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### Warnings:

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| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |        |
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## 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 and cyclosporine, used in combination, to prevent hair loss and/or grow hair. The present invention is also directed to formulations containing prostaglandin analogues and cyclosporine to grow hair or prevent hair loss on the scalp and other areas of the body. The present invention is also  
10 directed to formulations and methods for treating certain hair loss disorders such as alopecia areata.

### 2. Summary of the Invention

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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 and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.
- 20 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.
- 25 5. A composition for use in growing hair on a patient that experiencing hair loss comprising about 0.05% – 0.1% w/w latanoprost or latanoprost acid and 0.05% - 0.1% w/w cyclosporine A and 5.0% – 15.0% w/w CAPTEX 300 EP/NF.
6. The composition of embodiment 5 wherein composition comprises 0.06% w/w lanaoprost or latanoprost acid and 0.08% w/w cyclosporine A.
- 30 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% – 0.1% w/w travoprost or travoprost acid and 0.05% - 0.1% 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.
13. The method of embodiment 11 wherein the formulation is applied twice a 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 0.06% 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 and cyclosporine.
20. The method of claim 19 wherein the cyclosporine is cyclosporine A.
21. A composition for use in the treatment of hair loss comprising about 0.05% – 0.1% w/w bimatoprost and 0.05% - 0.1% cyclosporine A and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.

22. A composition for use in growing hair comprising about 0.05% – 0.1% w/w bimatoprost and 0.05% - 0.1% cyclosporine A and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.

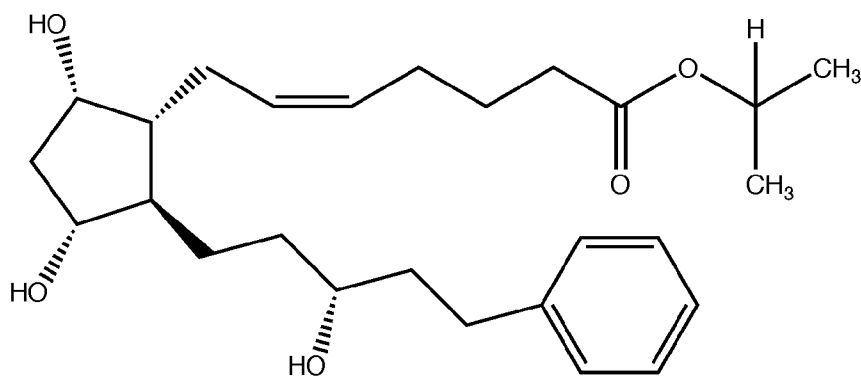
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### 3. Detailed Description of the Invention

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

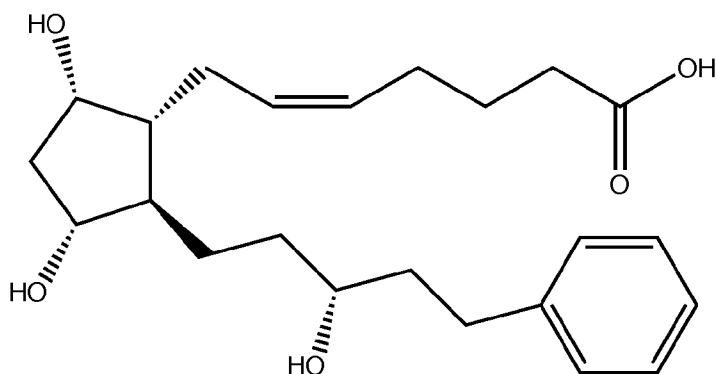
Latanoprost has the following structure:

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

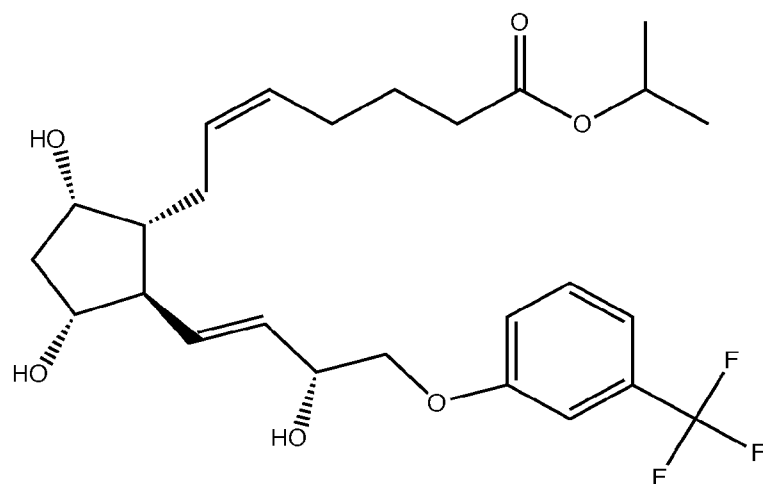


Latanoprost is an isopropyl ester, and is a prodrug which converts to latanoprost free acid by endogenous esterase enzymes. The free acid form is 200 times more potent than latanoprost as an FP receptor ligand for the human recombinant FP receptor. Latanoprost free acid is a potent FP receptor agonist with an  $EC_{50}$  of 3.6 nM for human FP receptors, which is twice the potency of  $PGF_{2\alpha}$ . 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.

Latanoprost 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%, 0.2%, 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%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

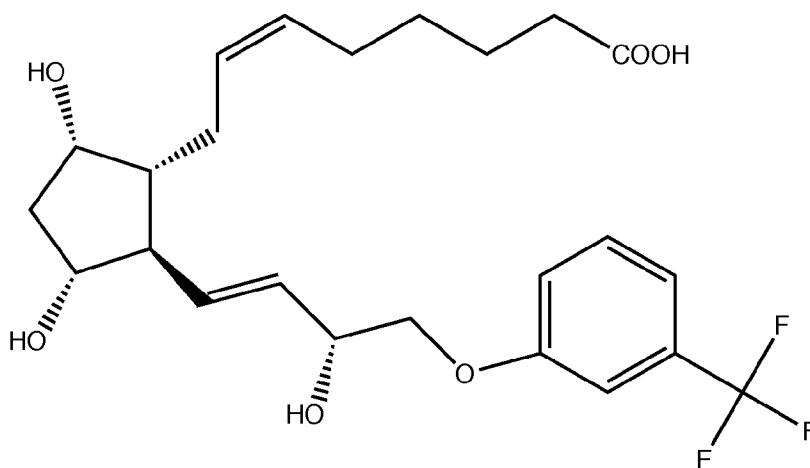
Latanoprost and latanoprost acid may be present in the formulations of the present invention alone or in combination with other prostaglandin analogs.

Travoprost is a synthetic prostaglandin F analogue and isopropyl ester of the biologically active free acid. Its chemical name is [1R [1 $\alpha$ (Z),2 $\beta$ (1E,3R\*),3 $\alpha$ ,5 $\alpha$ ]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3 (trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester. It has a molecular formula of  $C_{26}H_{35}F_3O_6$  and a molecular weight of 500.55



Travoprost free acid has the following structure:

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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%, .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%,

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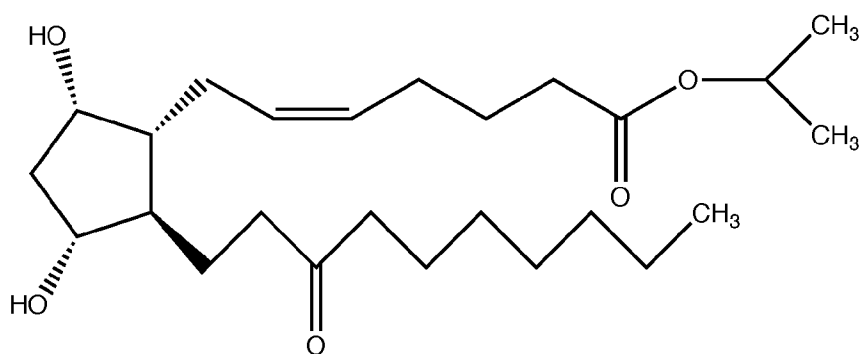
1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 6.0%, 7.0 %, 8.0 %, 9.0 %, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

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Travoprost and travoprost free acid may be present in the formulations of the present invention alone or in combination with other prostaglandin analogs.

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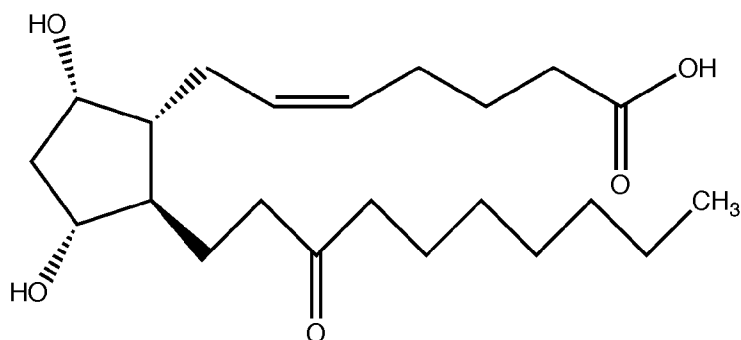
Unoprostone isopropyl ester has the following structure:



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

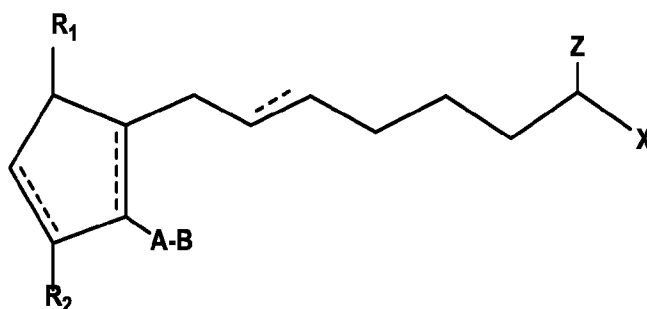
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Uenoprostone isopropyl ester and uenoprostone free acid while efficacious at lowering intraocular pressure, have been shown to cause no hair growth and in fact may inhibit hair growth (McCarey B. E., Kapik B. M., Kane F. E. [2004] Low incidence of iris pigmentation and eyelash changes in 2 randomized clinical trials with unoprostone isopropyl 0.15%. Ophthalmology 111, 1480–1488). This demonstrates that unpredictability of prostaglandin analogs for use in growing hair.

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Bimatoprost may be represented generally by the formula I:

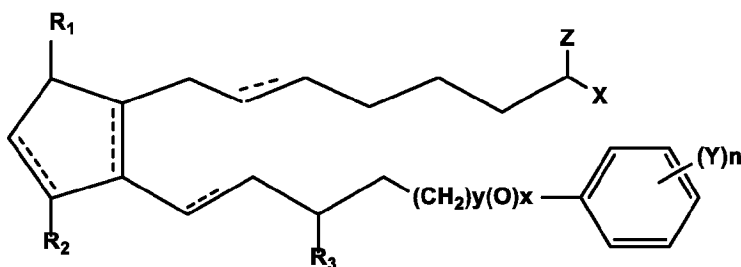


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy 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

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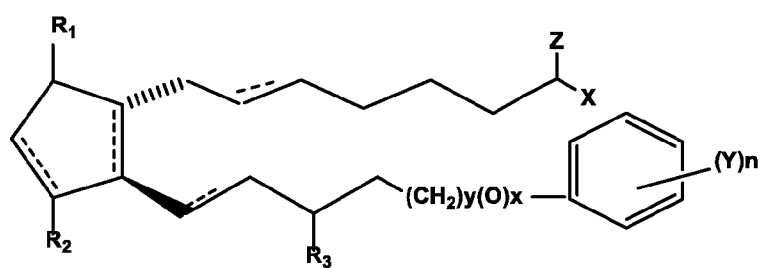
from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is a radical selected from the group consisting of  $-OR^4$  and  $-N(R^4)_2$  wherein  $R^4$  is independently selected from the group consisting of hydrogen, a lower alkyl 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 may also be represented by the following general formula II:

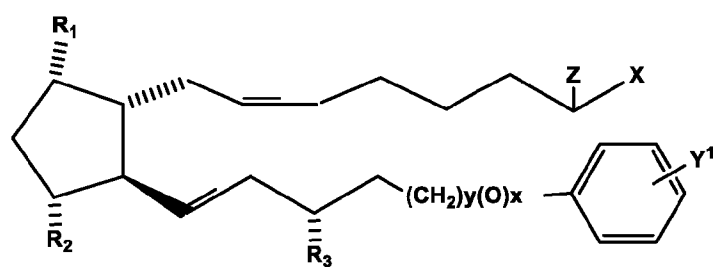


wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to about 3 and  $R_3$  is  $=O$ ,  $-OH$  or  $-O(CO)R_6$  wherein  $R_6$  is as defined above. Preferably, n is 1 or 2.

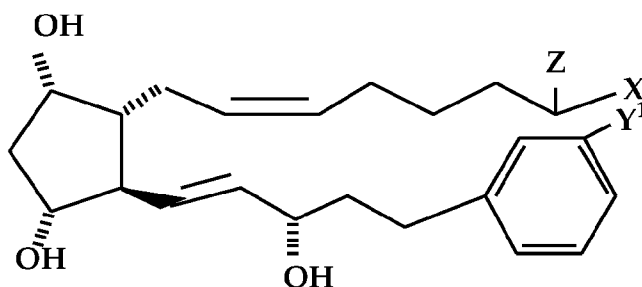
Bimatoprost may also be represented by the general formula (III).



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



Or represented by the general Formula V:



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  $\alpha$  configuration. If one were to draw the  $\beta$  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  $\alpha$  or  $\beta$  configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cyclopentane ring indicate substituents in the  $\alpha$  configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the  $\alpha$  configuration. Also, the broken line attachment of the hydroxyl group or other substituent to the C-11 and C-15 carbon atoms signifies the  $\alpha$  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.

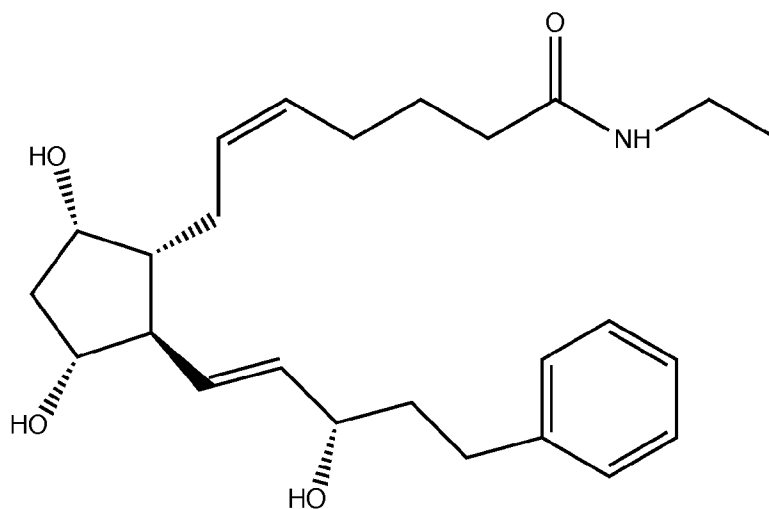
X may be selected from the group consisting of -OR<sup>4</sup> and -N(R<sup>4</sup>)<sub>2</sub> wherein R<sup>4</sup> is independently selected from the group consisting of hydrogen, a lower alkyl radical having from one to six

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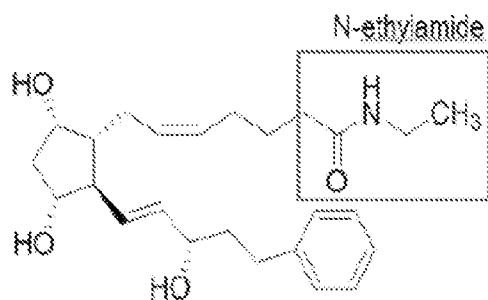
carbon atoms,  $R^5 - \overset{\overset{O}{\parallel}}{C} -$  or  $R^5 - O - \overset{\overset{O}{\parallel}}{C} -$  wherein R<sup>5</sup> is a lower alkyl radical having from one to six carbon atoms.

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Bimatoprost may also be represented by the following formula:

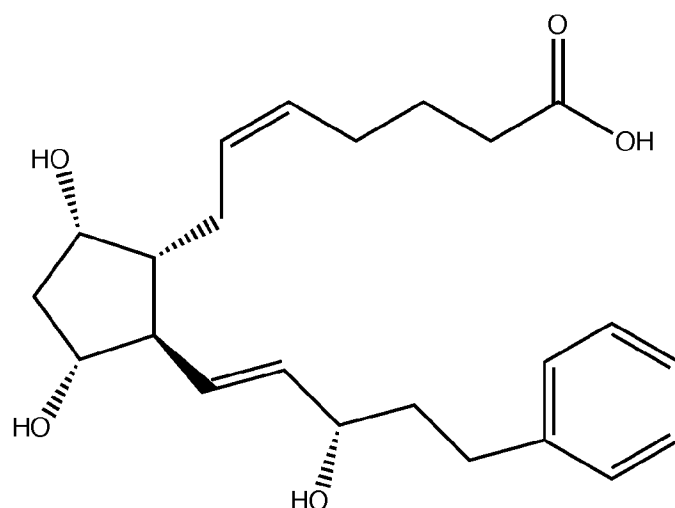


15 Bimatoprost is not a prodrug and is not converted into another compound. Bimatoprost differs from the other compounds in that it is an amide:



While there is a bimatoprost free acid:

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10 Bimatoprost is believed to exert its biological activity as a hair growth agent as an ethyl amide and not as a free acid.

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%,  
 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%,  
 15 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%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

5 Bimatoprost and bimatoprost free acid may be present in the formulations of the present invention alone or in combination with other prostaglandin analogs.

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.

10 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

15 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

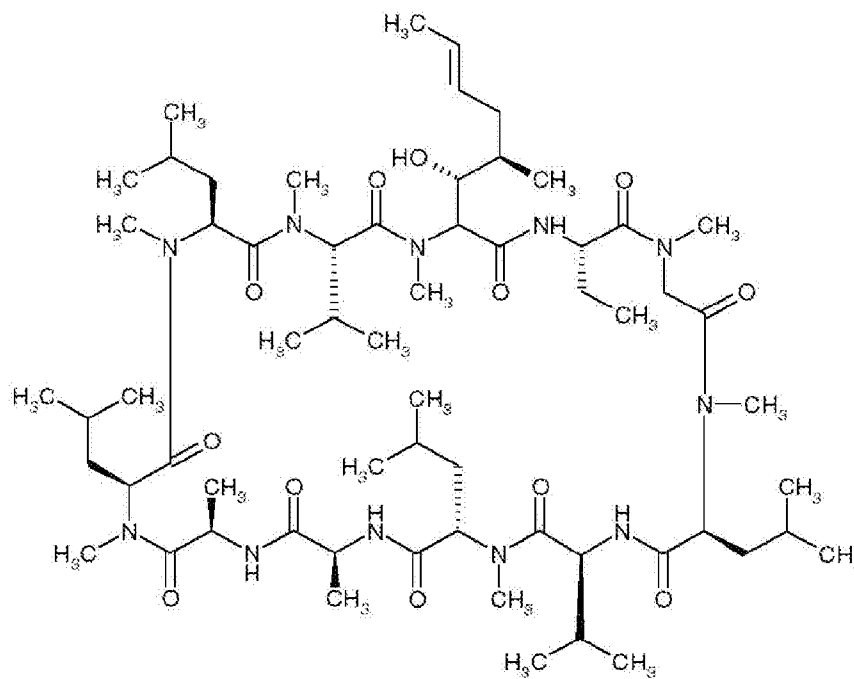
20 acid residues with a total molecular weight of about 1,200 Dalton, but with different substituents or configurations of some of the amino acids. Thus the present invention also contemplates mixtures of different types of cyclosporine or cyclosporine components. The term "cyclosporine component" as 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

25 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:

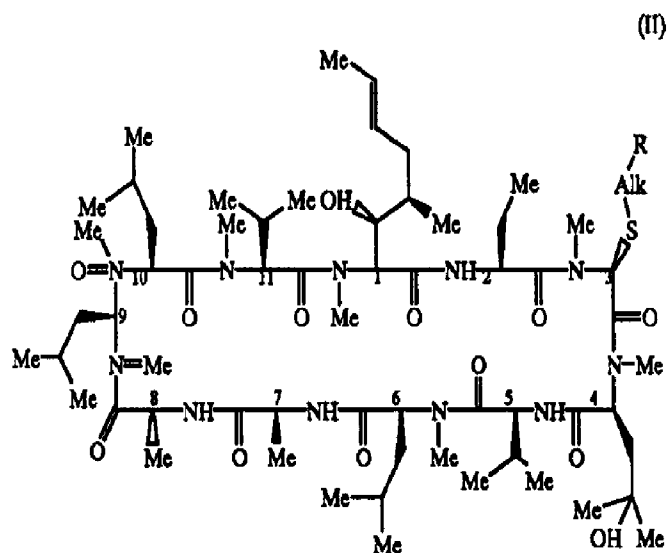
Formula I



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  
15 compositions and methods. Included, without limitation, within the useful cyclosporine A derivatives are those selected from ((R)-methylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu) cyclosporine A, ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-(4'-hydroxy-MeLeu)<sup>4</sup>-cyclosporine A, and ((R)-(Cyclo)alkylthio-Sar)<sup>3</sup>-cyclosporine A derivatives described below.

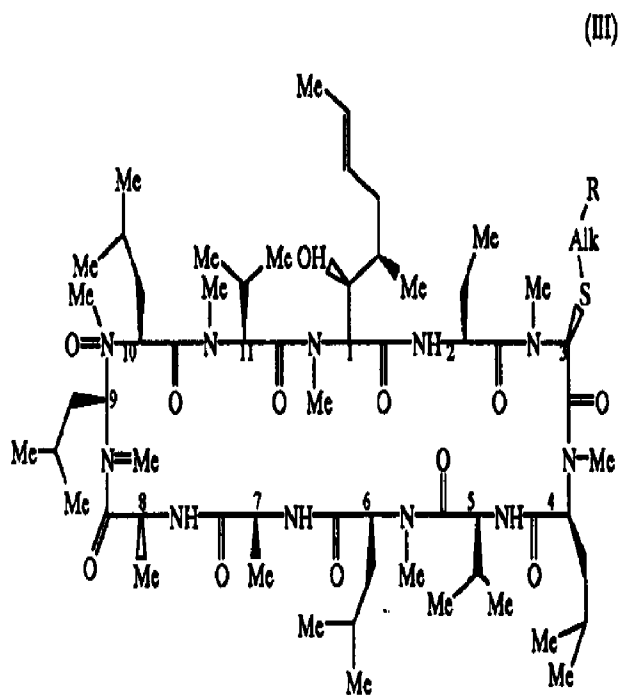
These cyclosporine derivatives are represented by the following general formulas (II) and (III), respectively:

Formula II



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Formula III



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wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, -NR<sub>1</sub>R<sub>2</sub> or N(R<sub>3</sub>)—(CH<sub>2</sub>)—NR<sub>1</sub>R<sub>2</sub>; wherein R<sub>1</sub>,R<sub>2</sub> is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR<sub>1</sub>R<sub>2</sub> is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R<sub>3</sub> 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%, 0.2%, 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%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24% and 25 % w/w.

Hair growth is generally divided into three phases:

- 1) Anagen – active hair growth which last two to six years;
- 2) Catagen – transition growth which lasts two to three weeks;

- 3) Telogen – resting phase which lasts two to three months and at the end of the growth phase where the hair is shed and the cycle repeats.

### Definitions

5 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  
10 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., 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,  
15 and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations.

“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.

20 “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  
25 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 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.

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.

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 root sheath, and rapid diffusion into the dermis by the outer root 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  $\mu$ m to 80

um, 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.

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### Vehicles

Table 1 lists solvents and penetration enhancers:

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|                     |                             |                |
|---------------------|-----------------------------|----------------|
| 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/Caprates | 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<br>and 26402-26-6  |
| CAPMUL INJ MCM EP                  | Glyceryl Caprylate/Caprates                                      | 91744-32-0, or 26402-22-2,<br>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<br>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<br>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<br>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 /<br>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-<br>PHOSPHOCHOLINE   | 18194246                                  |
|                                              | DIISOPROPANOLAMINE                                | 110974                                    |
|                                              | DIISOPROPYL ADIPATE                               | 6938949                                   |
|                                              | DIPROPYLENE GLYCOL                                | 25265718                                  |
|                                              | FATTY ACID ESTERS<br><br>(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: .0.01%, 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:

##### Example 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.

##### Example II

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

##### Example III

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

#### Example IV

- 10 0.06% w/w bimatoprost;  
0.08% w/w cyclosporine A;  
10.0% w/w Glyceryl Monooleate;  
5.0% w/w oleic acid;  
15 5% w/w ethanol; and,  
79.8% w/w water.

#### Example V

- 20 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,  
25 79.8% w/w water.

#### Example VI

- 0.08% w/w latanoprost acid;  
30 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.

5    Example VII

0.05% w/w bimatoprost;  
0.07% w/w cyclosporine A;  
10.0% w/w oleyl alcohol;  
10    10.0% w/w diethylene glycol monoethyl ether; and,  
79.0% w/w water.

Example VIII

15    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,  
20    74.87% w/w water.

Example IX

0.06% w/w uenoprostone free acid;  
25    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.

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Example X

- 0.07% w/w travoprost free acid;  
0.08% w/w cyclosporine A;  
5.0% w/w diethylene glycol monoethyl ether;  
5 10.0% w/w CAPTEX 300 EP/NF;  
10.0% PEG; and,  
74.87% w/w water.

#### Example XI

- 10 0.1% w/w bimatoprost  
0.05% w/w cyclosporine A;  
20% w/w 2-(2-Ethoxyethoxy)-Ethanol;  
5% w/w propanediol;  
15 3% w/w oleic acid; and,  
71% w/w water.

#### Example XII

- 0.1% w/w latanoprost;  
20 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.

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#### Example XIII

A 42-year old Caucasian man with alopecia areata applies the formulation of Example 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 XIV

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

#### 10 Example XV

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

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Claims:

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 and 5.0% – 15.0% w/w diethylene glycol monoethyl ether.
2. The composition of claim 1 wherein the composition has about 0.1% w/w latanoprost or latanoprost acid and about 0.05% w/w cyclosporine A and at least 5% w/w diethylene glycol monoethyl ether.
3. The composition of claim 2 further comprising oleyl alcohol or ethanol.
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% – 0.1% w/w latanoprost or latanoprost acid and 0.05% - 0.1% w/w cyclosporine A and 5.0% – 15.0% w/w CAPTEX 300 EP/NF.
6. The composition of claim 5 wherein composition comprises 0.06% w/w latanoprost acid and 0.08% w/w cyclosporine A.
7. The composition of claim 6 further comprising 10% w/w CAPTEX 300 EP/NF.
8. A composition for use in treating hair loss comprising about 0.05% – 0.1% w/w travoprost or travoprost acid and 0.05% - 0.1% w/w cyclosporine A.
9. The composition according to claim 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 claims 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 claims 1, 5 and 9 to a patient in need thereof.
12. The method of claim 11 wherein the formulation is applied once a day.
13. The method of claim 11 wherein the formulation is applied twice a day.
14. A method for causing hair growth in a patient suffering from hair loss comprising administering a formulation according to one of claims 1, 5 and 9 to a patient in need thereof.
15. The method of claim 14 wherein the patient experiences hair growth to a greater extent by applying the formulation of one of claims 1, 5 and 9 as compared to if the patient had not applied the formulation.

16. The method of claims 10 – 15 wherein the formulation maintains hair in anaphase longer than if the formulation had not been applied.

17. The method of claim 14 wherein the patient reverses a substantial amount of hair loss.

5 18. The method of claim 14 wherein the formulation comprises 0.06% w/w linaoprost acid and 0.08% w/w cyclosporine A and a pharmaceutically acceptable solvent and a penetration enhancer.

19. The method of growing hair wherein the formulation comprises 0.1% w/w travoprost or travoprost free acid and cyclosporine.

20. The method of claim 19 wherein the cyclosporine is cyclosporine A.

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## ABSTRACT

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

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