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PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
John	Wurst	Poway, CA
Additional inventors are being named on the _____ separately numbered sheets attached hereto.		
TITLE OF THE INVENTION (500 characters max):		
Methods and Compositions for the Treatment of Hair Loss		
Direct all correspondence to: CORRESPONDENCE ADDRESS		
☐ The address corresponding to Customer Number:		
OR		
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ENCLOSED APPLICATION PARTS (check all that apply)		
☐ Application Data Sheet. See 37 CFR 1.76.		
☐ CD(s), Number of CDs _____		
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☐ Other (specify) _____		
☒ Specification (e.g., description of the invention) Number of Pages 48		
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No.



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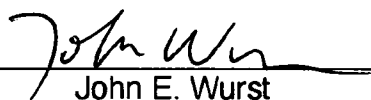
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SIGNATURE



DATE

3/18/2020

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40,283

(if appropriate)

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DOCKET NUMBER

Methods and Compositions for the Treatment of Hair Loss

1. Field of the Invention

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The present invention is directed to the use of certain prostaglandin analogues alone and in combination with other compounds such as cyclosporine, to prevent hair loss and/or grow hair. The present invention is also directed to formulations containing prostaglandin analogues and cyclosporine or other compounds such as minoxidil and finasteride to grow hair or prevent hair loss on the scalp and other areas of the body. The present invention is also directed to formulations and methods for treating certain hair loss disorders such as androgenetic alopecia and alopecia areata.

2. Background of the Invention

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Hair loss is a psychologically devastating condition causing significant psychological stress in both men and women. Thirty percent of all males will experience some hair loss by the age of thirty years, fifty percent by the age of fifty years, and eighty percent by the age of seventy years. By age sixty, forty percent of women experience hair loss. Negative effects on quality of life due to hair loss have been reported by men and in particular adolescents and women.

Hair growth is generally divided into three phases. The anagen phase is the phase of active hair growth which last two to six years but generally three to five years with scalp hair. The catagen phase is a short transitional phase between the anagen phase and the telogen phases which lasts seven to fourteen days with scalp hair. The telogen phase is called the “resting phase” where hair growth ceases and the hair is eventually shed. The anagen phase begins again with new hair growth. In humans without a hair loss disorder, about ninety percent of the hairs on the scalp are in the anagen phase, about one to two percent are in the catagen phase and about eight to nine percent of scalp hair are in the telogen phase, which is the active growth phase which lasts approximately three to four months. With the onset of androgenetic alopecia, a

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greater proportion of hair are in the telogen phase and fewer hairs are in the anagen phase. In people with androgenetic alopecia, the patient has significantly fewer follicles than people suffering no hair loss, with a typical bald person having roughly three hundred hair follicles per square inch on their scalp while a person with little to no hair loss will have about four hundred and fifty hair follicles per square inch. Perhaps more importantly, in the active hair follicles in a person suffering from alopecia, more of the hairs in the follicles will be vellus hairs rather than terminal hairs which are longer, thicker in diameter and more pigmented. Also, an increased number of hairs will be in the telogen phase. The difference between producing a long or short human hair is generally due the length of anagen, the growing part of the hair growth cycle, rather than the rate of hair growth, which is relatively constant *in vivo*.

3. Summary of the Invention

The Summary of Invention includes the following embodiments:

1. A composition for use in the treatment of hair loss comprising about 0.05% – 0.1% w/w latanoprost or latanoprost acid and 0.05% - 0.1% cyclosporine A.
2. The composition of embodiment 1 wherein the composition has about 0.05% w/w latanoprost or latanoprost acid and about 0.06% w/w cyclosporine A and about 10% w/w diethylene glycol monoethyl ether.
3. The composition of embodiment 2 further comprising oleyl alcohol.
4. The composition further comprising polyethylene glycol.
5. A composition for use in growing hair on a patient that experiencing hair loss comprising about 0.05% – 0.3% w/w latanoprost or latanoprost acid and 0.05% - 0.3% w/w cyclosporine A and 5.0% – 15.0% w/w CAPTEX 300 EP/NF.
6. The composition of embodiment 5 wherein composition comprises 0.08% w/w latanoprost or latanoprost acid and 0.08% w/w cyclosporine A.
7. The composition of embodiment 6 further comprising 10% w/w CAPTEX 300 EP/NF.

8. A composition for use in treating hair loss comprising about 0.05% – 0.3% w/w travoprost or travoprost acid and 0.05% - 0.3% w/w cyclosporine A.
9. The composition according to embodiment 8 further comprising one selected from the group consisting of diethylene glycol monoethyl ether, CAPTEX 300 EP/NF and polyethylene glycol.
10. The composition according to embodiments 1, 5 and 9 further comprising oleic acid.
11. A method of preventing hair loss on a patient comprising administering a formulation according to one of embodiments 1, 5 and 9 to a patient in need thereof.
12. The method of embodiment 11 wherein the formulation is applied once a day at approximately 1ml/day.
13. The method of embodiment 11 wherein the formulation is applied twice a day at approximately 2ml/day.
14. A method for causing hair growth in a patient suffering from hair loss comprising administering a formulation according to one of embodiments 1, 5 and 9 to a patient in need thereof.
15. The method of embodiment 14 wherein the patient experiences hair growth to a greater extent by applying the formulation of one of embodiments 1, 5 and 9 as compared to if the patient had not applied the formulation.
16. The method of embodiments 10 – 15 wherein the formulation maintains the hair in anaphase longer than if the formulation had not been applied.
17. The method of embodiment 14 wherein the patient reverses a substantial amount of hair loss.
18. The method of embodiment 14 wherein the formulation comprises 0.08% w/w latanoprost acid and 0.08% w/w cyclosporine A and a pharmaceutically acceptable solvent and a penetration enhancer.
19. The method of growing hair on a scalp of a patient wherein the formulation comprises 0.1% w/w latanoprost or latanoprost free acid.
20. The method of embodiment 19 wherein the formulation also contains cyclosporine and is cyclosporine A.

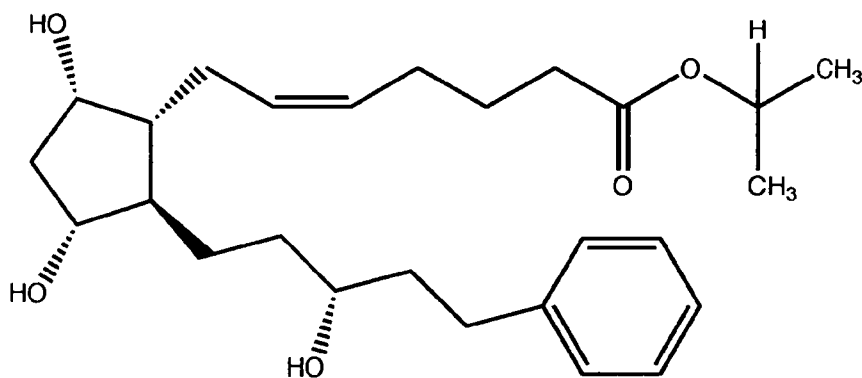
21. A composition for use in the treatment of hair loss comprising about 0.05% – 0.3% w/w bimatoprost and 0.05% - 0.3% cyclosporine A and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.
- 5 22. A composition for use in growing hair comprising about 0.05% – 0.3% w/w bimatoprost and 0.05% - 0.5% cyclosporine A and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.
23. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.5% w/w latanoprost or latanoprost acid and 1.0% - 7.0% minoxidil or minoxidil sulphate.
- 10 24. The composition of embodiment 23 wherein the composition has about 0.1% w/w latanoprost or latanoprost acid and about 5.0% w/w minoxidil.
25. The composition of embodiment 23 further comprising oleyl alcohol or ethanol.
26. The composition of embodiment 23 further comprising polyethylene glycol.
- 15 27. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.5% w/w bimatoprost or bimatoprost acid and 1.0% - 7.0% w/w minoxidil or minoxidil sulphate.
28. The composition of claim 27 wherein the composition has about 0.3% w/w latanoprost or latanoprost acid and about 5.0% w/w minoxidil.
29. The composition of claim 27 further comprising oleyl alcohol or ethanol.
- 20 30. The composition of claim 27 further comprising polyethylene glycol.
31. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.5% w/w travoprost or travoprost free acid and 1.0% - 7.0% minoxidil or minoxidil sulphate.
- 25 32. The composition of claim 31 wherein the composition has about 0.1% w/w travoprost or travoprost free acid and about 5.0% w/w minoxidil and at least 5% w/w diethylene glycol monoethyl ether.
33. The composition of any of the embodiments 1 – 32 wherein the composition is applied to the eyebrows of a patient to cause eyebrows to grow.
- 30 34. The composition of any of the embodiments 1 – 32 wherein the composition is applied to the eyelashes of a patient to cause eyelashes to grow.

35. The composition of any of the embodiments 1 – 32 wherein the composition is applied to the mustache or beard of a patient to cause mustache or beard to grow.
36. A method of converting vellus hair to terminal hair by application of the formulation of embodiment 23 to the locale of the vellus hair on a patient.
37. A method of converting intermediate hair to terminal hair by application of the formulation of embodiment 23 to the locale of the vellus hair on a patient.
38. A method of increasing at least one selected from length, thickness and pigmentation by the application of a composition of embodiment 1, 21, 22, 23, 24, 27, 28, 31 or 32.

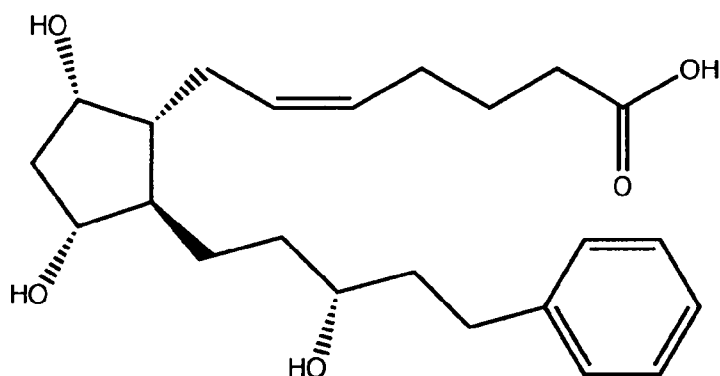
4. Detailed Description of the Invention

Prostaglandin analogues of the present invention include latanoprost, bimatoprost, travoprost, unoprostone isopropyl, the free acids of those compounds and other known prostaglandin analogues known in the literature.

Latanoprost has the following structure:



Latanoprost is a prostaglandin analogue and is in fact a prodrug with its acid form (Latanoprost acid) being biologically active:



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Latanoprost is an isopropyl ester, and is a prodrug which converts to latanoprost free acid by endogenous esterase enzymes. Latanoprost is also called (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoic acid. The free acid form of latanoprost is two-hundred times more potent than latanoprost as an FP receptor ligand for the human recombinant FP receptor. Latanoprost free acid is a potent FP receptor agonist with an EC₅₀ of 3.6 nM for human FP receptors, which is twice the potency of PGF_{2α}. The efficacy of PG analog esters for the treatment of glaucoma or elevated IOP correlates closely with the FP receptor binding affinity of the free acid. Other forms of latanoprost which may be used in the present invention include 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol and latanoprost ethyl amide-d4.

Latanoprost including 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4 and latanoprost acid may be present in the formulations of the present invention in the following concentrations: 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, .0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, %, 0.11%. 0.12%. 0.13%, 0.14%, 0.15%; 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%,

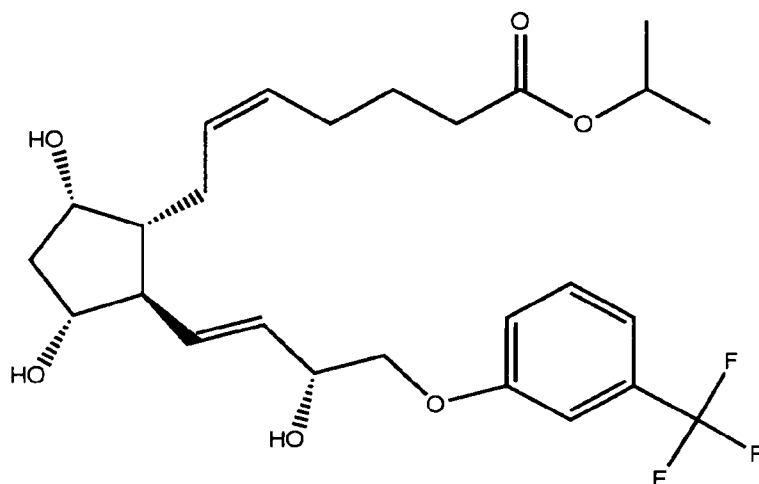
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1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w or w/v.

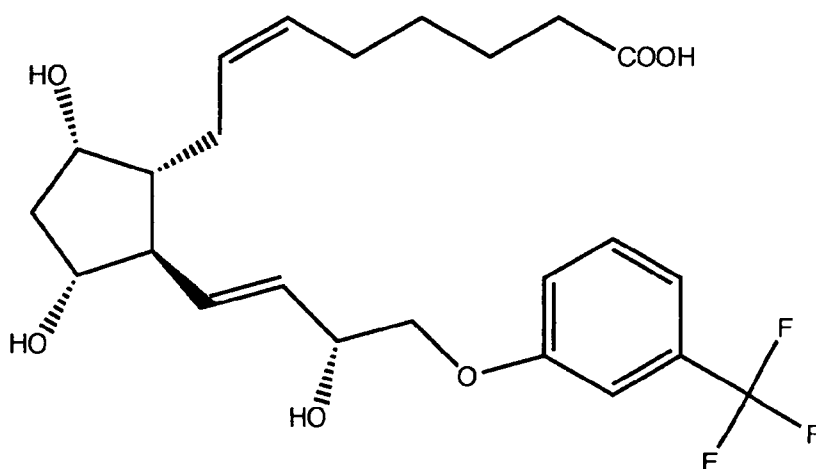
5 Latanoprost, including 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4 and latanoprost acid may be present in the formulations of the present invention alone or in combination with other prostaglandin analogs. Latanoprost including 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4 and latanoprost acid
10 may be present in the formulations of the present invention alone or in combination with topical minoxidil or topical or oral finasteride. Latanoprost including 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4 and latanoprost acid may be present in the formulations of the present invention alone or in combination with cyclosporine formulas I, II and III.

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Travoprost is a synthetic prostaglandin F analogue and isopropyl ester of the biologically active free acid . Its chemical name is [1R [1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3 (trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-
20 methylethylester. It has a molecular formula of C₂₆H₃₅F₃O₆ and a molecular weight of 500.55:



Travoprost free acid has the following structure:

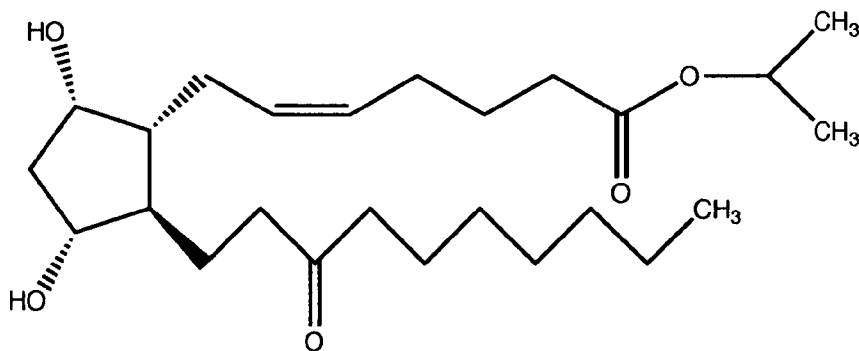


Travoprost and travoprost free acid may be present in the formulations of the present invention in the following concentrations: 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%,

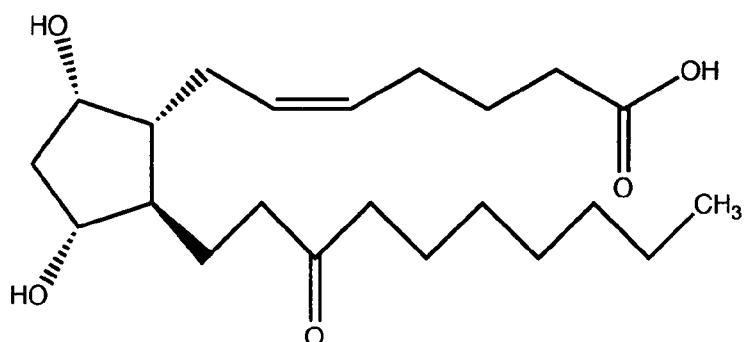
0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%,
0.46%, 0.47%, 0.48%, 0.49%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%,
0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%,
2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%,
3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%,
24% and 25 % w/w or w/v.

Travoprost and travoprost free acid may be present in the formulations of the present
invention alone or in combination with other prostaglandin analogs or other hair growth
compounds. Travoprost and travoprost free acid may be present in the formulations of the
present invention alone or in combination with topical minoxidil or topical or oral finasteride.
Travoprost and travoprost free acid may be combined with cyclosporine formulas I, II or III.

Unoprostone isopropyl ester has the following structure:



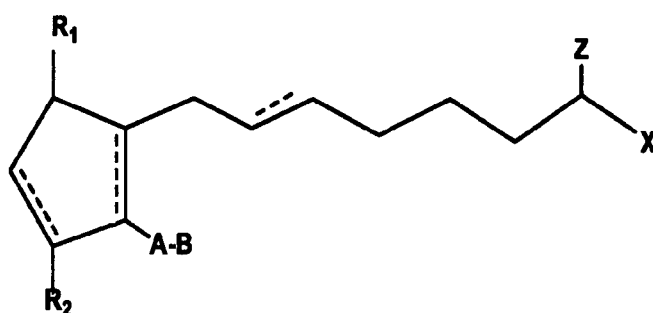
Unoprostone isopropyl ester is a prodrug which converts to unoprostone free acid
which has the following structure:



- 5 Utenoprostone isopropyl ester and utenoprostone free acid while efficacious at lowering intraocular pressure, have been shown to cause no hair growth and in fact may inhibit hair growth (McCarey B. E., Kapik B. M., Kane F. E. [2004]). Low incidence of iris pigmentation and eyelash changes in 2 randomized clinical trials was reported with utenoprostone isopropyl 0.15%. (Ophthalmology 111, 1480–1488). This demonstrates that unpredictability of
- 10 prostaglandin analogs for use in growing hair and that many prostaglandin analogs do not grow hair.

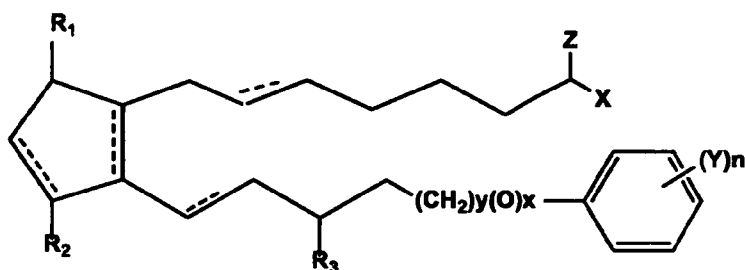
Bimatoprost is a prostamide which are a recently discovered group of biological lipids, which are related to prostaglandins, but contain a terminal ethanolamide group and which target different receptors than prostaglandin analogues such as latanoprost. Bimatoprost and other compounds may be represented generally by the formula I:

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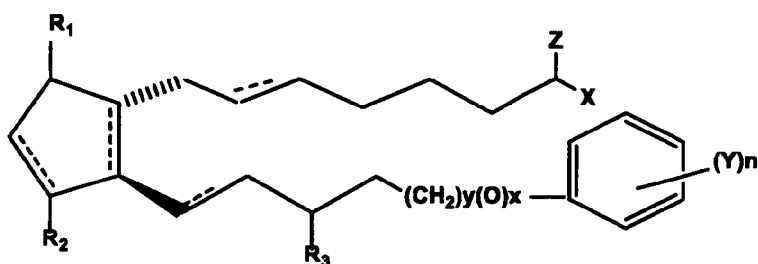
wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or alkylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 may be the same or different and is independently selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms, R^5-C- or R^5-O-C- wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is $=O$ or represents 2 hydrogen radicals; one of R_1 and R_2 is $=O$, $-OH$ or a $-O(CO)R_6$ group, and the other one is $-OH$ or $-O(CO)R_6$, or R_1 is $=O$ and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $-(CH_2)_mR_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above, or a pharmaceutically-acceptable salt thereof, provided, however, that when B is not substituted with a pendant heteroatom-containing radical, and Z is $=O$, then X is not $-OR^4$. That is, the cycloalkyl or hydrocarbyl aryl or heteroaryl radical is not substituted with a pendant radical having an atom other than carbon or hydrogen.

Bimatoprost and other compounds may also be represented by the following general formula II:

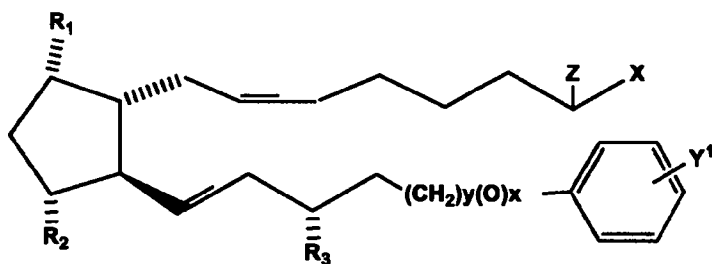


wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and R₃ is =O, -OH or -O(CO)R₆ wherein
 5 R₆ is as defined above. Preferably, n is 1 or 2.

Bimatoprost and other compounds may also be represented by the general formula (III).

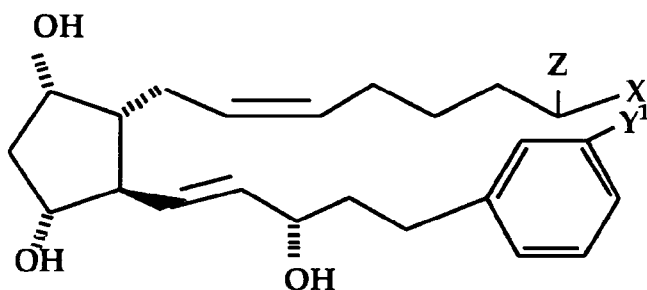


Bimatoprost and other compounds may also be represented by the general Formula (IV):



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Or represented by the general Formula V:



15

In all of the above formulae, as well as in those provided hereinafter, the dotted lines on bonds between carbons 5 and 6 (C-5), between carbons 13 and 14 (C-13), between carbons 8 and 12 (C-8), and between carbons 10 and 11 (C-10), indicate a single or a double bond which can be in the cis or trans configuration. If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-9, C-11 and C-15 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used.

In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 or C-15 substituents in the α or β configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cyclopentane ring indicate substituents in the α configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the α -configuration. Also, the broken line attachment of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the α configuration.

For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acyclic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to about 6, preferably one to about 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

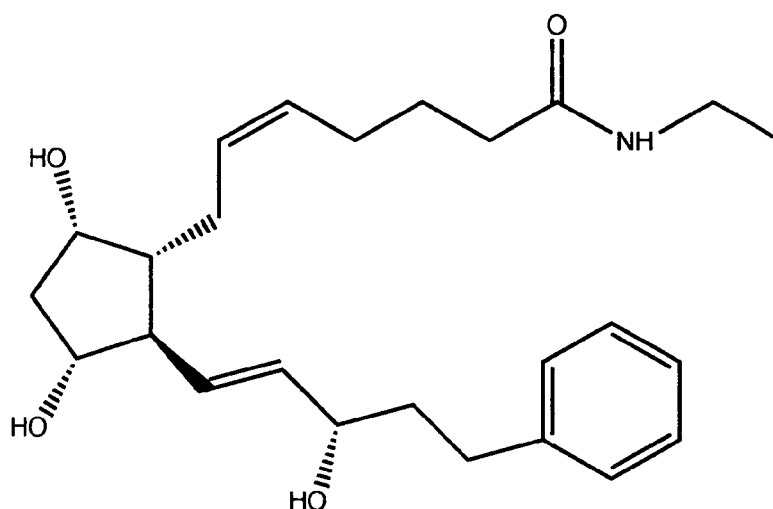
The definition of R_6 may include a cyclic component, $-(CH_2)_mR_7$, wherein n is 0 or an integer of from 1 to 10, R_7 is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3-7 carbon atoms, inclusive. As an aromatic ring, R_7 preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e. R_7 may be thienyl, furanyl, pyridyl, etc. Preferably m is 0 or an integer of from 1 to 4.

Z is $=O$ or represents two hydrogen atoms.

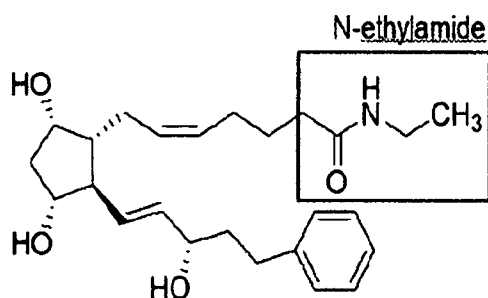
X may be selected from the group consisting of $-OR^4$ and $-N(R^4)_2$ wherein R^4 is independently selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

carbon atoms, $R^5 - \overset{\overset{O}{\parallel}}{C} -$ or $R^5 - O - \overset{\overset{O}{\parallel}}{C} -$ wherein R^5 is a lower alkyl radical having from one to six carbon atoms.

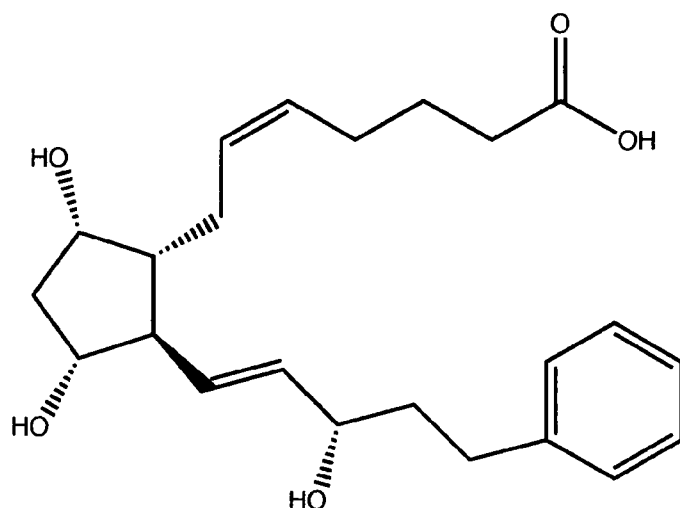
5 Bimatoprost may also be represented by the following formula:



10 Bimatoprost is not a prodrug and is not converted into another compound or only small amounts (under 5%) are believed converted into bimatoprost free acid. Bimatoprost differs from the other compounds in that it is an amide:



While there is a bimatoprost free acid:



5

Bimatoprost is believed to exert its biological activity as a hair growth agent as an ethyl amide and not as a free acid. This is in contrast to latanoprost and travoprost which are prodrugs and exert their physiological effects on different receptors than bimatoprost which illustrates the lack of predictability bimatoprost, latanoprost, travoprost and uenoprostone isopropyl ester in their use in hair growth.

10

The action of prostamides such as bimatoprost involve mechanisms different from prostanoid FP receptor-mediated responses with ligands such as latanoprost and travoprost, in the eye.

Bimatoprost's effects in monkeys with elevated intraocular pressure has been shown to be additive to that of latanoprost ("Additivity of Bimatoprost or Travoprost to Latanoprost in

5 Glaucomatous Monkey Eyes", Gagliuso et al., 2004). Other pharmacological distinctions

between latanoprost and bimatoprost have been demonstrated. For example, some human patients suffering from glaucoma were non-responsive to latanoprost but responsive to bimatoprost in reducing elevated intraocular pressure ("Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost"

10 Gandolfi 2003). It appears highly likely that latanoprost, bimatoprost and travoprost interact with different receptors.

Bimatoprost and bimatoprost free acid may be present in the following concentrations:

0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, .0.01%, 0.02%,
15 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, %, 0.11%. 0.12%. 0.13%, 0.14%,
0.15%; 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%,
0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%,
0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, 0.5%, 0.55%,
0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%,
20 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%,
3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%,
4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10%, 11%, 12%, 13%, 14%,
15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

25 Bimatoprost and bimatoprost free acid may be present in the formulations of the present invention alone or in combination with other prostaglandin analogs. Bimatoprost may be combined with topical minoxidil or with topical or oral finasteride and may be combined with cyclosporine I, II or III.

30 Cyclosporine occurs naturally and was isolated from the fungus *Tolypocladium inflatum* in 1971. Cyclosporine is an immunosuppressant and is used in Crohn's disease, nephrotic

syndrome, rheumatoid arthritis, in organ transplants to prevent rejection and dry eye disease.

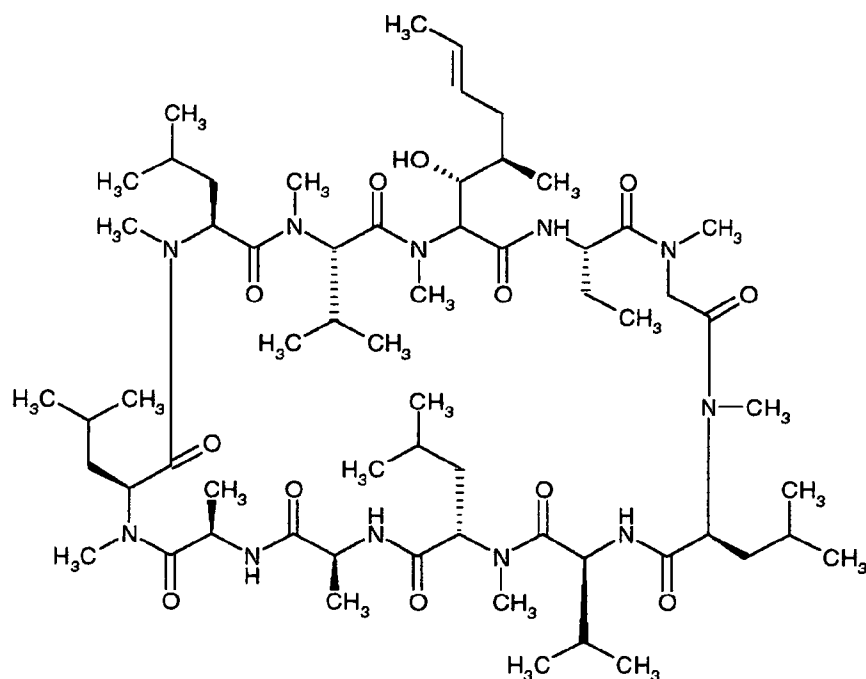
Cyclosporines are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporine A, along with several other minor metabolites, as well as cyclosporine B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y and Z, have been identified. In addition, derivatives, salts and the like of such cyclosporines and a number of synthetic analogs have been prepared and may be useful in the present invention. The use of cyclosporine A and cyclosporine A derivatives to treat various ophthalmic conditions, has been the subject of various patents, for example US Patent Nos. 5,474,979; 6,254,860; 6,350,442; and 7,368,436, the disclosure of each of which are incorporated by reference in their entireties.

In general, commercially available cyclosporines may contain a mixture of several individual cyclosporines which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200 Dalton, but with different substituents or configurations of some of the amino acids. Thus the present invention also contemplates mixtures of different types of cyclosporine or cyclosporine components. The term "cyclosporine component" as used herein is intended to include any individual member of the cyclosporine group, salts thereof, derivatives thereof, analogs thereof and mixtures thereof, as well as mixtures of two or more individual cyclosporines salts thereof, derivatives thereof, analogs thereof and mixtures thereof.

Particularly preferred cyclosporine components include, without limitation, cyclosporine A, derivatives of cyclosporine A, salts of cyclosporine A and the like and mixtures thereof. Cyclosporine A is an especially useful cyclosporine component.

The chemical structure for cyclosporine A is represented by Formula 1:

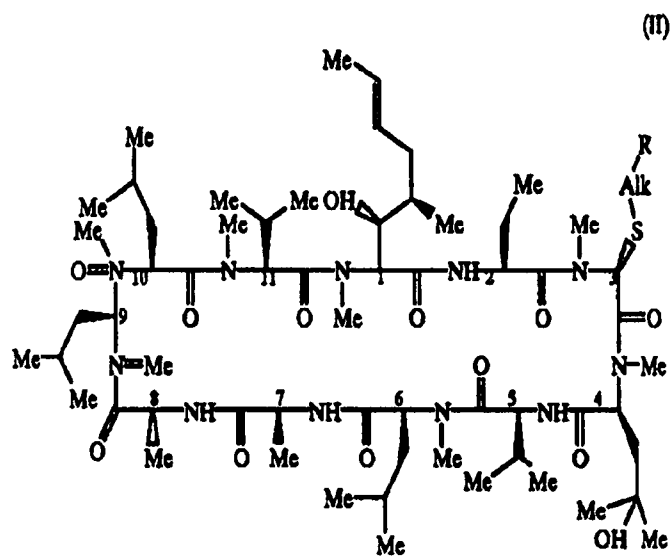
Formula I



- 10 As used herein, the term “derivatives” of a cyclosporine refer to compounds having structures sufficiently similar to the cyclosporine so as to function in a manner substantially similar to or substantially identical to the cyclosporine, for example, cyclosporine A, in the present compositions and methods. Included, without limitation, within the useful cyclosporine A derivatives are those selected from ((R)-methylthio-Sar)³-(4'-hydroxy-MeLeu) cyclosporine A,
- 15 ((R)-(Cyclo)alkylthio-Sar)³-(4'-hydroxy-MeLeu)⁴-cyclosporine A, and ((R)-(Cyclo)alkylthio-Sar)³-cyclosporine A derivatives described below.

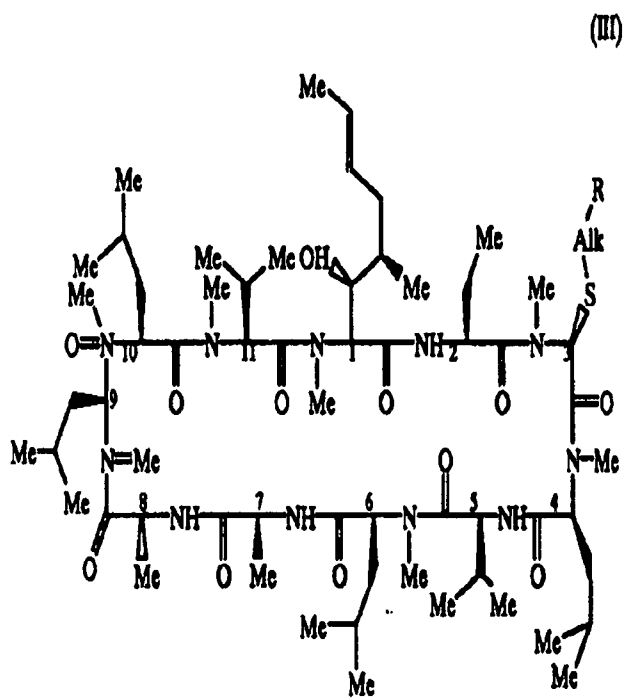
These cyclosporine derivatives are represented by the following general formulas (II) and (III), respectively:

Formula II



5

Formula III



10

15

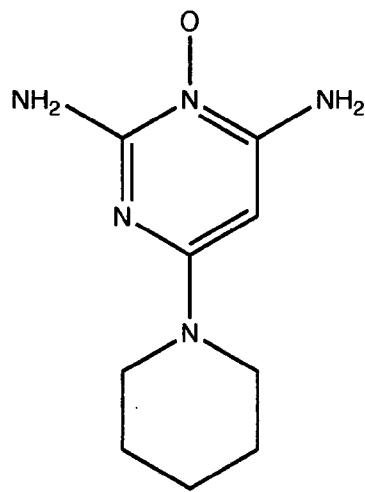
wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxy, carbonyl, -NR₁R₂ or N(R₃)-(CH₂)-NR₁R₂; wherein R₁,R₂ is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxy, carbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR₁R₂ is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R₃ is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

The present compositions and methods may be practiced employing any suitable compositions or combinations of compositions including therapeutically effective amounts of cyclosporine component in conjunction with bimatoprost useful to promote hair growth. The cyclosporine component is present in an amount and/or concentration effective enough to provide the desired therapeutic effect when the cyclosporine-containing composition is administered to a human or animal in accordance with the present invention. Mixtures of cyclosporine components are contemplated. In one embodiment of the invention, the cyclosporine component advantageously is present in the compositions in amounts ranging from about 0.01-0.05% w/v, 0.05 - 0.1% w/v, 0.1% to about 0.5% w/v, 0.5% - 5% w/v, 5% - 15% w/v, and 15% or about 20% or 25% w/v of the composition.

In another embodiment, the cyclosporine component is present in an amount of about 0.01% to about 5% or about 10% or about 15% by weight of the composition. Cyclosporine may be present in the following concentrations: 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, .0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, %, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%; 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

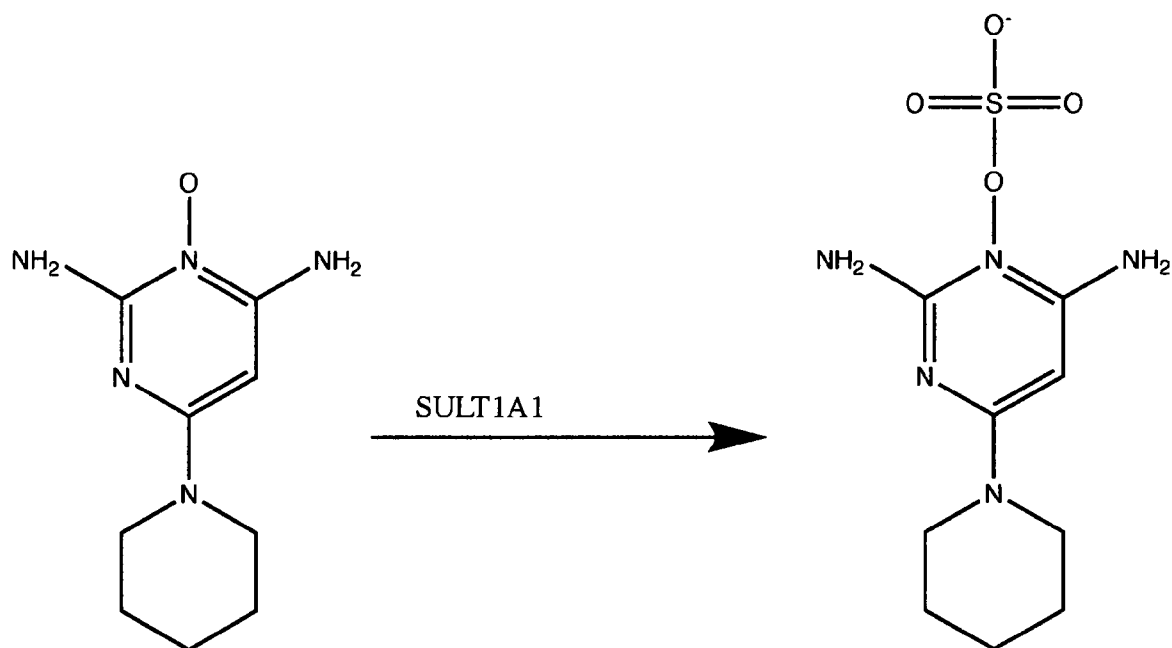
Cyclosporine, both topical and oral, in all its various forms may be present in combination with bimatoprost, latanoprost, travoprost, minoxidil and oral or topical finasteride.

5 Minoxidil:



10 Minoxidil is believed to open potassium channels and vasodilates blood vessels allowing more nutrients, blood and oxygen into the follicles. There is some evidence that minoxidil may cause hair in the telogen phase to shed, which are replaced by newer and thicker hairs in the anagen phase. Minoxidil is a prodrug which converts to minoxidil sulphate by the sulfotransferase enzyme SULT1A1.

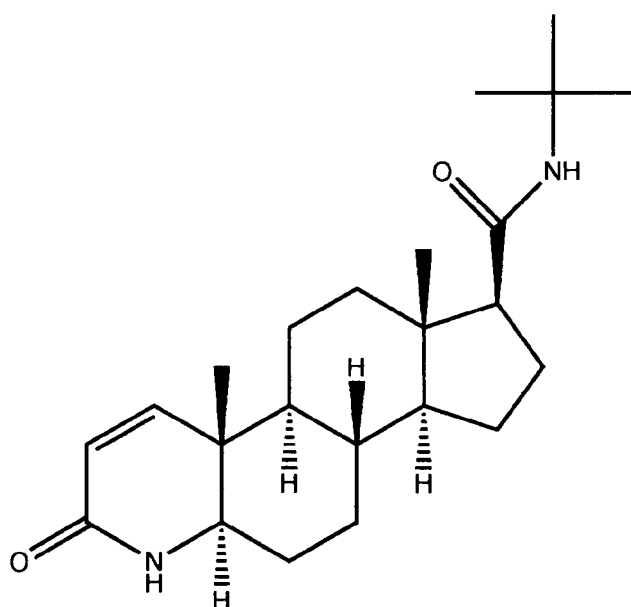
15



Minoxidil can be combined with bimatoprost, latanoprost, 15-keto latanoprost, 15(S)-
 5 latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4
 and latanoprost acid, travoprost and travoprost acid which in theory causes entry into anaphase
 more quickly and lengthens anaphase. Minoxidil can also be combined with cyclosporine.
 Minoxidil can be combined with those compounds at the following concentrations: 0.001%,
 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, .001%, 0.02%, 0.03%,
 10 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, %, 0.11%. 0.12%. 0.13%, 0.14%, 0.15%;
 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%,
 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%,
 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, 0.5%, 0.55%, 0.6%, 0.65%,
 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%,
 15 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%,
 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%,
 4.7%, 4.8%, 4.9%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0 %, 7.5%, 8.0 %, 8.5%, 9.0 %, 9.5%, 10%,
 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

Finasteride

5



Finasteride ($C_{23}H_{36}N_2O_2$), also known as (1*S*,3*aS*,3*bS*,5*aR*,9*aR*,9*bS*,11*aS*)-*N*-*tert*-butyl-9*a*,11*a*-dimethyl-7-oxo-1,2,3,3*a*,3*b*,4,5,5*a*,6,9*b*,10,11-dodecahydroindeno[5,4-*f*]quinoline-1-

10 carboxamide, is a 5 α -reductase inhibitor originally used to treat enlarged prostates in males. Oral finasteride works by decreasing the production of dihydrotestosterone (DHT) by about 70%, including in the prostate gland and the scalp. There have been some reports of success in growing scalp hair using topical finasteride. Finasteride can be combined with the prostaglandin analogs of the present invention including bimatoprost, latanoprost and travoprost and their analogs.

15

Finasteride can be combined with bimatoprost, latanoprost, 15-keto latanoprost, 15(S)-
latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, latanoprost ethyl amide-d4
and latanoprost acid, travoprost and travoprost acid which in theory causes entry into anaphase
more quickly and lengthens anaphase. Finasteride can be combined with those compounds at the
5 following concentrations: 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%,
0.009%, .0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, %, 0.11%,
0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%,
0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%,
0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%,
10 0.48%, 0.49%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%,
1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%,
2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%,
4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0 %,
7.5%, 8.0 %, 8.5%, 9.0 %, 9.5%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%,
15 21%, 22%, 23%, 24% and 25 % w/w.

Definitions

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
20 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 “prophylactically effective amount” of a drug is an amount of
a drug that, when administered to a subject, will have the intended prophylactic effect, e.g.,
25 preventing or delaying the onset (or reoccurrence) a disease, disorder or condition, or reducing
the likelihood of the onset (or reoccurrence) of a disease, disorder or condition or symptoms
thereof. The full prophylactic effect does not necessarily occur by administration of one dose,
and may occur only after administration of a series of doses. Thus, a prophylactically effective
amount may be administered in one or more administrations.

30 “Growing hair” refers to causing hair growth to increase as compared to the rate of hair

growth without applying the drugs and/or formulations of the present invention.

“Hairs” may be vellus hairs which are fine, thin, non-pigmented short hairs in which the hair bulb is located superficially in the dermis. Intermediate hairs that are in a growth stage between vellus (baby or immature) hair, such as on your face, and mature hair stage of growth such as the hair on the scalp. Terminal hairs are coarse, pigmented, long hairs in which the bulb of the hair follicle is seated deep in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

“Hair loss” may refer to alopecia areata, androgenetic alopecia, male pattern hair loss, female pattern hair loss, telogen effluvium, anagen effluvium, tinea capitis, cicatricial alopecia, lichen planopilaris, discoid lupus erythematosus, folliculitis decalvans, dissecting cellulitis of the scalp, central centrifugal cicatricial alopecia, frontal fibrosing alopecia, loose anagen syndrome, hair shaft abnormalities, involutional alopecia, androgenic alopecia, trichotillomania, hair loss due to chemotherapy, hair loss due to infectious agents, trichorrhexis nodosa and senescent alopecia.

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.

“Preventing hair loss” means slowing down or preventing hair loss that would occur as compared to if the formulation was not applied. The methods and compositions of the present invention of the present invention can be used to prevent hair loss, to treat hair loss, to treat or thicken thinning hair, loss of eyebrows, loss of eyelashes or facial hair, and can be used to treat all types of alopecia,

The term “prodrug” is used according to its plain ordinary meaning and is intended to mean compounds that require a chemical or enzymatic transformation in order to release the active parent drug *in vivo* prior to producing a pharmacological effect.

The term “soluble” refers the ability of the solvent to dissolve an amount of the active pharmaceutical ingredient that is relevant for its pharmacological effect.

The terms "solvent" and "solvent system" define one component of the formulation, the liquid or semi-solid phase that contains the API.

5 The terms "stable" and "stability" are used here in relation to the shelf-life of a pharmaceutical product, and are related to the physical change, degradation or chemical decomposition of active pharmaceutical ingredients, which limits the shelf-life of a product.

10 “Synergism” between two drugs, for example in a fixed combination, can occur when the two drugs interact in a manner that enhance or magnify one or more effects, or side effects, of those drugs. Negative effects of synergy are a form of contraindication such as when more than one depressant drug is used that affects the central nervous system (CNS), an example being alcohol and Valium. The combination can cause a greater reaction than simply the sum of the individual effects of each drug if they were used separately. In this particular case, the most serious consequence of drug synergy is exaggerated respiratory depression, which can be fatal if
15 left untreated.

“Synergism” has also been noted in describing how complex systems operate. For example, biological systems may react in a non-linear way to perturbations, so that the outcome may be greater than the sum of the individual component alterations.

20 In describing the present invention, synergism means that the combination of the two active drugs, utilized in the methods and compositions of the invention achieves a result, e.g. stimulating the growth of hair such as eyelashes, in a mammal, e.g. a human, that is greater than the result achieved when the active drugs are utilized, alone, under the same conditions. Thus, to determine the combinations that are within the scope of the present invention, one may simply compare the result achieved by the combination of the two drugs with the result achieved with
25 each of the individual drugs, alone.

The terms “treat” “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. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or computerized imaging systems. For example, the certain methods presented herein successfully treat acne by decreasing the incidence of acne, in inhibiting its symptoms and or cause.

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 skin. The term "topical epidermal pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directed to the epidermal layer of the skin, e.g., the palpebra, the supercilium, the face, or the body. The term "topically administering" refers to administering externally by direct contact with a topical treatment site. The term "topical epidermal administering" refers to administering externally by direct contact with the epidermis.

Orifices of hair follicles occupy only about 0.1% of the total skin surface area of humans, while hair follicles can occupy as much as 10% of the total surface area on the human scalp (Schaefer, H., et. al. (1990) "Follicular penetration" (pgs. 163 – 173)(1990). In general, follicular openings lead to epithelial surfaces that do not have the protective stratum corneum of surface skin. Consequently, hair follicles and sebaceous glands contribute significantly to transdermal drug delivery. Consequently, hydrophilic drugs can penetrate with high flux and usually through the intrafollicular routes, along the junction of the internal and external route sheath, and rapid diffusion into the dermis by the outer route sheath. Longer lag times for the scalp skin penetration of hydrophilic drugs, as compared to the shorter time for lipophilic drugs, suggest that the permeation of hydrophilic drugs via the upper dermis is a rate-limiting step. The penetration routes of lipophilic drugs is probably along the junction of internal and external root

sheath. Release of sebum by sebaceous glands associated with the hair follicle forms a lipoidal pathway for lipophilic materials in the follicles (Ebling et al., 1991). It is also believed that a penetration route for lipophilic permeants is the trans epidermal pathway. Thus, the penetration through the stratum corneum of scalp skin was also an important pathway but some drugs may use the trans follicular route. Sebum located in the follicles also plays an important role in drug penetration in the outer root sheath. Human hair follicles can vary in diameter from 5 μm to 80 μm , which can affect trans-follicular penetration. Certain penetration enhancers and solvents help fluidize lipids, in intercellular channels of the stratum corneum. Penetration of permeants and drugs through the scalp skin, is believed to be related to the rapid permeation into the hair follicles and the rapid diffusion through the outer root sheath, into the dermis, whereas the trans epidermal permeation of drugs is largely through was via the microchannels. Hydrophilic drugs also rapidly diffused into the dermis via the outer root sheath, but permeation of hydrophilic drugs via the upper dermis may be rate-limiting step and relatively slow. Human scalp anagen hair follicles are believed to express the genes and protein for three prostanoid receptors in the dermal papillae and the CTS surrounding the hair bulb, but not in the epithelial keratinocytes or the melanocytes of the hair bulb. One theory is that prostaglandin analogues binding to specific receptors on the plasma membrane of cells in the regulatory dermal papilla in the hair bulb, which probably stimulates intracellular signaling pathways, resulting in hair growth and the lessening of hair loss.

Eyebrows

Loss of eyebrow hair, also known as madarosis, is characterized by a lack of growth or loss of eyebrow hair. Loss of eyebrow hair can have cosmetic, functional, and social/psychological consequences. According to the research, the diameter of scalp hair is normally thicker than eyebrow hair in Asian patients, while the reverse is true in Caucasian Gandelman M. A Technique for Reconstruction of Eyebrows and Eyelashes. Semin Plast Surg. 19:153–8 (2005). Eyebrow hair is generally less dense laterally than medially which results in hair loss in the eyebrows bring more noticeable in the lateral portion. Eyebrows can be roughly divided into three areas. The medial third is usually below the orbital margin with the

hairs in this region oriented vertically. The middle third lies along the orbital margin with hairs oriented obliquely or horizontally. The lateral third usually lies above the orbital margin.

Madarosis of the eyebrows can be caused by disease such as dermatological diseases, endocrinopathy, such as thyroid disease and due to psychological disorders such as

5 trichotillomania. Heredity can also play a factor in conditions such as congenital aplasia.

Madarosis of the eyebrows can be caused by physical trauma such as burns, complications with cosmetic procedures such as tattooing and complications from implantation.

Eyelashes

LATISSE® is a 0.03% w/v bimatoprost solution and is indicated for treating

10 hypotrichosis of the eyelashes and grows eyelashes. However, some androgens stimulate hair growth in many areas, such as the face or body while inhibiting some scalp follicles, causing balding, and have no effect on eyelashes. Therefore, it is not possible to extrapolate the effect of substances on eyelashes to scalp or other follicles.

15 Vehicles

Table 1 lists solvents and penetration enhancers:

Capmul 808G EP/NF	Glyceryl Monocaprylate	26402-26-6
Capmul GDB EP/NF*	Glyceryl Dibehenate	94201-62-4
Capmul GMO-50 EP/NF	Glyceryl Monooleate	25496-72-4
Capmul MCM C8 EP/NF	Glyceryl Monocaprylate	26402-26-6
Capmul MCM EP/NF	Glyceryl Caprylate/Caprate	91744-32-0, or
		26402-22-2, and

		26402-26-6
Capmul INJ MCM EP/NF	Glyceryl Caprylate/Caprates	91744-32-0, or 26402-22-2 and 26402-26-6
CAPMUL INJ MCM EP	Glyceryl Caprylate/Caprates	91744-32-0, or 26402-22-2, and 26402-26-6
Capmul PG-2L EP/NF	Propylene Glycol Dilaurate	22788-19-8
Capmul PG-8 NF	Propylene Glycol Monocaprylate	68332-79-6, or 31565-12-5
Capmul PG-8-70 NF	Propylene Glycol Monocaprylate, NF Type 1	68332-79-6
Capmul PG-12 EP/NF	Propylene Glycol Monolaurate	27194-74-7
CAPTEX® 170 EP	Coco-Caprylate/Caprates	95912-86-0
CAPTEX 200P	Propylene Glycol Dicaprylocaprate	68583-51-7
CAPTEX 300 EP/NF	Glyceryl Tricaprylate/Tricaprate	65381-09-1
CAPTEX INJ 300 LOW C6 EP/NF/JPE	Glyceryl Tricaprylate/Tricaprate	65381-09-1, or 73398-61-5
CAPTEX 355 EP/NF/JPE	Glyceryl Tricaprylate/Tricaprate	65381-09-1, or 73398-61-5
CAPTEX INJ 355 EP/NF/JPE	Glyceryl Tricaprylate/Tricaprate	65381-09-1, or 73398-61-5
CAPTEX 8000	Glyceryl Tricaprylate, Tricaprylin	538-23-8
CAPTEX INJ 8000 NP	Glyceryl Tricaprylate, Tricaprylin	538-23-8
Captex 100	Propylene Glycol Dicaprate	53824-77-4
Captex 170	Caprylic/Capric Acid Ester of Saturated Fatty Alcohol C12-C18	95912-86-0

Captex GTO	Triolein	122-32-7
Captex NPGC	Decanoic acid, mixed esters with neopentyl glycol and octanoic acid	
CAPTEX INJ 300 LOW C6 EP/NF/JPE	Glyceryl Tricaprylate/Tricaprate	65381-09-1, or 73398-61-5
CAPTEX INJ 355 EP/NF/JPE	Glyceryl Tricaprylate/Tricaprate	65381-09-1, or 73398-61-5
CAPTEX INJ 8000 NP	Glyceryl Tricaprylate, Tricaprylin	538-23-8
Capmul INJ MCM EP*	Caprylic capric mono- & diglycerides	91744-32-0, or 26402-22-2, and 26402-26-6
Acconon INJ MC8-2 EP/NF*	PEG-8 caprylic/capric glycerides	91744-32-0, 223129-75-7
CremerCOOR® MCT 60-40	Caprylic / Capric Triglyceride	65381-09-1
CremerCOOR® MCT 70-30	Caprylic / Capric Triglyceride	65381-09-1
CremerCOOR® EHC	2-Ethylhexyl Cocoate	92044-87-6
CremerCOOR® EHL	2-Ethylhexyl Laurate	20292-08-4
CremerCOOR® EHP	2-Ethylhexyl Palmitate	29806-73-3
CremerCOOR® EHS	2-Ethylhexyl Stearate	91031-48-0
CremerCOOR® GMS 40 / SE (self-emulsifier)	Glycerol stearate	67701-33-1
CremerCOOR® IPM	Isopropyl Myristate	110-27-0
CremerCOOR® IPP	Isopropyl Palmitate	142-91-6
CremerCOOR® Triacetin	Glycerol Triacetate	102-76-1

	1,2-DIMYRISTOYL-SN-GLYCERO-3-PHOSPHOCHOLINE	18194246
	DIISOPROPANOLAMINE	110974
	DIISOPROPYL ADIPATE	6938949
	DIPROPYLENE GLYCOL	25265718
	FATTY ACID ESTERS (Medium and short chain)	
	MYRISTYL ALCOHOL	112721
	N,N-DIMETHYLACETAMIDE	127195
	POLYOXYL 35 CASTOR OIL	61791126
	POLYOXYL 40 STEARATE	9004993
	POLYOXYL 40 HYDROGENATED CASTOR OIL	61788850

The solvents and penetration enhancers may be present in the following concentrations: .001%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10% w/w, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25 %, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% w/w of the formulation.

Carbomer may be at a concentration of about 0.05-3.0% w/w, isopropyl myristate at a concentration of about 0.1 to about 10% w/w; PEG 40 castor oil at a concentration of about 0.1 to 20% w/w; carboxymethyl cellulose from 0.1 – 5.0 % w/w ethanol about 1 to about 70% w/w; diethylene glycol monoethyl ether at a concentration of about 1.0 to about 50% w/w; polysorbate 20 at a concentration of about 0.1 to about 5.0% w/w; polysorbate 40 at a concentration of about 0.1 to about 5.0% w/w; polysorbate 60 at a concentration of about 0.1 to about 5.0% w/w; glycerin at a concentration of about 1.0 to about 30% w/w; polysorbate 80 at a concentration of about 0.1 to about 5.0% w/w; PPG-5 ceteth-20 at a concentration of about 0.1 to about 5.0% w/w; oleic acid at a concentration of about 0.1 to about 5.0% w/w; isostearyl isostearate at a concentration of about 0.1 to about 10% w/w; dipropylene glycol dimethyl ether at a concentration of about 1 to about 50% w/w; diethylene glycol at a concentration of about 1 to about 50% w/w; dipropylene glycol at a concentration of about 1 to about 50% w/w; caprylic/capric at a concentration of about 0.1 to about 10% w/w; benzyl alcohol at a concentration of about 0.1 to about 2.0% w/w; silicone at a concentration of about 0.1 to about 10% w/w; PEG 40 castor oil at a concentration of about 0.1 to 20% w/w; PEG 35 castor oil at a concentration of about 0.1 to 20% w/w; oleyl alcohol at a concentration of about 0.1 to 10% w/w; glyceryl monooleate at a concentration of about 0.1 to 10% w/w; and/or water at a concentration of about 0 to about 90% w/w.

Examples:

Formulation I

0.05% w/w latanoprost acid;
0.06% w/w cyclosporine A;
10.0% w/w diethylene glycol monoethyl ether;
5.0 % w/w oleyl alcohol; and,
84.9% water.

Formulation II

- 0.08% w/w latanoprost acid;
0.1% w/w cyclosporine A;
5 15.0% w/w diethylene glycol monoethyl ether;
5% w/w PEG;
6.0% w/w oleyl alcohol; and,
73.8% w/w water.

10 Formulation III

- 0.08% w/w latanoprost acid;
0.1% w/w cyclosporine A;
15.0% w/w diethylene glycol monoethyl ether;
15 5% w/w PEG;
6.0% w/w oleyl alcohol; and,
73.8% w/w water

Formulation IV

- 20
0.06% w/w bimatoprost;
0.08% w/w cyclosporine A;
10.0% w/w glyceryl monooleate;
5.0% w/w oleic acid;
25 5% w/w ethanol; and,
79.8% w/w water.

Formulation V

- 30 0.08% w/w bimatoprost;
0.1% w/w cyclosporine A;

10.0% w/w diethylene glycol monoethyl ether;
5.0% w/w oleic acid;
5.0% oleyl alcohol; and,
79.8% w/w water.

5

Formulation VI

0.08% w/w latanoprost acid;
0.08% w/w cyclosporine A;
10.0% w/w polyethylene glycol;
10.0% w/w diethylene glycol monoethyl ether;
5.0 % w/w oleyl alcohol; and,
74.9% water.

10

15 Formulation VII

0.05% w/w bimatoprost;
0.07% w/w cyclosporine A;
10.0% w/w oleyl alcohol;
10.0% w/w diethylene glycol monoethyl ether; and,
79.0% w/w water.

20

Formulation VIII

0.05% w/w latanoprost acid;
0.08% w/w cyclosporine A;
5.0% w/w diethylene glycol monoethyl ether;
10.0% w/w CAPTEX 300 EP/NF;
10.0% PEG; and,
74.87% w/w water.

25

30

Formulation IX

0.06% w/w uenoprostone free acid;

0.08% w/w cyclosporine A;

5 5.0% w/w diethylene glycol monoethyl ether;

10.0% w/w CAPTEX 300 EP/NF;

10.0% PEG; and,

74.87% w/w water.

10 Formulation X

0.07% w/w travoprost free acid;

0.08% w/w cyclosporine A;

5.0% w/w diethylene glycol monoethyl ether;

15 10.0% w/w CAPTEX 300 EP/NF;

10.0% PEG; and,

74.87% w/w water.

Formulation XI

20

0.1% w/w bimatoprost

0.05% w/w cyclosporine A;

20% w/w 2-(2-Ethoxyethoxy)-Ethanol;

5% w/w propanediol;

25 3% w/w oleic acid; and,

71% w/w water.

Formulation XII

0.1% w/w latanoprost;

30 0.05% w/w cyclosporine A;

20% w/w 2-(2-Ethoxyethoxy)-Ethanol;
5% w/w propanediol;
3% w/w oleic acid; and
71% w/w water.

5

Formulation XIII

0.1% w/w latanoprost;
5.0% w/w minoxidil;
10% w/w 2-(2-Ethoxyethoxy)-Ethanol;
5% w/w propanediol;
3% w/w oleic acid; and
76.9% w/w water.

10

Formulation XIV

0.1% w/w latanoprost;
5.0% w/w minoxidil;
20% w/w 2-(2-Ethoxyethoxy)-Ethanol;
5% w/w propanediol;
3% w/w oleic acid; and,
66.9% w/w water.

15

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Formulation XV

0.1% w/w latanoprost;
2.0% w/w minoxidil;
20% w/w 2-(2-Ethoxyethoxy)-Ethanol;
5% w/w propanediol;
3% w/w oleic acid; and,

25

69.9% w/w water.

Formulation XVI

0.1% w/w bimatoprost;

5 5.0% w/w minoxidil;

20% w/w 2-(2-Ethoxyethoxy)-Ethanol;

5% w/w propanediol;

3% w/w oleic acid; and,

66.9% w/w water.

10

Formulation XVII

0.1% w/w travoprost;

5.0% w/w minoxidil;

20% w/w 2-(2-Ethoxyethoxy)-Ethanol;

15 5% w/w propanediol;

3% w/w oleic acid; and,

66.9% w/w water.

Formulation XVIII

20 5.0 % w/v minoxidil

0.1% w/v latanoprost

30.0% w/v ethanol

50% w/v propylene glycol

q.s. water

25

Formulation XVIII

0.1% latanoprost;

5.0 % w/v minoxidil;

30.0% w/v ethanol;

50% w/v propylene glycol; and,
q.s. water

Formulation XX

5 0.3% w/v latanoprost;
5.0% w/v minoxidil;
30.0% w/v ethanol;
50% w/v propylene glycol; and,
q.s. water

10

Formulation XXI

5.0 % w/v minoxidil
0.05% w/v latanoprost
30.0% w/v ethanol
15 50% w/v propylene glycol
q.s. water

Formulation XXII

5.0 % w/v minoxidil
20 0.05% w/v latanoprost
30.0% w/v ethanol
50% w/v propylene glycol
q.s. water

25 Formulation XXIII

5.0 % w/v minoxidil
0.008% w/v latanoprost
30.0% w/v ethanol
50% w/v propylene glycol
30 q.s. water

Formulation XXIV

5.0 % w/v minoxidil

0.007% w/v latanoprost

30.0% w/v ethanol

5 50% w/v propylene glycol

q.s. water

Formulation XXV

5.0 % w/v minoxidil

10 0.005% w/v latanoprost

30.0% w/v ethanol

50% w/v propylene glycol

q.s. water

15 Formulation XXVI

3.0 % w/v finasteride

0.1% w/v latanoprost

30.0% w/v ethanol

50% w/v propylene glycol

20 q.s. water

Formulation XXVII

5.0 % w/v finasteride

0.3% w/v latanoprost

25 30.0% w/v ethanol

50% w/v propylene glycol

q.s. water

Formulation XXVIII

30 5.0 % w/v finasteride

0.3% w/v bimatoprost

30.0% w/v ethanol
50% w/v propylene glycol
q.s. water

5 Formulation XXVIII

5.0 % w/v finasteride
0.1% w/v bimatoprost
30.0% w/v ethanol
50% w/v propylene glycol
10 q.s. water

Formulation XXX

5.0 % w/v finasteride
0.1% w/v travoprost
15 30.0% w/v ethanol
50% w/v propylene glycol
q.s. water

Formulation XXXI

20 5.0 % w/v finasteride
0.3% w/v travoprost
30.0% w/v ethanol
50% w/v propylene glycol
q.s. water

25

Example I

A 42-year old Caucasian man with alopecia areata applies the formulation of Formulation
30 VIII twice a day to areas on his scalp where hair loss was evident, presenting as small patches of

hair loss approximately the size of a quarter. After thirty days of application, the patient's hair will begin to grow on the patches.

Example II

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A 32-year old male with androgenetic alopecia applies the formulation of Formulation VI to areas of hair loss on his scalp at least once a day. After forty-five days of continuous application, hair will begin to regrow on the patient's scalp in the areas of hair loss.

10 Example III

A 43-year old female suffering from telogen effluvium applies the formulation of Formulation IX to her scalp twice a day. After thirty-five days of daily application, hair will begin to regrow on the patient's scalp in areas where the patient suffered hair loss.

15

Example IV

A 53-year old male shaved the underside of his left and right forearm and applied Formulation XI once each day to the left forearm but left the right forearm untreated. After 20 days, the hairs on the left forearm were more numerous, longer, darker and thicker as compared to the hairs on the right forearm which were less numerous, shorter, lighter and not as thick.

Example V

A 53-year old male shaved a four inch by two-inch area above his left and right knee to remove all hair and applied the formulation of Formula XI to the shaved area above the left knee once a day and 5% minoxidil solution above the right knee once a day. After twenty days the hair growth in the area shaved above the left knee is slightly greater (more hair, longer hair) than in the area shaved above the right knee. After 30 days the hair in the area above the left knee is longer, darker and thicker than the area above the right knee. After 45 days, the hair above the left knee is significantly longer, thicker in diameter, darker and more numerous than the area above the left knee which was treated with a 5% minoxidil solution.

Example VI

A Caucasian male in his 40s with significant balding on his crown extending to his vertex, with little to no hair on his crown with mainly vellus hair on his crown, began to apply Formulation XVIII once a day at approximately 1 – 2 ml/day. After 60 days, there was significant regrowth of hair which was darker and thicker than the hairs previously on his crown. After Day 100, the patient had mostly full growth of intermediate and terminal hairs on his scalp and the crown of his head was no longer visible.

Example VII

A 54 year old male shaved three areas of his thigh above his knee in approximately two inch by three inch areas where the hair was closely shaved down to the surface of the dermis. Two areas on the left thigh separated by several inches in distance and an area on his right thigh. The subject applied no formulation to Area 1 and left that area untreated, applied a generic 5% minoxidil solution to Area 2 at approximately 1 ml/day, and applied a minoxidil/latanoprost formulation (Formulation XVIII) to Area 3 at approximately 1 ml/day. After approximately 15 days, the untreated area showed some hair growth while Area 2 and Area 3 experienced more pronounced hair growth as compared to Area 1. Area 2 and Area 3 were very similar in numbers and lengths of hairs but the hairs of Area 3 appeared slightly darker. At Day 30, all three areas experienced regrowth with Areas 2 and 3 having significantly greater numbers of hair, which were longer, darker and with greater diameter as compared to Area 1. At Day 30, the number of hairs in Areas 2 and 3 were roughly the same but the hairs of Area 3 appeared slightly darker and thicker than Area 2. At Day 45, Area 1 had significant regrowth, approximately half of the hairs were regrown but was significantly less than Areas 2 and 3. At Day 45, Area 3 had more hairs than Area 3, with greater length, darkness and thickness as compared to Area 3.

Example VIII

A 62 year old woman with thinning eyebrows applies formulation XXII to her eyebrows with an applicator once a day. Within 45 – 90 days the patient will experience increased growth

of eyebrow hairs and eyebrows which are longer, thicker and darker than eyebrow hairs had she not have applied formulation XXII.

Example IX

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A 52 year old woman suffering from hypertrichosis of the eyelashes applies formulation XVIII to her upper eyelid margin once a day. After approximately 45 days, the patient notices longer and thicker eyelashes.

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Claims:

1. A composition for use in the treatment of hair loss comprising about 0.05% – 0.5 % w/v of one selected from the group consisting of latanoprost, latanoprost acid 15-keto
5 latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, and latanoprost ethyl amide-d4 and 0.05% - 0.1% cyclosporine A.
2. The composition of claim 1 wherein the composition has about 0.05% w/v latanoprost or latanoprost acid and about 0.05% w/w cyclosporine A and at least 5% w/v diethylene glycol monoethyl ether.
- 10 3. The composition of claim 1 further comprising oleyl alcohol or ethanol.
4. The composition of claim 3 further comprising polyethylene glycol.
5. The composition of claim 1 wherein the hair loss is due to androgenetic alopecia.
6. The composition of claim 1 wherein the hair loss is due to alopecia areata.
7. A composition for use in growing hair on a patient that experiencing hair loss comprising
15 about 0.05% – 0.3% w/v of one selected from the group consisting of latanoprost, latanoprost acid, latanoprost, latanoprost acid 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol, and latanoprost ethyl amide-d4, bimatoprost, bimatoprost acid, travoprost and travoprost acid and 0.05% - 0.1% w/w cyclosporine A and 5.0% – 30.0% w/v ethanol.
- 20 8. The composition of claim 7 wherein composition comprises 0.06% w/v latanoprost acid and 0.08% w/v cyclosporine A.
9. The composition of claim 8 further comprising 10% w/w CAPTEX 300 EP/NF.
10. A composition for use in treating hair loss comprising about 0.05% – 0.1% w/w travoprost or travoprost acid and one selected from the group consisting of 0.05% - 0.1%
25 w/w cyclosporine A and 1 – 8% w/v minoxidil.
11. The composition according to claim 10 further comprising one selected from the group consisting of diethylene glycol monoethyl ether, CAPTEX 300 EP/NF and polyethylene glycol.
12. The composition according to claims 1, 7 and 10 further comprising oleic acid.
- 30 13. A method of preventing hair loss on a patient comprising administering a formulation according to one of claims 1 - 12 to a patient in need thereof.
14. The method of claim 13 wherein the formulation is applied once a day.

15. The method of claim 14 wherein the formulation is applied twice a day.
16. The method of any one of the claims 1 – 15 wherein between 1 ml – 2ml of composition is applied daily.
- 5 17. A method of growing hair in a patient suffering from hair loss comprising administering a formulation according to one of claims 1, 7 and 10 to a patient in need thereof.
18. The method of claim 17 wherein the patient experiences hair growth to a greater extent by applying the composition of at least one selected from the group consisting of claims 1, 7, 10 as compared to if the patient had not applied the composition of claim claims 1, 7 and 10.
- 10 19. The method of claim 18 wherein the patient experiences at least one selected from the group consisting of greater length, earlier onset of growth, longer anagen phase, greater pigment of the hair and thicker diameters of individual hair as compared to if the patient had not applied the composition.
20. The method of claim 19 wherein the formulation maintains hair in anaphase longer than
15 if the formulation had not been applied.
21. The method of claim 19 wherein the patient reverses a substantial amount of hair loss.
22. The method of claim 13 wherein the formulation comprises 0.05% - 0.5% w/v latanoprost and 1 - 5% w/v minoxidil and a pharmaceutically acceptable solvent and a penetration enhancer.
- 20 23. The method of claim 13 wherein the formulation comprises 0.05% w/w travoprost and 1 - 5% w/v minoxidil and a pharmaceutically acceptable solvent.
24. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.3% w/v latanoprost or latanoprost acid and 1.0% - 7.0% w/v minoxidil or minoxidil sulphate.
- 25 25. The composition of claim 24 wherein the composition is useful for growing one selected from the group consisting of scalp hair, eyebrows, eyelashes and facial hair.
26. The composition of claim 25 comprising about 0.05% latanoprost and about 5% w/v minoxidil or minoxidil sulphate.
- 30 27. The composition of claim 25 comprising about 0.08% latanoprost about 5% w/v minoxidil or minoxidil sulphate.

28. The composition of claim 25 comprising about 0.1% w/v latanoprost about 5% w/v minoxidil or minoxidil sulphate.

29. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.1% w/w bimatoprost or bimatoprost acid and 1.0% - 5.0% minoxidil or minoxidil sulphate.

30. The composition of claim 25 wherein the composition has about 0.1% w/w bimatoprost or bimatoprost acid and about 5.0% w/w minoxidil and at least 5% w/w diethylene glycol monoethyl ether.

31. The composition of claim 25 further comprising oleyl alcohol or ethanol.

32. The composition of claim 25 further comprising polyethylene glycol.

33. A composition for use in the treatment of hair loss or to grow hair comprising about 0.05% – 0.1% w/w travoprost or travoprost free acid and 1.0% - 5.0% minoxidil or minoxidil sulphate.

34. The composition of claim 29 wherein the composition has about 0.1% w/w travoprost or travoprost free acid and about 5.0% w/w minoxidil and at least 5% w/w diethylene glycol monoethyl ether.

35. The composition of claim 29 further comprising oleyl alcohol or ethanol.

36. The composition of claim 29 further comprising polyethylene glycol.

ABSTRACT

Compositions and methods for the treatment of hair growth and the prevention of hair loss.

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