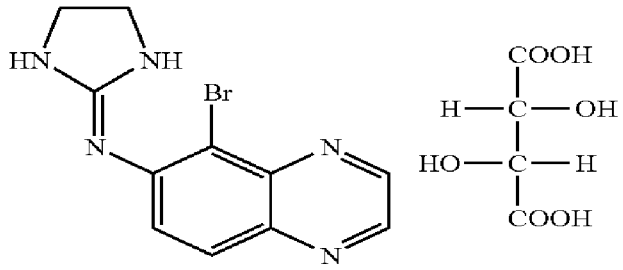
	Lipid Nanoparticle	Silicone with dispersed lipid nanoparticle
Active Ingredients	w/w%	
Bimatoprost	0.01	
Brimonidine	0.1	
Excipients	% (w/w)	
Silicone fluid		QS 100%
Dimethiconol blend 20		0-20
Crodamol MM	10-40	
Water	QS 100%	
Castor Oil		0-5
Solutol HS	0.01-5	
Glycerin	QS to 270-320 mOsm	
BAK	0.01	

The formulations of the present invention can be topically administered once, twice or three times a day in order to lower intraocular pressure in a patient.

The present formulations may be preserved or preservative free. Although the concentrations of actives in Tables 1 and 2 are preferred, bimatoprost may be present in

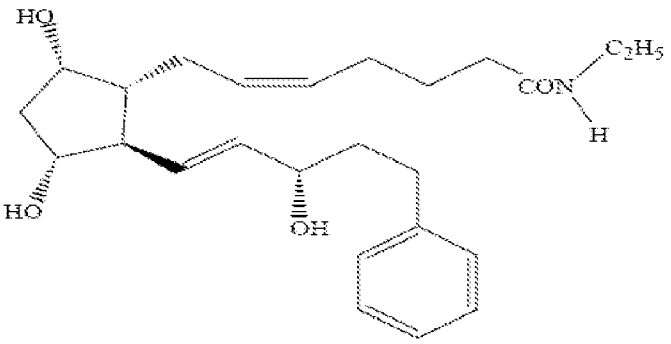
w/w. Concentrations of actives and excipients may be present in about the concentrations listed herein, wherein "about" refers to variations of the concentrations considered to be bioequivalent by the FDA or EMEA in making similar or generic compositions.

Brimonidine includes pharmaceutically acceptable salts of brimonidone such as brimonidine tartrate. Brimonidine tartrate is an alpha adrenergic agonist represented by the following formula:



The chemical name for brimonidine is 5-Bromo-6-(2-imizazolidinylideeneamno) quinoxaline L-tartrate.

Bimatoprost is represented by the following chemical structure:



Bimatoprost's chemical name is (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-

phenyl-1-pentenyl]cyclopentyl]-5-*N*-ethylheptenamide, and its molecular weight is 415.58. Its molecular and its formula is $C_{25}H_{37}NO_4$.

Table 3. Brimonidine/Bimatoprost Fixed Dose Combination Formulations for Stability Evaluation

Formulation#		1	2	3	4	5	6	7	8
Active Ingredients (% w/w)	Bimatoprost	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	Brimonidine (190342-LF)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Solubilizers (% w/w)	Na-CMC (Low viscosity 7LFPH)			0.5	0.5				
	Soluplus®	1	1						1
Buffers (% w/w)	Sodium phosphate dibasic heptahydrate	0.268		0.268		0.268	0.268	0.268	0.268
	Citric acid monohydrate	0.014		0.014		0.014	0.014	0.014	0.014
	Sodium borate decahydrate		0.095		0.095				
	Boric acid		0.229		0.229				
	Target pH	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.7 (7.4-8.0)	7.0 (6.7-7.3)	7.0 (6.7-7.3)	7.0 (6.7-7.3)	7.7 (7.4-8.0)
	1N Sodium Hydroxide/ 1N Hydrochloric Acid	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH	QS to pH
Tonicity Modifiers (% w/w)	NaCl			0.8	0.8	0.8	0.8	0.8	0.8
	Glycerin	2.3	2.3						
Preservatives (% w/w)	BAK	0.005				0.02	0.01	0.003	0.01
	Purite		0.01					0.01	
Vehicle (% w/w)	Purified Water	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100

Formulation stability for the formulation shown in Table 3 was as follows:

Formulation Stability

Table 4: Potency of Brimonidine in B2 Formulations (expressed as percent of label strength) over 3 months:

Stability		Time Zero	1 Month		3 Month	
			25C/40%RH	40C/25%RH	25C/40%RH	40C/25%RH
Soluplus ® containing formulation, pH 7.7	Formulation 1	100.3	102.1	101.7	99.7	100.2
	Formulation 2	99.4	101.4	102.2	N/A	N/A
	Formulation 8	100.9	101.9	104.1	101.8	102.6
Na CMC containing formulation, pH 7.7	Formulation 3	99.7	101.7	103.3	101.4	101.3
	Formulation 4	99.5	102.1	102.6	100.4	102.1
pH 7.0 formulation	Formulation 5	101.6	102.5	104.1	101.5	103.5
	Formulation 6	102.4	N/A	N/A	102.1	101.6
	Formulation 7	101.6	101.9	104.1	N/A	N/A

Table 5: Potency of Bimatoprost in B2 Formulations (expressed as percent of label strength) over 3 months

Stability		Time Zero	1 Month		3 Month	
			25C/40%RH	40C/25%RH	25C/40%RH	40C/25%RH
Soluplus ® containing formulation, pH 7.7	Formulation 1	101.6	99.8	100.5	99.0	100.4
	Formulation 2	88.6	82.1	81.8	N/A	N/A
	Formulation 8	100.1	97.1	98.6	96.6	97.3
Na CMC containing formulation, pH 7.7	Formulation 3	100.5	102.4	101.4	98.6	100.6
	Formulation 4	101.5	100.7	102.0	99.1	99.7
pH 7.0 formulation	Formulation 5	100.9	99.2	96.9	99.6	100.8
	Formulation 6	100.0	N/A	N/A	97.9	99.8
	Formulation 7	98.6	96.1	98.6	N/A	N/A

Note: Formulation 2 and 7 that contain purite were discontinued after 1 month pull due to drug degradation .

Table 6: Brimonidine/Bimatoprost Fixed Dose Combination Formulations for Rabbit PK Assessments

Formulation		Soluplus® Containing Formulation (pH 7.7)				NaCMC (pH 7.7)	pH 7.0 Formulation		Control	
		SP 0	SP 50	SP 100	SP 100 NaCl	NaCMC 0	LP 50	LP 100	Alphagan 0.2%	Lumigan 0.03%
Active Ingredients (% w/w)	Bimatoprost	0.01	0.01	0.01	0.01	0.01	0.01	0.01		0.03
	Brimonidine Tartrate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	
Solubilizers (% w/w)	**Na-CMC**					**0.5**				
	Soluplus®	**1**	**1**	**1**	**1**					
Buffers (% w/w)	Sodium phosphate dibasic heptahydrate	0.268	0.268	0.268	0.268	0.268	0.268	0.268		0.268
	Citric acid monohydrate	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.050	0.014
	Sodium Citrate Dihydrate								0.45	
	Target pH	**7.7**	**7.7**	**7.7**	**7.7**	**7.7**	**7.0**	**7.0**	**6.3**	**7.3**
Tonicity Modifiers (% w/w)	NaCl				0.8	0.80	0.80	0.8	0.70	0.83
	Glycerin	2.3	2.3	2.3						
Preservatives (ppm)	**BAK**		**50**	**100**	**100**		**50**	**100**	**50**	**50**
Vehicle (% w/w)	Purified Water	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100	Q.S. to 100		

Table 7: Brimonidine and Bimatoprost in Aqueous Humor

Matrix	Treatment		Brimonidine			Bimatoprost		
			Tmax (hr)	Cmax (ng/mL)	AUClast (ng.hr/mL)	Tmax (hr)	Cmax (ng/mL)	AUClast (ng.hr/mL)
Aqueous Humor	Control	Alphagan 0.2% BID	1	472	927			
	pH 7.0 Formulation	LP 50 BID	0.5	295	494	1	9.46	35.1
		LP 100 BID	0.5	296	628	2	23.4	63.6
	Control	Lumigan 0.03% QD				1	39.9	140
	NaCMC pH 7.7	NaCMC 0 BID	0.5	463	758	1	9.44	34.3
	Soluplus® Containing Formulation, pH 7.7	SP 0 BID	0.5	349	611	2	5.16	16.7
		SP 50 BID	0.5	304	662	2	7.95	24.1
		SP 100 BID	0.5	445	677	2	6.35	23.9
		SP 100 NaCl BID	0.5	428	688	1	7.80	26.0
	LLOQ (AQH) = 0.1 ng/mL							

Examples

Example 1 - A 58 year old Caucasian male with elevated intraocular pressure ("IOP") is unresponsive to both brimonidine (0.15% w/v and 0.01% w/v) and bimatoprost monotherapy (both 0.03% w/v and 0.01% w/v) and unable to adequately control his elevated IOP. The 58 year old male administers Formulation 6, in Table 3 twice a day, once in the morning and once in the evening. Administration is 12 hours apart and every day. Within three days of use, the patient's IOP falls to clinically acceptable levels and remains at clinically acceptable levels as long as the patient applies Formula 6 twice a day.

Example 2 - a 71 year old African American female with ocular hypertension is unresponsive to both brimonidine and bimatoprost monotherapy and unable to control her IOP through the use of conventional glaucoma medications. The 71 year old patient administers Formulation 8, in Table 3, once each day. Within seven days of use, the patient's IOP falls to clinically acceptable levels and remains at clinically acceptable levels for over 120 days of daily administration of Formulation 8.

Example 3 – A 68 year old Caucasian male with elevated intraocular pressure, open-angle glaucoma and with sensitivity to ophthalmic preservatives is administered Formulation 3 in Table 3 on a once daily basis. After several days of use, the patients intraocular pressure drops to therapeutically acceptable levels and stays at therapeutically acceptable levels so long as daily administration of Formulation 3 is continued. After 6 months of daily use of Formulation 3, there is no further worsening of the patient's glaucoma and no further detectable damage to the optic nerve.

Example 4 – A 73 Hispanic female suffering ocular hypertension ranging from 17 – 20 mm Hg is unresponsive to commercially available brimonidine and bimatoprost monotherapy. The patient is administered Formulation 5 of Table 3 once a day and after two days the patient's intraocular pressure lowers to acceptable levels. The patient continues administering Formulation 5 every day and intraocular pressure levels remained at therapeutically acceptable levels.

Claims:

1) A topical composition for ophthalmic application for use in lowering intraocular pressure in a patient comprising about 0.01 % w/w bimatoprost and about 0.1% w/w brimonidine.

2) The composition of claim 1 wherein the bimatoprost is present in the concentration of 0.01% w/w and brimonidine is brimonidine tartrate and is present in the amount of 0.1% w/w in an aqueous vehicle.

3) The composition of claim 2 further comprising a solubilizer selected from the group consisting of Na-CMC and Soluplus®.

4) The composition of claim 2 further comprising buffers selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

5) The compositions of claim 2 further comprising tonicity agents wherein the tonicity agents are selected from the group consisting of NaCl and glycerin.

6) The composition of claim 2 further comprising preservatives wherein the preservatives are selected from the group consisting of benzalkoniun chloride and Purite.

7) The topical composition of claim 2 wherein the composition is a solution and is administered at least once a day.

8) The topical composition of claim 2 wherein the composition is administered twice a day.

9) The topical composition of claim 2 wherein the composition is useful in treating glaucoma wherein the glaucoma is selected from the group consisting of open-angle glaucoma, closed-angle glaucoma, angle-closure glaucoma, normal-tension glaucoma, and congenital glaucoma.

10) The composition of claim 2 wherein the composition of claim 2 lowers intraocular pressure more than either bimatoprost or brimonidine administered alone and with fewer side-effects.

11) A method of treating elevated intraocular pressure the method comprising administering a composition to a patient suffering elevated intraocular pressure wherein the composition comprises about 0.01% w/w bimatoprost and about 0.1% w/w brimonidine tartrate.

12) The method of claim 11 wherein the composition comprises 0.01% w/w bimatoprost and 0.1% w/w brimonidine.

13) The method of claim 11 wherein the composition further comprises a solubulizer selected from the group consisting of Na-CMC and Soluplus® and a buffer selected from the group consisting of sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium borate decahydrate, sodium hydroxide and hydrochloric acid.

14) The method of claim 11 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy or bimatoprost monotherapy.

15) The method of claim 14 wherein the composition of claim 11 lowers intraocular pressure more effectively than either brimonidine monotherapy or bimatoprost monotherapy and with fewer overall ocular side effects than either brimonidine and bimatoprost monotherapy.

16) The method of claim 11 wherein the method is effective in treating glaucoma.

17) The method of claim 11 wherein the method is effective in lower ocular hypertension.

18) The method of claim 11 wherein the composition further comprises a preservative.

19) The method of claim 11 wherein the composition is administered at least once a day.

20) The method of claim 11 wherein the composition is applied topically to the eye.