

TOPICAL COMPOSITION COMPRISING CLASCOTERONE AND LATANOPROST FOR ALOPECIA

RELATED APPLICATION

5 This application claims the benefit of Indian Provisional Application No. 202421002308 filed on January 11, 2024; which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The present invention relates to the use of combination of antiandrogen and prostaglandin analogues for preventing hair loss and/or stimulating hair growth. The present invention also relates to topical composition containing antiandrogen and prostaglandin analogues for preventing hair loss and/or stimulating hair growth on the scalp. The present invention also relates to composition and methods for treating certain hair loss disorders such
15 as alopecia.

BACKGROUND

 Hair loss is a natural phenomenon. Hair growth follows a cycle which involves the birth and development of the follicle, a stationary phase, and a final phase during which the hair is
20 expelled. This alternation between the phases of growth (the anagenic phase), regression (the catagenic phase), and the rest (the telogenic phase) is due to the specific secretion of the hair follicle which acts as a gland, and progressively produces a mass of keratin which it eliminates and replaces after a resting period.

 The cycle begins with the development of the hair follicle that rises up from the dermis
25 which contains large numbers of mesenchymatous cells, resulting in the formation of a dermal papilla. In the final stage (the anagenic phase) the cells surrounding the dermal papilla divide actively every 12 hours in order to produce cells which line up, grow longer, and begin to keratinize. This is hair growth. During the catagenic phase mitosis no longer occurs and the bulb detaches itself from the papilla and rises towards the surface. In the telogenic phase the
30 hair is fully keratinized and is ready to be expelled. After three to four months, another mitotic cycle begins in the germination zone of the hair and another hair follicle is formed.

 Male pattern alopecia is dependent on male hormones and is thus directly related to the amount of male hormones. Therefore, extensive research aimed at preventing and treating hair loss by inhibiting the activity of male hormones has recently been reported. The mechanism of

hair loss related to male hormones is briefly described below. The testosterone, which is one of the male hormones, is converted into dihydrotestosterone, which is an active male hormone, by a 5 α -reductase, and the active male hormone binds to a specific receptor to produce a protein that triggers hair loss, thus causing hair loss. Also, this mechanism produces excessive sebum, which causes acne or seborrheic dermatitis, eventually causing hair loss accompanied by inflammation in the scalp. As a result, the cause of male pattern alopecia is the synthesis of excessive dihydrotestosterone and thus it is possible to effectively prevent and treat male pattern alopecia by competitive inhibition with the androgen dihydrotestosterone from binding to androgen receptors in the sebaceous gland and hair follicles.

Treatments for the various forms of hair loss have limited success. Three medications have evidence to support their use in male pattern hair loss: oral finasteride (PROPECIA®, Merck), oral dutasteride and topical minoxidil (ROGAINE®, Pfizer/Johnson & Johnson). These treatments require prolonged usage of the drug and if treatment is stopped any benefits gained will be lost and the hair thickness will regress to levels as if no treatment was undertaken. Reversible side effects associated with the use of these androgen inhibitors have been reported such as decreased libido, erectile dysfunction and dermatologic discomfort.

Androgenetic alopecia is a common form of hair loss in both men and women. In men, this condition is also known as male-pattern baldness. Some of the current challenges in AGA include:

Understanding the underlying causes: Despite significant progress in the understanding of the genetics and biology of AGA, there is still much that is not fully understood about the condition. Researchers are still working to identify the precise genetic and environmental factors that contribute to AGA.

Developing effective treatments: Although there are several treatments available for AGA, including medications and hair transplant surgery, there is still no cure for the condition. Current treatments are often expensive, time-consuming, and may have side effects.

Addressing psychological impact: AGA can have a significant psychological impact on those affected, causing anxiety, depression, and low self-esteem. More research is needed to better understand the psychological aspects of AGA and develop effective interventions to address these issues.

Preventing hair loss: While there are treatments available to slow down or even reverse hair loss in some cases, preventing hair loss altogether remains a challenge. Lifestyle

changes, such as reducing stress and eating a healthy diet, may be beneficial, but more research is needed to determine the most effective ways to prevent hair loss.

Overall, the challenges in AGA highlight the need for continued research and development of new and more effective treatments, as well as increased focus on the psychological impact of the condition.

The combination of actives described herein constitute a major improvement to the currently available therapies of alopecia, and specifically AGA, and would allow the physicians to have an effective, valuable and safe treatment of alopecia, and in particular AGA.

The use of combination of antiandrogen and prostaglandin analogue for preventing hair loss and stimulating hair growth provides an equal or superior hair loss prevention and hair growth stimulating effects compared to existing treatment options currently available in the marketplace.

Inventors of the present invention have surprisingly found that the combination use of clascoterone and latanoprost, is an effective approach for treating androgenetic alopecia (AGA).

When used in combination, clascoterone, and latanoprost, target different aspects of the hair loss process, potentially providing more comprehensive and effective treatment for AGA. However, it is important to note that combination therapy may also increase the risk of side effects, such as scalp irritation, dizziness, and sexual dysfunction.

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SUMMARY OF THE INVENTION

The invention relates to topical pharmaceutical composition comprising: a. a pharmaceutically effective amount of a. antiandrogen, b. a pharmaceutically effective amount of a prostaglandin analogues and c. pharmaceutically acceptable vehicle.

The invention relates to topical pharmaceutical composition comprising: a. a pharmaceutically effective amount of a clascoterone, b. a pharmaceutically effective amount of a latanoprost; and c. pharmaceutically acceptable vehicle.

The invention relates to stable topical pharmaceutical composition about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle.

In certain embodiments, the pharmaceutically acceptable vehicle comprises one or more antioxidant, one or more emulsifier, one or more penetration enhancer, one or more preservative, one or more solvent, one or more pH adjusting agent and combinations thereof.

In some embodiments, the pharmaceutically acceptable vehicle is aqueous.

In some embodiments, the pharmaceutically acceptable vehicle is non-aqueous or anhydrous.

In another embodiment, the invention relates to a stable composition comprising: a. clascoterone, b. latanoprost; and d. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 6 months at room temperature (25°C/60%RH).

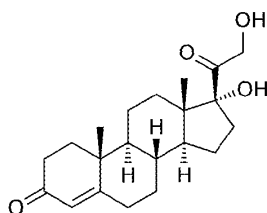
The invention relates to a stable topical pharmaceutical composition the method for preventing hair loss and/or stimulating hair growth comprising: a. a pharmaceutically effective amount of a. antiandrogen, b. a pharmaceutically effective amount of prostaglandin analogues, and c. pharmaceutically acceptable vehicle, wherein the composition is suitable for preventing and/or treating the hair loss and/or stimulating hair growth.

DETAILED DESCRIPTION

Disclosed herein is detailed descriptions of specific aspects of the invention related to the combination of clascoterone and latanoprost comprising pharmaceutically acceptable vehicle comprising one or more solvent. Further invention relates to method of treating hair loss and/or stimulating hair growth comprising: a. clascoterone, and b. pharmaceutically acceptable vehicle comprising one or more solvent.

A. Cortisolone

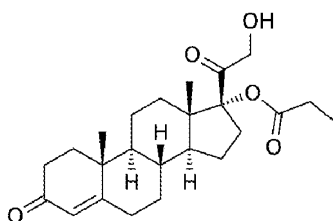
Cortisolone is known as "11-Deoxycortisol" or "Reichstein's substance" in Formula I



Formula I

The Cortisolone exists as cortisolone base form or its esters such as 17 α -monoesters and/or 17 α ,21-diester of cortisolone, a class of compounds provided with a strong local ant androgenic activity. Example of cortisolone esters are cortisolone 17 α -propionate, cortisolone 17 α -valerate, cortisolone 17 α ,21-dibutirrate and any combinations of any of the foregoing.

In a specific aspect, the cortisolone or its ester(s) as used herein refers to clascoterone i.e., cortisolone 17 α -propionate and is chemically known as 17 α -propionyloxy-21-hydroxy-pregna-4-ene-3,20-dione. The chemical structure of clascoterone is



Formula II

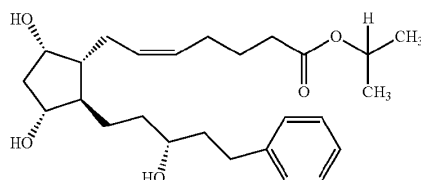
In some aspects, the clascoterone refers to the pharmaceutically acceptable salt forms, esters, polymorphs, crystalline forms or degradation product. For example, the ester forms of corticosterone refers to esterified organic solvents including, but not limited to, acetate, butyrate, benzoate, ethyl acetate and ethyl lactate, the polymorphs or crystalline forms of corticosterone refers to, but not limited to, various polymorphic/crystalline forms disclosed in WO2009019138, or the salts refers to any acid or alkaline addition salts such as hydrochloride, sodium etc.

In a specific aspect, the corticosterone as used herein refers to corticosterone-17 α -propionate in Formula II or its crystalline forms.

The therapeutically effective amount of clascoterone is from about 1% w/w to 15% w/w based on the total weight of the composition, or from about at least 2% w/w to about 10% w/w based on the total weight of the composition or preferably from about at least 5% w/w to about 10% w/w based on the total weight of the composition or most preferably of about 7.5% w/w based on the total weight of the composition. In a specific aspect, the concentration of clascoterone in the composition is selected from about 1% w/w, 1.5% w/w, 2% w/w, 2.5% w/w, 3% w/w, 3.5% w/w, 4% w/w, 4.5% w/w, 5% w/w, 5.5% w/w, 6% w/w, 6.5% w/w, 7% w/w, 7.5% w/w, 8% w/w, 8.5% w/w, 9% w/w, 9.5% w/w, 10% w/w, 10.5% w/w, 11% w/w, 11.5% w/w, 12% w/w, 12.5% w/w, 13% w/w, 13.5% w/w, 14% w/w, 14.5% w/w, or 15 % w/w based on total weight of the composition.

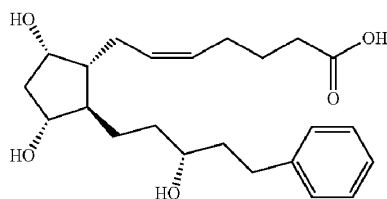
B. Latanoprost

Latanoprost has the following structure as Formula III



Formula III

Latanoprost is a prostaglandin analogue and is in fact a prodrug with its acid form (Latanoprost acid) being biologically active as in Formula IV.



Formula IV

5 Latanoprost is an isopropyl ester, and is a prodrug which converts to latanoprost free acid by r[(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 PGF2 α . The efficacy of
10 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 invention include 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol and latanoprost ethyl amide-d4.

Latanoprost is poorly soluble in water but is generally fat soluble. The solubility of
15 latanoprost in PBS (pH 7.2) is approximately 50 μ g/mL. For maximum solubility in aqueous buffers, latanoprost should first be dissolved in ethanol or propylene glycol and then diluted with the aqueous buffer of choice. Latanoprost has a solubility of 400 μ g/mL in a 1:4 solution of ethanol: PBS (pH 7.2) using this method.

In acidic or basic aqueous solutions, latanoprost is stable for no more than 48 hours and
20 in neutral aqueous solutions it has shown to be stable for up to one month at room temperature. Latanoprost is the isopropyl ester of 17-phenyl-13,14-dihydro prostaglandin F2 α (17-phenyl-13,14-dihydro PGF2 α).

The therapeutically effective amount of latanoprost is from about 0.001% w/w to 1% w/w, or from about at least 0.01% w/w to about 0.1% w/w, or preferably from about at least
25 0.02% w/w to about 0.08% w/w b, or preferably of about 0.025% w/w to about 0.06% w/w, or most preferably about 0.03% w/w based on the total weight of the composition. In a specific aspect, the concentration of latanoprost in the composition is selected from about 0.001% w/w, 0.005% w/w, 0.01% w/w, 0.02% w/w, 0.03% w/w, 0.04% w/w, 0.05% w/w, 0.06% w/w, 0.07% w/w, 0.08% w/w, 0.09% w/w, 0.1% w/w, 0.15% w/w; 0.2% w/w, 0.25% w/w, 0.3% w/w, 0.35%

w/w, 0.4% w/w, 0.45% w/w, 0.5% w/w, 0.55% w/w, 0.6% w/w, w/w 0.65%, 0.7% w/w, 0.75% w/w, 0.80% w/w, 0.85% w/w, 0.9% w/w, 0.95% w/w, or 1% w/w.

Definitions:

5 The terms “active” and “active agent” as used herein refers to therapeutically active agent used in the treatment of a disease or disorder. For example, therapeutically active agent used herein is useful for the treatment, alleviation or prevention of hair loss, and/or the stimulation of hair growth. Exemplary agents are a hair growth stimulant, and/or hair growth stimulating agent and/or hair density increasing agent and/or hair loss prevention agent.

For example, an active agent may be clascoterone or latanoprost or combination thereof.

10 The term “effective amount” refers to an amount that is sufficient to achieve the desired modification of a physical property of the composition or material. For example, an “effective amount” of a therapeutic agent refers to an amount that is sufficient to achieve the desired improvement in clinical condition modulated by the formulation component, e.g. achieving the desired level of hair growth or mitigation of hair loss. Therapeutic agents should be understood
15 to include the neutral forms of the drug and pharmaceutically acceptable forms thereof. “Pharmaceutically acceptable” refers to those compounds, materials, compositions, salts and/or dosage forms which, are suitable for administration to patients without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio, when used in the compositions of the invention, including when
20 the compositions are applied topically according to methods described herein.

By “pharmaceutically acceptable forms” thereof is meant any pharmaceutically acceptable derivative or variation, including stereoisomers, stereoisomer mixtures, enantiomers, solvates, hydrates, isomorphs, polymorphs, pseudomorphs, salt forms and prodrugs. Preferably in some aspects, the pharmaceutically acceptable forms include salt forms.
25 In other preferable aspects the pharmaceutically acceptable forms include, any stereoisomer or stereoisomeric mixture of the therapeutic agent. The specific level in terms of % w/w in a composition required as an effective amount will depend upon a variety of factors including the amount and type of therapeutic agent and formulation type, e.g., solution, emulsion, suspension, spray, ointment, cream, gel, and the like.

30 The term “comprising” is to be interpreted as specifying the presence of the stated features, integers, steps, or components as referred to, but does not preclude the presence or addition of one or more features, integers, steps, or components, or groups thereof. Moreover, each of the terms “by”, “comprising,” “comprises”, “comprised of,” “including,” “includes,” “included,” “involving,” “involves,” “involved,” and “such as” are used in their open, non-

limiting sense and may be used interchangeably. Further, the term “comprising” is intended to include examples and aspects encompassed by the terms “consisting essentially of” and “consisting of.” Similarly, the term “consisting essentially of” is intended to include examples encompassed by the term “consisting of”.

5 The term “safe and effective amount” as used herein means an amount of a compound or composition sufficient to significantly induce a positive benefit, for example, hair growth, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

 The term “hair growth,” “regulating hair growth,” “hair growth regulation,” and
10 “regulating the growth of hair,” are meant to include: stimulating hair growth; stimulating hair thickening; preventing, reducing, arresting and/or retarding the loss of hair; preventing, reducing, arresting and/or retarding the thinning of hair; increasing the rate of hair growth; inducing the formation of a greater number of hair strands; increasing the diameter of the hair strand; lengthening the hair strand; changing the hair follicle from a vellus or miniaturized
15 follicle to a large terminal follicle; inducing the formation of vellus and terminal follicles.

 The term “alopecia” as used herein refers to, collectively, or individually as specified, androgenetic alopecia (AGA) (including male pattern and female pattern), alopecia areata (including persistent patchy alopecia areata, diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia
20 universalis), cicatricial alopecia, lichen planopilaris (including frontal fibrosing alopecia, central centrifugal cicatricial alopecia (CCCA), alopecia barbae, postpartum alopecia, chemotherapy induced hair loss, telogen effluvium, anagen effluvium, and traction alopecia.

 As used herein, the terms “about,” “approximate,” “at or about,” and “substantially” mean that the amount or value in question can be the exact value or a value that provides
25 equivalent results or effects as recited in the claims or taught herein. That is, it is understood that amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art such that equivalent results or effects are obtained. In some
30 circumstances, the value that provides equivalent results or effects cannot be reasonably determined. In such cases, it is generally understood, as used herein, that “about” and “at or about” mean the nominal value indicated $\pm 20\%$ variation unless otherwise indicated or inferred. In general, an amount, size, formulation, parameter or other quantity or characteristic is “about,” “approximate,” or “at or about” whether or not expressly stated to be such. It is understood that

where “about,” “approximate,” or “at or about” is used before a quantitative value, the parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances
5 where said event or circumstance occurs and instances where it does not.

As used herein, the term “administration” refers to the act of administering a drug, prodrug, or other active agent, or therapeutic treatment (e.g., compositions of the invention) to a subject. Exemplary routes of administration to the human body can be on the skin, e.g., on
10 the scalp. Administration may be in one or more administrations, applications or dosages, and is not intended to be limited to a particular time period. “Administered” and “applied” are used to describe the act of “administration” and are used synonymously.

The term “substantially solubilized,” as used herein, means that the therapeutic agent is dissolved in the compositions and is at a concentration which is less than about its solubility
15 limit in the compositions.

The term “partially solubilized,” as used herein, means that the therapeutic agent is insoluble in the compositions and is at a concentration which is less than about its solubility limit in the compositions.

The term “topical” or “topically” in reference to administration or application of a composition or a product refers to epicutaneous administration or application, or administration
20 onto the surface of the skin. The term “topically active agent” as used herein refers to a compound that is effective in a treatment of a skin condition when administered topically. The term “topical,” when used in reference to a composition, formulation or a product refers to a composition or a product formulated for topical application. “Formulation” and “composition”
25 can be interchangeable.

The term “pharmaceutical composition” as used herein refers to compositions comprising antiandrogen and prostaglandin analogues together with one or more pharmaceutically acceptable excipients as required to prepare a dosage form for the effective delivery of the active agent. Such pharmaceutical compositions can be in the form of solutions,
30 ointments, creams, gels, lotions, suspensions, sprays, foams, microspheres, microemulsions, nanoemulsions, nanoparticles, nanosuspensions, dermal sticks, roll-ons, pumps, patches, tapes, and the like.

“Scalp” according to the present invention means the skin covering the head and is bordered by the face anteriorly and the neck to the sides and posteriorly.

The term “treatment duration” as used herein, means that the composition prescribed or used or administered for said period of time for example one month, two months, six months, 1 year or two year).

5 The term “solvent” as used herein refers to a substance that solubilizes active agent or one or more excipient and provides uniform distribution of active agent or one or more excipient throughout the composition. As used herein “solvent” and “solubilizer” can be interchangeable. Solvent or vehicle can be uses from 1% w/w to 99%w/w of composition.

The term “pharmaceutical acceptable vehicle” as used herein refers to a one or more solvent and additional excipient or water.

10 The term “subject” as used herein refers to human subject or an animal including mammals (such as monkeys, guinea pig, domestic pets, for instance cats and dogs).

The invention relates to the topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle.

15 The invention relates to the topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle comprising one or more solvent.

The invention relates to the stable topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle.

20 The invention relates to the stable topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle comprising one or more solvent.

The invention relates to the topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein at least one of the active is partially solubilized.

25 In another embodiment, the invention relates to a topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein clascoterone is partially solubilized or supersaturated or suspended.

30 In another embodiment, the invention relates to a topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein latanoprost is partially solubilized or supersaturated or suspended.

In another embodiment, the invention relates to a topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein clascoterone and latanoprost are fully solubilized.

In another embodiment, the invention relates to a topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle comprising one or more solvent.

5 In another embodiment, the invention relates to a topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle comprising one or more solvent, antioxidant and pH adjusting agent.

10 In another embodiment, the invention relates to a topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein clascoterone is partially solubilized; and latanoprost is solubilized.

15 In another embodiment, the invention relates to a topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein clascoterone is solubilized; and latanoprost is partially solubilized.

In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 1% w/w to about 15% w/w of the clascoterone or a pharmaceutically acceptable salt thereof, b. about 0.001% w/w to about 1% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

20 In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 3% w/w to about 12% w/w of the clascoterone or a pharmaceutically acceptable salt thereof, b. about 0.01% w/w to about 0.1% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

25 In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 5% w/w to about 10% of the clascoterone or a pharmaceutically acceptable salt thereof, b. about 0.02% w/w to about 0.08% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

30 In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 6% w/w to about 8% of the clascoterone or a pharmaceutically acceptable salt thereof, b. about 0.02% w/w to about 0.06% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 7.5% w/w of the clascoterone or a pharmaceutically acceptable salt thereof,

b. about 0.03% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical pharmaceutical composition comprising a. about 5% w/w of the clascoterone or a pharmaceutically acceptable salt thereof,
5 b. about 0.03% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to topical pharmaceutical composition selected from the group consisting of hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch,
10 hair serum, foam, and spray.

In certain embodiments, the pharmaceutically acceptable vehicle comprises one or more antioxidant, one or more emulsifier, one or more penetration enhancer, one or more preservative, one or more solvent, one or more pH adjusting agent and combinations thereof.

In certain embodiments, the one or more pharmaceutically acceptable solvents are
15 selected from the group consisting of a polyol and a C₁-C₇ alcohol.

In some embodiments, the pharmaceutically acceptable vehicle comprises at least about 10% w/w solvent. In other embodiments, the pharmaceutically acceptable vehicle comprise at least about 20% w/w, at least about 30% w/w solvent, at least about 40% w/w solvent, at least about 50% w/w solvent, at least about 55% w/w solvent, at least about 60% w/w solvent, at
20 least about 65% w/w solvent, at least about 70% w/w solvent, at least about 75% w/w solvent, at least about 80% w/w solvent, at least about 81% w/w solvent, at least about 82% w/w solvent, at least about 83% w/w solvent, at least about 84% w/w solvent, at least about 85% w/w solvent, at least about 86% w/w solvent, at least about 87% w/w solvent, at least about 88% w/w solvent, at least about 89% w/w solvent, at least about 90% w/w solvent, at least about 91% w/w solvent,
25 at least about 92% w/w solvent, at least about 93% w/w solvent, at least about 94% w/w solvent, at least about 95% w/w solvent.

In certain embodiments, the solvent comprise a C₁-C₇ alcohol includes but are not limited to, methanol, ethanol, isopropanol, n-butanol, n-propanol, benzyl alcohol, and the like. Without wishing to be bound by any particular theory, it is believed that C₁-C₇ alcohols, and
30 particularly short chain C₁-C₃ alcohols, like ethyl, propyl or isopropyl alcohols, exert a solubilizing activity on cortexolone-17 α -propionate. It is further believed that such C₁-C₇ alcohols contribute to the spreadability of the composition described herein. Preferably C₁-C₇ alcohols used as described herein is not having irritant properties when applied to skin or scalp.

In some embodiments, the C₁-C₇ alcohol is ethanol, isopropanol, or methanol. In other embodiments, the C₁-C₇ alcohol is isopropyl alcohol.

In other embodiments, the C₁-C₇ alcohol is isopropyl alcohol. In particular embodiment C₁-C₇ alcohol can be used in a range of about 10% w/w to about 50% w/w. In particular
5 embodiments, the composition can comprise from about 15% w/w to about 45% w/w of the C₁-C₇ alcohol; from about 20% to about 40% w/w of the C₁-C₇ alcohol; or from about 25% to about 35% w/w of the C₁-C₇ alcohol. In particular embodiments, the composition can comprise about 30% w/w of the C₁-C₇ alcohol. In particular embodiments, the composition can comprise about 40% w/w of the C₁-C₇ alcohol. In particular embodiments, the C₁-C₇ alcohol is isopropanol. In
10 some embodiments, the isopropanol comprises about 30% w/w of the total composition.

In certain embodiments, the solvent comprise a polyol comprises propylene glycol, ethylene glycol, glycerol, hexanetriol, hexylene glycol, and combinations thereof. In particular embodiments, the polyol can be glycerin. In other embodiments, the polyol can be propylene glycol. In other embodiments, the polyol can be hexylene glycol. In a further embodiment, the
15 polyol comprising mixture of propylene glycol and hexylene glycol. In a further embodiment, the ratio of propylene glycol and hexylene glycol is 1:3 to 3:1.

In particular embodiments, the polyol can be present in an amount ranging from about 10% w/w to about 50% w/w of the total composition; from about 15% w/w to about 45% w/w of the total composition; from about 20% w/w to about 40% w/w of the total composition; and
20 in certain embodiments, from about 25% w/w to about 40% w/w. In a particular embodiment, the polyol comprises about 30% w/w of the total composition. In a further embodiment, the polyol comprising about 35% w/w of the total composition can be propylene glycol.

In certain embodiments, the solvent comprises a mixture of a C₁-C₇ alcohol, a polyol, polyol ether. In such embodiments, the composition comprises from about 10 to about 50% w/w of the one or more polyol; and about 10 to about 50% w/w of the C₁-C₇ alcohol. In certain
25 embodiments, the solvent comprises a mixture of any one of C₁-C₇ alcohol, a polyol ether, and polyol in amounts of about 30 weight percent.

In another embodiment invention relates to pharmaceutical composition, comprising one or more glycol and isopropyl alcohol.

30 In another embodiment invention relates to pharmaceutical composition, comprising combination of at least two glycol and isopropyl alcohol.

In certain embodiments, the solvent comprises C₁-C₇ alcohol, a polyol, water and combinations of any of the foregoing.

In particular embodiment, the composition is free of diethylene glycol monoethyl ether.

In particular embodiment, the composition is free of ethanol.

In a particular embodiment, the invention relates to a composition comprising a. clascoterone and b. latanoprost and c. pharmaceutically acceptable vehicle comprising one or more solvent wherein vehicle is substantially free of ethanol.

5 In a particular embodiment, the invention relates to a composition comprising a. clascoterone and b. latanoprost and c. pharmaceutically acceptable vehicle comprising one or more solvent wherein vehicle is free of ethanol.

In a particular embodiment, the invention relates to a composition comprising a. clascoterone and b. latanoprost and c. pharmaceutically acceptable vehicle comprising one or
10 more solvent wherein vehicle is substantially free of diethylene glycol monoethyl ether.

In a particular embodiment, the invention relates to a composition comprising a. clascoterone and b. latanoprost and c. pharmaceutically acceptable vehicle comprising one or more solvent wherein vehicle is free of diethylene glycol monoethyl ether.

In certain embodiments, the pharmaceutically acceptable vehicle comprises an
15 antioxidant. In some embodiments, the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, ascorbic acid, alpha tocopherol (also known as Vitamin E), propyl gallate, carotenoid (for example Lycopene, Lutein), resveratrol, niacinamide, coenzyme Q10, monothioglycerol, potassium metabisulfite, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium sulfite,
20 sodium thiosulfate, sodium metabisulfite, acai oil, alpha lipoic acid, green tea extract, retinol, isoflavones, polyphenols, curcumin, turmeric, pomegranate, rosemary extract, glutathione, selenium, zinc, a chelating such as ethylenediaminetetraacetic acid (EDTA), disodium EDTA, tetrasodium EDTA, pentasodium penetate, sodium metasilicate and phosphate derivatives, etidronic acid and/or its derivatives, and/or galactaric acid. The antioxidant is present in an
25 amount of between about 0.01% w/w to about 5% w/w, preferably about 0.01% w/w to about 1%, most preferably about 0.01% w/w to about 0.05% w/w.

In certain embodiments, the pharmaceutically acceptable vehicle comprises a preservative. In certain embodiments, the preservative is selected from one or more sodium benzoate, benzoic acid, phenol, cresol, alcohol, chlorbutanol, phenoxyethanol, benzalkonium
30 chloride, methyl paraben or its salts, propyl paraben or its salts, methyl paraben or its salts. In some embodiments, the preservative is phenoxyethanol. The preservative may be present in an amount of between about 0.001% w/w to about 5% w/w, preferably about 0.01% w/w to about 2%, most preferably about 0.1% w/w to about 1% w/w.

In certain embodiments, the pharmaceutically acceptable vehicle comprises a pH adjusting agent. In certain embodiments, pH adjusting agent include those pharmaceutically acceptable organic and inorganic acids known to those of ordinary skill in the art. Examples of such acids, include, but are not limited to 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, L-ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, L-malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, L-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, and undecylenic acid. In particular embodiments, the pH adjusting agent can be lactic acid. The pH adjusting agent may be present in an amount of between about 0.001% w/w to about 2% w/w, preferably about 0.01% w/w to about 1%, most preferably about 0.1% w/w to about 0.5% w/w.

In certain embodiments, the pH adjusting agent is a buffering agent. Exemplary buffering agents include but are not limited phosphate/phosphoric acid, citrate/citric acid, acetate/acetic acid, propionate/propionic acid, lactate/lactic acid, ammonium/ammonia and edetate/edetic acid, borate/boric acid, succinate/succinic acid, maleate/malic acid and any combination thereof.

In one of the embodiment the invention relates to a topical composition comprising clascoterone, at a concentration of about 5% w/w to 15% w/w and 0.01% w/w to 0.06% w/w latanoprost and a pharmaceutically acceptable vehicle comprising one or more solvent, wherein the pH of composition is about 3 to about 7.

In certain embodiments, the pH of the composition is about 3 to about 6, about 3 to about 5, about 3 to about 4, about 4 to about 7, about 4 to about 6, about 4 to about 5, about 3 to about 3.5 or about 3.5 to about 4.

It has now been surprisingly found that by maintaining the composition disclosed herein at a pH of less than about 7, and in certain embodiments, less than about 5, between about 3 to

about 4, the degradation of clascoterone to cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) can be dramatically slowed. While pH can be important to stability, it has also been discovered that addition of an antioxidant to the composition can assist in maintaining storage stability. The antioxidant can be present in addition to a pH modifier. But in some embodiments, the pH modifier can be substantially or completely absent.

In another embodiment, the invention relates to a stable topical pharmaceutical composition comprising: a. clascoterone, b. latanoprost; and d. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 1 month at room temperature (25°C/60%RH).

In another embodiment, the invention relates to a stable topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and d. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 2 months at room temperature (25°C/60%RH).

In another embodiment, the invention relates to a stable topical pharmaceutical composition for treating hair loss and/or stimulating hair growth comprising: a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 3 months at room temperature (25°C/60%RH).

In another embodiment, the invention relates to a stable topical pharmaceutical composition comprising a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 3 months.

In another embodiment, the invention relates to a stable topical pharmaceutical composition comprising a. clascoterone, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 40°C/75%RH for at least about 1 months.

In another embodiment invention relates to a stable topical pharmaceutical composition, wherein composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione).

In another embodiment invention relates to a stable topical pharmaceutical composition, wherein composition comprises less than 3% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione).

In another embodiment invention relates to a stable topical pharmaceutical composition, wherein composition comprises less than 8% w/w of total degradation of cortexolone-17 α -propionate.

In one of the embodiment, a stable topical pharmaceutical composition comprising
5 about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6
10 months.

In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein
15 the composition comprises less than 3% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6 months.

In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-
20 17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein the composition comprises less than 2% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6 months.

In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-
30 propionyloxy-pregna-4-ene-3,20-dione) when stored at 40°C/75%RH for at least about 6 months.

In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from

group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein the composition comprises less than 8% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 40°C/75%RH for at least about 6 months.

5 In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; wherein the composition is suitable for treating hair loss and/or stimulating hair growth.

10 In one of the embodiment, a stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising a solvent selected from group comprising of polyol, C₁-C₇ alcohol; an antioxidant; a pH adjusting agent; and wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6
15 months; wherein the composition is suitable for treating hair loss and/or stimulating hair growth.

In an embodiment the invention relates to a topical composition which is applied to the skin of the affected area of hair loss.

20 In an embodiment invention relates to the topical composition is applied to the affected area of hair loss, grows hair to a greater extent than the same composition with the same amount and concentration of latanoprost but without clascoterone applied to the same area.

In an embodiment invention relates to the topical composition of applied to the affected area of hair loss, grows hair to a greater extent than the same composition with the same amount and concentration of clascoterone but without latanoprost applied to the same area.
25

In an embodiment invention relates to the topical composition of applied to the affected area of hair loss, grows hair to a greater extent than the same composition with the 5% concentration of minoxidil applied to the same area.

In an embodiment invention relates to the topical composition of applied to the affected
30 area of hair loss, grows hair to a greater extent than the 5% minoxidil composition available commercially applied to the same area.

In an embodiment invention relates to the topical composition which is applied to the affected area which is scalp.

In an embodiment invention relates to the method according to present invention, wherein the composition is applied at least once a day to the affected area of hair loss.

In an embodiment invention relates to the method according to present invention, wherein the composition is applied at least twice a day to the affected area of hair loss.

5 A method of treating androgenetic alopecia in a patient suffering therefrom comprising applying a composition to an area experiencing hair loss wherein the active agents of the composition consist of latanoprost and clascoterone.

10 In an embodiment invention relates to the method according to present invention, wherein the active agent comprises 0.02% w/w to 1% w/w latanoprost and 5% w/w to 15% w/w clascoterone.

In an embodiment invention relates to the method according to present invention, wherein the patient experiences more hair growth in the area experiencing hair loss where the composition is applied as compared to if the patient had not applied the composition to the area experiencing hair loss.

15 In an embodiment invention relates to the method according to present invention, wherein new hair growth results in the area experiencing hair loss where the composition is applied in which the individual hairs are thicker in diameter as compared to hair growth in areas where the patient did not apply the composition.

20 In an embodiment invention relates to the method according to present invention, wherein the application of the composition to an area experiencing hair loss grows hair to a greater extent than the same amount of clascoterone applied at the same concentration but without latanoprost to the same area.

25 In an embodiment invention relates to the method according to present invention, wherein the application of the composition to an area experiencing hair loss grows hair to a greater extent than the same amount of latanoprost applied at the same concentration but without clascoterone to the same area.

In an embodiment invention relates to the method according to present invention, wherein the application of the composition to the scalp results in a faster onset of new hair growth as compared to the patient not applying the composition.

30 In an embodiment, the invention relates to the method of treating or preventing hair loss in a patient suffering from a hair loss disorder comprising applying a topical pharmaceutical composition wherein the active agent comprises 0.02% w/w to 1% w/w latanoprost and clascoterone.

In an embodiment, the invention relates to the method of treating or preventing hair loss in a patient suffering from a hair loss disorder comprising applying a topical pharmaceutical composition wherein the active agent comprises latanoprost and clascoterone of 5% w/w to 15% w/w.

5 In another embodiment, the invention relates to the method of treating or preventing hair loss in a patient suffering from a hair loss disorder comprising applying a topical pharmaceutical composition comprising about 0.06 % w/w latanoprost and about 15% w/w cortexolone-17 α -propionate.

10 In one of the embodiment composition according to invention relates to a topical composition comprising active ingredients consisting of: a. clascoterone, at a concentration of about 7.5% w/w of the composition; b. latanoprost at a concentration of about 0.03% w/w by weight of the composition and c. a pharmaceutically acceptable vehicle, wherein solution comprises a solvent; and wherein the composition comprising the clascoterone and latanoprost at said concentrations is capable of providing synergistic efficacy.

15

EXAMPLES

The compositions described herein are now further detailed with reference to the following examples. These examples are provided for the purpose of illustration only and the embodiments described herein should in no way be construed as being limited to these
20 examples. Rather, the embodiments should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Example-1

Table-1:

Ingredients	% w/w
Clascoterone	5 - 15
Latanoprost	0.01 - 0.2
Solvent	2.0 – 98.0
Purified water	q.s

25 Brief Manufacturing Process:

Clascoterone and latanoprost were added to mixture of one or more solvents and purified water in suitable vessel; mixed under stirring, to obtain clear solution phase.

Example-2: Clascoterone and Latanoprost Composition

- A composition of cortexolone-17 α -propionate and latanoprost having the components shown in Table-2, below, was prepared by adding cortexolone-17 α -propionate in the mixture of solvents followed by the addition of the ascorbyl palmitate & phenoxyethanol, latanoprost was added to isopropyl alcohol to make clear solution and added to cortexolone-17 α -propionate phase.

Table-2:

Ingredients	Amount % w/w
Cortexolone-17 α -propionate	5 to 15
Propylene Glycol	10 to 40
Latanoprost	0.01 to 0.06
Phenoxyethanol	0.01 to 2
Ascorbyl Palmitate	0.001 to 1
Hexylene glycol	5 to 30
IPA	10 to 50
Water	q.s.

Example-3: Clascoterone and Latanoprost Composition

- A composition of 7.5% w/w cortexolone-17 α -propionate and 0.03% w/w latanoprost having components shown in Table-3, below, was prepared by adding the cortexolone-17 α -propionate in the mixture of solvents and phenoxyethanol, in part of the isopropyl alcohol amount latanoprost, ascorbyl palmitate and vitamin E were dissolved to obtain clear phase and mixed with solvent mixture and added remaining amount of isopropyl alcohol, clascoterone was added to the mixture obtained in previous step.

Table-3:

Ingredients	Amount % w/w
Cortexolone-17 α -propionate	7.50
Latanoprost	0.03
Propylene Glycol	31.26
Phenoxyethanol	1.00
Ascorbyl Palmitate	0.50
Vitamin E	0.01
Hexylene glycol	14.00
Isopropyl Alcohol	40.00

Ingredients	Amount % w/w
Purified Water	q.s

Example-4: Clascoterone and Latanoprost Composition

A composition of 15% w/w of cortexolone-17 α -propionate having the components shown in Table-4, below, was prepared by adding the cortexolone-17 α -propionate in the mixture of solvents followed by the addition of the vitamin E & phenoxyethanol, latanoprost was added to isopropyl alcohol to make clear solution and added to cortexolone-17 α -propionate phase.

Table-4:

Ingredients	Amount % w/w
Cortexolone-17 α -propionate	15.00
Latanoprost	0.06
Propylene Glycol	35.00
Phenoxyethanol	1.00
Vitamin E	0.01
Hexylene glycol	14.00
IPA	34.59
Lactic acid	q.s. to obtain pH 3.0 to 7

10

Example-5: Clascoterone and Latanoprost Composition

A composition of 7.5% w/w cortexolone-17 α -propionate having the components shown in Table-5, below, was prepared by solubilizing the cortexolone-17 α -propionate in the mixture of solvents followed by the addition of the ascorbyl palmitate & phenoxyethanol, latanoprost was added to isopropyl alcohol to make clear solution and added to cortexolone-17 α -propionate phase

15

Table-5:

Ingredients	Amount % w/w
Cortexolone-17 α -propionate	7.50
Latanoprost	0.03
Propylene Glycol	37.00
Phenoxyethanol	1.00
Ascorbyl palmitate	0.50

Ingredients	Amount % w/w
Hexylene glycol	14.00
IPA	40.00

Example-6: The stability study results

Below are the stability study results of Example-3 at 25 °C/60% RH & 40 °C/75% RH is shown in Table-6.

5 Table-6:

Storage condition	Period	% Assay of Clascoterone	% Assay of latanoprost	Specific gravity	Viscosity	pH
Stability specification		90-110%	90-110%	0.8-1.2	5-25cP	3.0-7.0
-	Initial	100.2	99.2	0.92	9.22	4.40
25 °C/60% RH	1M	101	99.6	0.92	8.84	3.52
	2M	99	98.0	0.92	9.24	3.59
	3M	98.8	96.6	0.92	9.0	3.53
	6M	97.9	97.7	0.92	9.02	3.18
40 °C/75% RH	1M	100.2	99.1	0.92	8.88	3.40
	2M	98.4	96.45	0.92	9.24	3.45
	3M	96.9	96.0	0.92	9.0	3.41
	6M	91.7	98.8	0.93	8.92	3.15

The stability study results and impurity profile of Example-3 – Latanoprost component at 25 °C/60% RH & 40 °C/75% RH is shown in Table-7.

Table-7:

	Period	Latanoprost Impurity B	Latanoprost Impurity E	Latanoprost Impurity A	Any other individual impurity	Total impurities
Specification		-	-	-	1.0%	3.0%
	Initial	ND	0.15	ND	ND	0.15
25 °C/60% RH	1M	ND	0.15	ND	ND	0.15
	2M	ND	0.15	ND	ND	0.15
	3M	ND	0.30	ND	ND	0.30
	6M	ND	0.40	ND	ND	0.40

	Period	Latanoprost Impurity B	Latanoprost Impurity E	Latanoprost Impurity A	Any other individual impurity	Total impurities
40 °C/75% RH	1M	ND	0.25	ND	ND	0.25
	2M	ND	0.36	ND	ND	0.36
	3M	ND	0.71	0.06	ND	0.71
	6M	ND	0.92	ND	ND	0.92

ND: Not detected

The stability study results and impurity profile of Example-3 Clascoterone at 25 °C/60% RH & 40 °C/75% RH is shown in Table-8.

Table-8:

Related substances of Clascoterone						
	Period	Cortisolone	Clascoterone 1,4-Diene	Cortisolone 21- propionate	Any other individual impurity	Total impurities
Specification		-	-	5%	0.5%	8%
Initial	-	0.01	0.03	0.19	0.05	0.31
25 °C/60% RH	1M	0.01	0.04	0.17	0.05	0.30
	2M	0.02	0.03	0.31	0.08	0.46
	3M	0.04	ND	0.58	0.15	0.81
	6M	0.03	0.04	1.13	0.15	1.53
40 °C/75% RH	1M	0.02	0.04	0.54	0.11	0.75
	2M	0.03	0.05	0.99	0.19	1.57
	3M	0.04	ND	2.07	0.36	2.57
	6M	0.14	0.05	4.49	0.38	5.65

5 ND: Not detected.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description and are encompassed within the scope of the present invention.

10 The phraseology or terminology herein is for the purpose of description and not of limitation. As such, the terminology and/or phraseology of the present specification should be interpreted by the skilled artisan in light of the teachings and guidance herein.

The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments but should be defined only in accordance with the following claims and their equivalents.

While the present disclosure shows and describes a number of exemplary embodiments,
5 it will be manifest to those skilled in the art that various further modifications may be made without departing from the spirit and scope of the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

We Claim:

1. A stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle.
- 5 2. The stable topical pharmaceutical composition of claim 1, wherein latanoprost is about 0.01% w/w to about 0.06% w/w and cortexolone-17 α -propionate is about 5% w/w to about 15% w/w.
3. The stable topical pharmaceutical composition of claim 1, wherein latanoprost is about 0.03% w/w and cortexolone-17 α -propionate is about 7.5% w/w.
- 10 4. The stable topical pharmaceutical composition of claim 1, wherein latanoprost is about 0.06% w/w and cortexolone-17 α -propionate is about 15% w/w.
5. The stable topical pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable vehicle is aqueous.
6. The stable topical pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable vehicle is non-aqueous.
- 15 7. The stable topical pharmaceutical composition of claim 1, wherein the composition is suitable for treating hair loss and/or stimulating hair growth.
8. A stable topical pharmaceutical composition comprising about 0.001% w/w to 1% w/w latanoprost and about 1% w/w to about 15% w/w cortexolone-17 α -propionate and a pharmaceutically acceptable vehicle comprising
- 20 a solvent;
a pH adjusting agent; and
wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6 months.
- 25 9. A stable topical pharmaceutical composition of claim 8, wherein the composition comprises a solvent selected from group comprising of polyol, C1-C7 alcohol, polyol ether.
10. A stable topical pharmaceutical composition of claim 8, further comprising an
- 30 antioxidant.
11. The stable topical pharmaceutical composition of claim 8, wherein the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, ascorbic acid, alpha tocopherol and propyl gallate.

12. A stable topical pharmaceutical composition of claim 8, comprising, a pH adjusting agent, wherein the pH adjusting agent is selected from hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid and L-malic acid.
13. The stable topical pharmaceutical composition of claim 8, wherein the pH of the composition is about 3 to about 7.
14. The stable topical pharmaceutical composition of claim 8, wherein the pH of the composition is about 3 to about 5.
15. The stable topical pharmaceutical composition of claim 8, wherein the composition comprises less than 3% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6 months.
16. The stable topical pharmaceutical composition of claim 8, wherein the composition comprises less than 2% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 25°C/60%RH for at least about 6 months.
17. The stable topical pharmaceutical composition of claim 8, wherein the composition comprises less than 5% w/w of cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione) when stored at 40°C/75%RH for at least about 6 months.
18. The stable topical pharmaceutical composition of claim 8, wherein the composition comprises less than 5% w/w of Latanoprost Impurity E, when stored at 25°C/60%RH for at least about 6 months.
19. The stable topical pharmaceutical composition of claim 8, wherein the composition comprises less than 2% w/w of Latanoprost Impurity E, when stored at 25°C/60%RH for at least about 6 months.
20. A stable topical pharmaceutical composition of claim 8; wherein the composition is suitable for preventing and/or treating hair loss and/or stimulating hair growth in patients suffering from alopecia.
21. A stable topical pharmaceutical composition as claimed in claim 8, wherein the composition comprises about 0.03% w/w latanoprost and about 7.5% w/w cortexolone-17 α -propionate.
22. A stable topical pharmaceutical composition as claimed in claim 8, wherein the composition comprises about 0.06% w/w latanoprost and about 15% w/w cortexolone-17 α -propionate.