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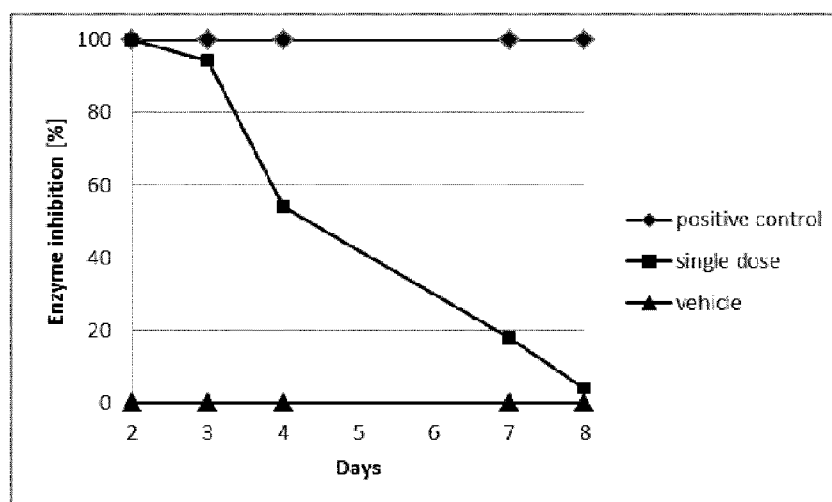
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(54) Title: FINASTERIDE FOR USE IN THE TREATMENT OF ANDROGENETIC ALOPECIA

Figure 1: 5 α -reductase type II inhibition (100 nM 24 hrs)

(57) Abstract: The present invention concerns finasteride for use in the treatment of alopecia, wherein the active agent is applied and administrated in a specific manner.

FINASTERIDE FOR USE IN THE TREATMENT OF ANDROGENETIC ALOPECIA

The present invention concerns finasteride for use in the treatment of alopecia, wherein the active agent is applied and administrated in a specific manner.

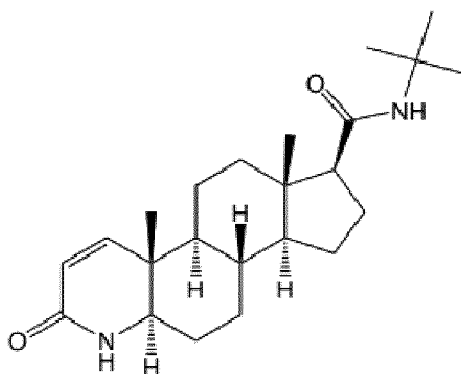
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Finasteride is a 5α -reductase inhibitor and is regarded as a synthetic steroid. Due to its similar structure compared with testosterone, finasteride is reported to irreversibly inhibit 5α -reductase and, thus, prevents testosterone from being converted to dihydrotestosterone (DHT). Currently a specific kind of hair follicle is reported to reduce its anagen-phase (growth-phase) when brought into contact with DHT. By preventing the formation of DHT, the growth phase of the hair follicle can be enhanced and the beginning of androgenetic alopecia can be postponed for years. However, this treatment has to be applied continuously since in case of an abandonment of the finasteride administration the level of DHT rises and the grown hair falls out again. Further, finasteride can be used in the treatment of benign prostatic hyperplasia (BPH) also known as enlarged prostate, wherein finasteride eases the symptoms associated with BPH such as difficulty urinating, having to get up during the night to urinate, hesitation at the start of urination and decreased urinary flow.

20

The IUPAC name of finasteride is (1S,3aS,3bS,5aR,9aR,9bS,11aS)-N-tert-butyl-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide and the compound is represented by the following chemical Formula (I)

25



Formula (I)

Finasteride for the treatment of androgenetic alopecia is marketed under the brand name "Propecia" and is orally administered 1 mg once daily. The treatment of androgenetic alopecia is applied as a long-term treatment. A cessation of the treatment of androgenetic alopecia may lead to sudden loss of the hair which had
5 been prevented from falling out by the before applied treatment with finasteride. However, long-term treatments with an active pharmaceutical ingredient are often associated with some disadvantages such decreasing patient compliance and undesirable side effects. Side effects which are reported to relate to the treatment with finasteride are reduced libido, erectile dysfunction and in very rare cases
10 depression.

For the patient's convenience a topical treatment with finasteride is reported to be desirable. Example 1 of US 2011/0183016 A1 describes a film-forming solution consisting of 0.25 wt.% finasteride, 55 wt.% ethanol, 5 wt.% propylene glycol,
15 1 wt.% hydroxypropyl chitosan and 28.75 wt.% water. The obtained clear solution forms a matte, elastic film which could adhere to the scalp surface. The treatment may leave behind a cold sensation, which is considered to be unpleasant by many patients, and inappropriately removes the protecting fatty substances of the epidermis. In addition, a treatment with the solution of Example 1 of
20 US 2011/0183016 A1 still seems to be further improvable with regard to the undesirable side-effects associated with a long-term treatment of finasteride.

Thus, it was an object of the present invention to overcome the above-illustrated drawbacks.

25 In particular, it was an object of the invention to provide a treatment of finasteride which can be easily conducted and which enhances patient compliance.

In addition, a treatment should be provided in which the therapeutic effect of
30 finasteride is substantially as good as the one with formulations known in the prior art, wherein the disadvantageous side effects are prevented or at least significantly reduced.

The objects of the present invention have been unexpectedly solved by a specific dosage regime for the treatment of androgenetic alopecia with finasteride.

The inventors found out that the dosage regime of the present invention unexpectedly provides a good efficacy while undesirable side effects are prevented or at least advantageously reduced. In addition the present dosage regime improves patient compliance.

Summary of the Invention

This invention provides a finasteride for use in the treatment of androgenetic alopecia, wherein finasteride is administered as a topical formulation once every 3 to 10 days.

Description of the Figures

Figure 1: Inhibition of 5α -reductase type II by finasteride administration

Figure 2: 5α -reductase activity in different sites of the boy after daily finasteride administration

Figure 3: 5α -reductase activity in different sites of the body after finasteride administration every third day

Detailed Description of the Invention

As described above the hair growth phase can be enhanced and the beginning of androgenetic alopecia can be postponed when the formation of dihydrotestosterone is significantly reduced or even prevented. Due to its property as 5α -reductase-inhibitor preventing the conversion from testosterone to dihydrotestosterone, finasteride is suitable for the treatment of androgenetic alopecia. Finasteride is referred to as the compound according to above Formula I. In addition, finasteride can be also referred to as a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, polymorph and/or mixtures thereof.

According to the present invention finasteride is administered as a topical formulation. Contrary to a systemic administration or formulation, the administration of a topical formulation can be considered as an administration in which the topical formulation is directly applied to the selected site of the body, such as the skin, mucous membranes and nails. Topical formulations can for example be solutions, gels, emulsions, creams, foams, lotions and ointments but also inhalation sprays. In a preferred embodiment the finasteride is administered as a topical formulation directly on the skin, in particular on the scalp.

According to the present invention finasteride is administered as a topical formulation once every 3 to 10 days, i.e. finasteride can be administered once in 3, 4, 5, 6, 7, 8, 9 or 10 days. Thus, contrary to a daily administration, according to the present invention the period from one finasteride administration to the next one lasts at least 3 days and at most 10 days. Thus, taken an administration of once every three days for example, after a first administration the second administration would be carried out three days later und the third administration would be carried out six days later than the first one and so on. It is preferred that finasteride is administered once every 4 to 9 days, more preferably once every 5 to 8 days, in particular once a week. It turned out that administering finasteride according to said dosage regime exhibits comparable results in the treatment of androgenetic alopecia with significantly reduced or even none of the undesirable side effects compared to a treatment with finasteride once daily.

In a preferred embodiment of the invention finasteride is administered in an amount of 0.2 to 20 $\mu\text{g}/\text{cm}^2$ skin, preferably 0.5 to 15 $\mu\text{g}/\text{cm}^2$ skin, more preferably 0.7 to 12 $\mu\text{g}/\text{cm}^2$ skin, in particular 1 to 10 $\mu\text{g}/\text{cm}^2$ skin. It is preferred that the skin is the scalp.

In a preferred embodiment of the invention finasteride can be preferably contained in the formulation in a concentration of from 0.025 to 1.0 wt.%, preferably from 0.10 to 0.75 wt.%, more preferably from 0.15 to 0.50 wt.%, in particular from 0.20 to 0.35 wt.%, based on the total weight of the formulation.

It is preferred that the finasteride-containing formulation is a liquid formulation.

A liquid formulation can be regarded herein as a formulation which is in a liquid state when the administration takes place. Preferably a liquid formulation is a liquid state at a temperature of from 0°C to 40°C, preferably from 5°C to 35°C, in particular from 10°C to 30°C.

In a preferred embodiment of the invention the finasteride-containing liquid formulation is an emulsion or a solution.

An emulsion can be regarded herein as the dispersion of two incompletely miscible liquids or systems of liquids. Commonly one liquid or system of liquids can be an oil or a system of oil, wherein "oil" refers to any liquid which is essentially water-insoluble. The second liquid or system of liquids can be water or system of water-miscible liquids. The average diameter of droplets in an emulsion, which is sometimes also referred to as macro-emulsion, can be close to one millimeter, i.e. 10^{-3} m. Macro-emulsions can be thermodynamically instable and the average droplet size grows with time.

In a preferred embodiment the emulsion can be preferably a micro-emulsion. A micro-emulsion can be regarded herein as a thermodynamically stable and anisotropic emulsion. Its properties usually are time independent and not influenced by its method for preparation, such as order of mixing or mechanical energy. A micro-emulsion preferably comprises an emulsifier. The entities of the dispersed phase are preferably stabilized by an emulsifier and/or emulsifier-coemulsifier system, wherein the coemulsifier can be for example an aliphatic alcohol. In a micro emulsion the diameter of droplets of the dispersed phase can vary from 0.5 to 200 nm. Further, in a micro-emulsion the domains of the dispersed phase can be either globular or interconnected to give a continuous micro-emulsion.

In a preferred embodiment the intensity-weighted particle size distribution of the dispersed phase has a Z-average of 1 to 100 nm, preferably 5 to 80 nm, more preferably 10 to 60 nm, in particular 20 to 40 nm. The intensity-weighted particle size distribution is determined by dynamic light scattering (DLS) with a Zetasizer Nano ZS by Malvern.

The Z-average can be expressed as the intensity based harmonic mean and can be calculated as follows:

$$D_z = \frac{\sum S_i}{\sum \left(\frac{S_i}{D_i} \right)}$$

wherein S_i corresponds to the scattered intensity from particle i ; and D_i corresponds to the diameter of particle i .

The parameters for the set up of the corresponding device are described in the experimental section.

In a preferred embodiment the emulsion can comprise 20 to 40 wt.%, preferably 22 to 37 wt.%, in particular 25 to 34 wt.% organic solvent, based on the total weight of the emulsion.

An organic solvent is referred to herein as an organic compound which can preferably be liquid at 23°C at 1013 mbar. In that regard the term "organic compound" generally refers to a compound the skeleton of which predominately contains carbon atoms, nitrogen atoms and/or oxygen.

Examples of organic solvents are aliphatic mono- or divalent or trivalent alcohols having 1 to 6 carbon atoms such as methanol, ethanol, propanol, isopropanol, 1,2-propandiol or 1,3-propandiol, butanol, *tert.*butanol, 1,6-hexanediol, glycerol, ketones such as acetone, *tert.*butyl methylketone, methyl ethylketone, ethers such as diethylether, tetrahydrofuran and dioxane, dimethyl formamide, dimethyl

sulfoxide, acetonitrile, carboxylic acid esters such as ethyl acetate, and mixtures thereof.

Preferred solvents are alcohols such as methanol, ethanol, propanol and isopropanol, more preferably ethanol and isopropanol, in particular ethanol.

In a further preferred embodiment the emulsion can further comprise 5 to 25 wt.% non-ionic emulsifier and/or 1.0 to 7.0 wt.% of a siloxane having 2 to 5 silicon atoms.

An emulsifier can be regarded as a compound which can enable the formation of emulsion from two non-miscible liquids and which can stabilize said emulsion preventing the separation of the liquids. Generally, an emulsifier can comprise a polar as well as a non-polar part. The non-polar part can be for example an alkyl group having more than 8 carbon atoms or an alkyl phenyl group.

The polar part of the emulsifier can be composed of various functional groups being suitable to classify the emulsifier into different categories. A non-ionic emulsifier comprises a non-polar part and a polar part, wherein the polar part does not bear an ionic group.

It is preferred that the non-polar part of the non-ionic emulsifier can comprise 4 to 40 carbon atoms, preferably 8 to 20 carbon atoms.

Further, the polar part of the non-ionic emulsifier can comprise for example one or a plurality of hydroxy or ether group(s), preferably polyether groups such as polyethoxyethylene groups. Examples for non-ionic emulsifiers can be for example polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, polyoxyethylene glycol sorbitan alkylesters and fatty alcohols.

In a preferred embodiment the non-ionic emulsifier can be an ethoxylated fatty alcohol.

A fatty alcohol can preferably comprise an even number of carbon atoms, preferably from 4 to 26 carbon atoms. A fatty alcohol can be saturated or unsaturated. Further, fatty alcohols can preferably comprise a straight chain having a single alcohol group bonded to the terminal carbon atom.

5

Examples of fatty alcohols are capryl alcohol (1-octanol), lauryl alcohol (1-dodecanol), cetyl alcohol (1-hexadecanol), stearyl alcohol (1-octadecanol), palmitoleyl alcohol (cis-9-hexadecen-1-ol) and oleyl alcohol (cis-9-octadecen-1-ol).

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Ethoxylated fatty alcohol can comprise 1 to 10 ethoxyethylene groups, preferably 3 to 9 ethoxyethylene groups, wherein the corresponding residue can be also referred to as PEG-X-residue with X being the number of the ethoxyethylene groups.

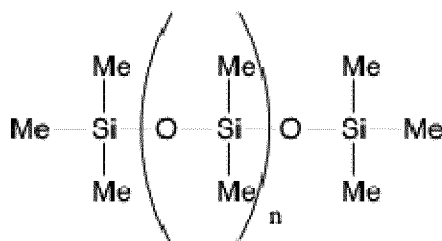
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In a particularly preferred embodiment the non-ionic emulsifier is PEG-5-oleylether.

The non-ionic emulsifier comprised in the emulsion can preferably amount to from 5 to 25 wt.%, preferably 8 to 22 wt.%, in particular 12 to 18 wt.%, based on the total weight of the emulsion.

A siloxane having 2 to 5 silicon atoms can preferably be represented by the following Formula (II)

25



Formula (II),

wherein n is 0, 1, 2 or 3.

30

It is preferred that the siloxane having 2 to 5 silicon atoms can have a boiling point at 1013 mbar of 85°C to 250°C, preferably 90°C to 200°C, more preferably 95° to 160°C.

- 5 In a particularly preferred embodiment the siloxane having 2 to 5 silicon atoms comprised in the emulsion is hexamethyldisiloxane. Hexamethyldisiloxane can be referred to as the component according to Formula (II) with n being 0.

10 In an alternatively particularly preferred embodiment the siloxane having 2 to 5 silicon atoms) comprised in the present emulsion is octamethyltrisiloxane. Octamethyltrisiloxane can be referred to the component according to Formula (II) with n being 1.

15 The siloxane having 2 to 5 silicon atoms comprised by the emulsion amounts to 1 to 7 wt.%, preferably 1.5 to 5 wt.%, in particular 2 to 4 wt.%, based on the total weight of the emulsion.

20 It is preferred that the emulsion further comprises water, preferably purified water, more preferably purified water according to Ph.Eur. 6. Supplement 6.3, pp. 4344-4346. The water, preferably the purified water, contained in the emulsion is present in amounts of 35 to 65 wt.%, preferably 40 to 60 wt.%, in particular 45 to 55 wt.%, based on the total weight of the emulsion.

In preferred embodiment the emulsion can comprise

25

- 0.025 to 1 wt.%, preferably 0.10 to 0.75 wt.%, more preferably 0.15 to 0.50 wt.%, in particular 0.20 to 0.35 wt.% finasteride
- 20 to 40 wt.%, preferably 22 to 37 wt.%, in particular 25 to 34 wt.% organic solvent
- 30 - 5 to 25 wt.%, preferably 8 to 22 wt.%, in particular 12 to 18 wt.% non-ionic emulsifier

- 1 to 7 wt.%, preferably 1.5 to 5 wt.%, in particular 2 to 4 wt.% siloxane having 2 to 5 silicon atoms
- 35 to 65 wt.%, preferably 40 to 60 wt.%, in particular 45 to 55 wt.% water,

5 wherein wt.% is based on the total weight of the emulsion.

The emulsion can preferably further comprise one or more additives. The emulsion can for example comprise additive(s) in an amount of 0.001 wt.% to 40 wt.%, preferably 0.01 wt.% to 35 wt.%, more preferably 0.1 wt.% to 30 wt.%, in
10 particular 0.5 wt.% to 20 wt.%, based on the total weight of the emulsion.

Additives are for example active substances, conditioning agents, preservatives, dyes, perfume substances, care substances, pH regulators and penetration enhancers. Each single additive can be present in an amount of 0.001 wt.% to
15 10 wt.%, in particular 0.01 wt.% to 5 wt.%, based on the total weight of the emulsion.

The term "active substances" means that besides finasteride a further substance having a pharmacological effect is contained in the formulation. Active substances
20 can preferably be selected from the extracts of plants, synthetically produced substances corresponding to extracts and analogous derivatives thereof, vitamins as well as substances that influence the skin and mixtures thereof.

Extracts of plants are, for example, those of ylang ylang, pine needles, cypress, thyme,
25 mint, limes, oranges, grapefruit, mandarin oranges, juniper, valerian, lemon balm, eucalyptus, thyme, palmarosa, rosemary, lavender, rosewood, lemon grass, spruce needles, pine needles, ginger, currant, linden blossom, calendula extract, magnolia, algae, aloe vera, pineapple, guava, echinacea, ivy leaf, birch leaf, hibiscus extract, burdock root, witch hazel, hydrocotylidis herba, quince, water lily, cinnamon, or
30 mixtures thereof.

Suitable vitamins are, for example, vitamins A, B, E, C or suitable derivatives thereof, such as esters, e.g. palmitate, acetate, or phosphate.

Other suitable active substances that influence the skin can be minerals and trace elements such as copper, zinc, magnesium or their derivatives, particularly salts, such as Zincidone[®] (zinc PCA), zinc gluconate, or copper gluconate.

Further, astringent and sebum-regulating substances, such as hydroxydecanoic acid, pyridoxine, niacinamide, glycerin, caproyl collagen amino acids, sebacic acid, cinnamonom zeylanicum, or cooling/soothing active substances such as menthyl lactate or sodium hyaluronate, wheat germ extract, saccharomyces cerevisiae extract can preferably be used.

Furthermore, active substances can preferably be active substances that promote blood circulation. Examples are nicotinic acid derivatives such as methyl nicotinate or tocopheryl nicotinate, alphahydroxy and betahydroxy acids and their derivatives.

Furthermore, substances having an antioxidant effect or a cell-protection effect, such as polyphenols, flavonoids, or isoflavones. Other active substances can preferably be UV filters such as UVB, UVA, and broadband filters, as they are generally known, e.g. cinnamic acid esters, salicylates, or inorganic UV filters. Further, active substances that can preferably be used are biotin, allantoin, panthenol, niacinamide, urea and inositol. Depending on the purpose of use, active substances that are soluble in oil or water can also be used or combined for cosmetic and/or dermatological/pharmaceutical purposes.

Dermatologically/pharmaceutically active substances can be, in particular, anti-microbially active substances (antibiotics; antimycotics, antiviral substances), hormones or hormonally active substances such as sex hormones, wound cleansing agents, analgesics, cytokins, cytostatics, anti-acne agents, immune suppressives, pigmentation regulators, agents against photodermatoses, or the vasoactive/antiphlogistic substances named above, or combinations thereof.

In contrast, strongly oxidative substances such as hydrogen peroxide are preferably not used.

Examples of conditioning agents can be acrylamides; polysaccharide such as xanthan gum; cellulose and its derivatives such as methyl cellulose, ethyl cellulose hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose; carmellose-Na; starch and mixtures thereof.

Furthermore, complexing agents such as EDTA, compounds such as citric acid, soda lye, solvents such as propylene glycol or alcohols, salts such as NaCl, starch or starch derivatives, or mixtures thereof, can be contained as conditioning agents. Other conditioning agents are monoalkyl and dialkyl phosphates or glyceryl stearate.

A preservative is a substance that can be added to the emulsion of the present invention to protect the emulsion and its ingredients from disadvantageous reactions such as oxidation or damage caused by microorganisms. A preservative can be a natural or synthetic substance.

Examples of suitable preservatives are imidazolidinyl urea, glutaraldehyde, formaldehyde, 2-phenoxyethanol, 1-phenoxy-propan-2-ol, undec-10-enoic acid iodopropynyl butyl carbamate, DMDM hydantoin, phenoxyethanol and other commonly used preservatives, such as sorbic acid and dehydracetic acid, and their salts, methyl dibromoglutaronitrile or combinations thereof; or other acids such as benzoic acid, propionic acid or salicylic acid, or benzyl alcohol or esters such as p-hydroxy benzoic acid esters, e.g. methyl paraben, ethyl paraben, propyl paraben, butyl paraben, isobutyl paraben, or climbazol or suitable combinations of the stated substances.

Dyes can preferably be naturally occurring and synthetically produced colouring agents. Examples are Acid Blue 7, disodium salt of 1-(3-sulfo-1-phenylazo)-2-naphthol-6-sulfonic acid (Food Orange 2), disodium salt of 1-(4-sulfo-1-phenylazo)-2-naphthol-6-sulfonic acid (Food Orange 3), Acid Orange 10 (Food Orange 4) or derivatives thereof, trisodium salt of 1-(4-sulfo-1-naphthylazo)-2-naphthol-6,8-

disulfonic acid (Acid Red), trisodium salt of 1-(4-sulfo-1-naphthyl-azo)-2-naphthol-3,6-disulfonic acid (Acid Red 27), tetrasodium salt of 1-(4-sulfo-1-naphthylazo)-2-naphthol-3,6,8-disulfonic acid (Acid Red 41), quinophthalonedisulfonic acid or suited combinations thereof.

5

Suitable perfume substances are, for example, the ether oils named under active substances or commercially available perfume mixtures.

Particularly suitable care substances are phytosterols (essentially mixtures of β -sitosterol, campesterol, and stigmasterol or ethoxylated derivatives thereof), such as those from canola oil. Also lecithin (e.g. soybean lecithin), phosphatidyl choline, phosphatidyl serine or diethanolamine, or mixtures thereof with the aforementioned phytosterols can preferably be used.

Furthermore, silicone oils such as dimethicones or silicone (co)polymers, e.g. di-cyclo-methicone or divinyl dimethicone/dimethicone copolymers, C12-13 parath-3/C12-13 parath-23) can preferably be used.

Other care substances can be moisturizing agents such as glycerin, propylene glycol, or polyethylene glycols, propylene glycol, butylene glycol, sorbitol, or polymers, e.g. polyquaternium types such as polyquaternium 39, collagen or its hydrolysates, amino acids, urea, polysaccharide (biosaccharide gum 1), glucosaminoglycanes, e.g. hyaluronic acid or sulfated glucosaminoglycanes such as chondroitin sulfate, dermatane sulfate, keratane sulfate, heparane sulfate or mixtures thereof.

25

Substances to adjust the pH-value of the emulsion can be referred to as pH regulators. A pH regulator can preferably be selected from indifferent and less irritated salts such as calcium chloride, barium chloride; or from acids, especially organic acids, such as acetic acid, citric acid, salicylic acid, lactic acid and other alpha hydroxy acids as well as inorganic acids such as HCl, from buffering substances such as phosphate buffer, lactate buffer or citric buffer, or from salts such as NaOH and KOH and from other bases. These regulators are used in amounts sufficient to provide the desired pH value

30

of the composition of the invention. In a preferred embodiment the pH value of the claimed formulation is between 3 and 7, and more preferably between 4.5 and 5.5.

Penetration enhancers can be chosen amongst polyvalent alcohol(s) and derivatives thereof, preferably esters, such as glycerol alone or with its esters or suitable combinations thereof; mono- or polyvalent glycols or derivatives thereof, such as propylenglycol, ethoxydiglycol, preferably Transcutol[®], or azocycloheptanone, preferably 1-dodecyl azocycloheptan-2-one as in Azone[®].

10 In a preferred embodiment the emulsion can be applied as a foam. For example, discharge from a conventional disperser and application in/with air can lead to a foam which can be distributed on the desired site. Alternatively, the emulsion can preferably be contained in a foam dispenser with a suitable pumping mechanism or together with a suitable propellant in an aerosol device. In this case, the foam product is
15 directly obtained. The aerosol device may comprise a compressed gas container containing foaming agent such as a propellant, a distribution device with a valve, spray nozzle as well as the composition.

Commercially available gasses or mixtures of gasses, like CO₂, N₂, N₂O, or
20 mixtures thereof, like CO₂:N₂O 1:1 to 0.5:1, are suitable as propellant. Particularly preferred are gasses such as butane/propane/isobutane or mixtures thereof as commonly used for aerosols, e.g. 3-5:20-25:65-73 as available e.g. as Drivosol[®] (35a). The gas may be present in compressed form in amounts of 2 to 20 wt.%, preferably 3-18 wt.%, in particular 5-15 wt.%, based on the finished product.
25 These amounts may, however, be varied depending on the total amount of the product and/or the size of the container.

Suitable devices for administering the emulsion as aerosol as well as for application without propellant are known. To this end, e.g. mechanical foam
30 dispensers working according to the principle of air pumps may be used, such as Squeeze Foamer (F2 Finger Pump Foamer, commercially available), Rieke Dispensing by Englass or foamers made by Airspray, into which the finished

emulsion is filled in a suitable manner. Preferably, the emulsion is provided in common dispensers. In particular it is dispensed from a foam dispenser or an aerosol container filled with a propellant.

- 5 In an alternatively preferred embodiment of the invention the topical formulation can be present in form of a solution.

A solution can be regarded herein as a homogenous mixture in a liquid form wherein finasteride and optionally further solutes are dissolved in a solvent or a mixture of solvents. Alternatively said solution can preferably be prepared by dissolving, preferably completely dissolving, the finasteride and optionally further solutes in a solvent or a mixture of solvents. As far as the solvent or a mixture of solvents is concerned the same applies as described above. Preferred solvents are water, aliphatic mono- or divalent or trivalent alcohols having 2 to 6 carbon atoms or mixtures thereof. Suitable alcohols are for example ethanol, propanol, isopropanol, 1,2-propandiol or 1,3-propandiol, preferably ethanol and isopropanol. Ethanol is particularly preferred. The volume ratio of water to alcohol can preferably be between 8:1 and 1:8, more preferably between 4:1 and 1:4, in particular between 2:1 and 1:1.5. This applies especially in regard with a mixture of water and ethanol.

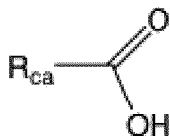
In a preferred embodiment the solution can be prepared by dissolving the finasteride in form of a cocrystal.

- 25 A cocrystal as used herein can be regarded as a solid being a crystalline single phase material and being composed of finasteride and one or more different molecular and/or ionic compounds. The one or more different molecular compound(s) can preferably be carboxylic acid having 3 to 11 carbon atoms. Preferably, all compounds of the cocrystal are in solid state.

30

A carboxylic acid is referred to as a substance bearing at least one carboxy group, which is also referred to as a carboxyl group. A carboxy group is regarded as a

group which can be represented by a carbon atom connected by a covalent double bond to one oxygen atom and by a further bond to another oxygen atom further otherwise bonded to a hydrogen atom. The carboxy group can also be referred to as a carboxylic acid functional group when the carbon bonded to the two oxygen atoms is further bonded to a carbon atom. A carboxylic acid is an organic compound which can be generally represented by the following structure:



wherein R_{ca} is an aliphatic or aromatic residue.

The carboxylic acid comprised by the cocrystal has 3 to 11 carbon atoms. It is preferred that the carboxylic acid having 3 to 11 carbon atoms is a solid at 25°C and 1013 mbar. That is to say, the melting point of the carboxylic acid has to be at least 25°C at 1013 mbar. The melting temperature is defined as the temperature at which a substance converts from its solid state to a liquid state. The melting temperature can for example be determined by DSC (differential scanning calorimetry).

An aliphatic residue can be a saturated residue which is joined by single bonds or an unsaturated residue joined by double bonds or triple bonds. The aliphatic residue can have a linear, branched or cyclic carbon skeleton and the carbon atom might be replaced by a heteroatom such as oxygen, sulfur or nitrogen. The aliphatic residue might be substituted by one or more substituent(s) at any position, i.e. the carbon skeleton can be bound to an atom or a group being different from hydrogen.

Examples of substituents are halogen, such as fluoride (-F), chloride (-Cl), bromide (-Br) and iodide (-I), hydroxy (-OH), alkoxy, such as methoxy (-OCH₃) and ethoxy -OC₂H₅, cyano (CN), mercapto (-SH), carboxylic acid (-COOH), carboxylic esters, such as carboxylic methyl ester (-COOCH₃), carboxylic ethyl

ester ($-\text{COOC}_2\text{H}_5$), and carboxamides, such as carboxamide ($-\text{CONH}_2$), methylcarboxamide ($-\text{CONHCH}_3$), dimethylcarboxamide ($-\text{CON}(\text{CH}_3)_2$).

5 Examples for aliphatic carboxylic acid suitable for the formation of cocrystals can be malonic acid, tartaric acid and hexanoic acid (caproic acid).

In a more preferred embodiment the carboxylic acid can preferably be a carboxylic acid having a substituted or non-substituted aromatic residue, i.e. the carboxylic acid can be referred to as an aromatic carboxylic acid.

10 An aromatic residue includes at least one ring system predominately containing carbon atoms, wherein said ring system comprises, according to the Hückel-Rule, a number of $4n+2$ ($n=0, 1, 2, \dots$) delocalized electrons in conjugated double bonds, free electron-pairs or unoccupied p-orbitals. Apart from carbon atoms the ring system can further comprise nitrogen, sulphur and/or oxygen. In a preferred
15 embodiment the aromatic residue can be substituted with one or more substituents. As far as the possible substituents are concerned the same applies as described above with regard to substituents of the aliphatic residues.

20 Examples of substituents for aromatic residues are alkyl, such as methyl ($-\text{CH}_3$), ethyl ($-\text{C}_2\text{H}_5$), isopropyl ($-\text{CH}(\text{CH}_3)_2$) and the substituents as mentioned above with regard to substituents of the aliphatic residues, preferably methyl, methoxy and hydroxy, in particular hydroxy.

25 Examples for aromatic residues are phenyl, tolyl, naphthyl, indolyl, indenyl, hydroxyphenyl, dihydroxyphenyl. Preferred are phenyl, hydroxyphenyl and dihydroxyphenyl, in particular hydroxyphenyl and dihydroxyphenyl.

It is preferred that the carboxylic acid having 3 to 11 carbon atoms is 3-hydroxy
30 benzoic acid or 2,4-dihydroxy benzoic acid.

It is further preferred that the cocrystals comprise finasteride and the carboxylic acid in a molecular ratio of 2.0 : 1.0 to 1.0 : 2.0, preferably 1.50 : 1 to 1 : 1.50, more preferably 1.30 : 1 to 1 : 1.30, especially 1.15 : 1 to 1 : 1.15, in particular 1.05 : 1 to 1 : 1.05. It is preferred that the cocrystal comprises finasteride and the
5 carboxylic acid in a molecular ratio of 1 : 1.

A cocrystal can be characterized by analytical data/methods such as powder X-ray diffraction. Unless indicated otherwise, XRPD peaks are recorded as described in the experimental section. Further, unless indicated otherwise, XRPD peaks are
10 reported as degrees 2 theta values with a standard error of ± 0.2 degrees 2 theta.

In a preferred embodiment the formulation of the present invention, preferably in form of a solution, can comprise one or more additives. The formulation, preferably in form of a solution, can comprise additive(s) in an amount of
15 0.01 wt.% to 40 wt.%, preferably 0.01 wt.% to 35 wt.%, more preferably 0.1 wt.% to 30 wt.%, in particular 0.5 wt.% to 20 wt.%. As far as the additives are concerned substantially the same applies as it is described above.

It is alternatively preferred that the liquid formulation being in form of a solution
20 can be, for example, the solution according to the above-mentioned Example 1 of US 2011/0183016 A1.

In an alternatively preferred embodiment of the invention the topical formulation can be in form of a semi-solid formulation.

25 As used herein, the term semi-solid formulation means a preparation which is not liquid, but which contains one or more liquid components. Preferably, the major liquid component is water. Optionally, the semi-solid composition may further comprise other liquid components, such as pharmaceutically acceptable organic
30 solvents, cosolvents, viscosity regulation polymers and emulsifiers. Examples of such other liquid components are ethanol, glycerol, propylene glycol, and poly-

ethylene glycol. Such water-miscible organic solvents may be incorporated for example in order to solubilize a poorly water-soluble ingredient.

The term semi-solid formulation can preferably be a crème, an ointment or a gel. A
5 crème, an ointment or a gel can be regarded as an inert carrier into which finasteride may be incorporated. An ointment in which the active ingredient has not been incorporated yet can be regarded as an ointment base. The same applies to a gel or a crème.

10 An example for an ointment base can be petrolatum, optionally stiffened with wax. Another type of ointment base contains lanolin, which can absorb water and aqueous emulsions or dispersions, such that a “water-in-oil type” emulsion is formed. Water-soluble ointment bases are often derived from polymers of ethylene glycol (PEGs); these will absorb water and ingredients dissolved in the water.

15 In comparison to a liquid composition these semi-solid formulations are not freely flowing. The viscosity of semi-solid compositions may be controlled by a viscosity enhancing polymer or by a combination of such polymers, like natural gums like xanthan gum, cellulose derivatives like cellulose ester or ether, lecithin poloxamer,
20 polyethylene glycols, polymethacrylates, polyvinyl alcohol, polyvinyl pyrrolidone, sodium starch glycolate starch, pregelatinised starch or derivatives.

In a preferred embodiment of the invention the semi liquid formulation contains a cocrystal comprising finasteride. For a cocrystal comprising finasteride the same
25 applies as described above.

The invention can be illustrated by the following examples. Further, the following analytical methods have been used.

Analytical methods:**1. X-Ray Powder Diffraction (XRPD)**

5 X-ray powder diffraction patterns were collected on a Bruker D8 diffractometer using Cu K α radiation (40 kV, 40 mA), θ - 2θ goniometer, and divergence of V4 and receiving slits, a Ge monochromator and a Lynxeye detector. The instrument is performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac *Plus* XRD Commander v2.6.1 and
10 the data were analyzed and presented using Diffrac *Plus* EVA v15.0.0.0.

Samples were run under ambient conditions as flat plate specimens using powder as received. The sample was gently packed into a cavity cut into a polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during
15 analysis. The data was collected using two separate settings, one for the screening samples and the other for the standard data collection.

The details of the data collection for standard method (7 minute method) are:

- 20
- Angular range: 2 to 42° 2θ
 - Step size: 0.05° 2θ
 - Collection time: 0.5 s/step

2. Dynamic Light Scattering (DLS)

25

DLS is conducted by Wessling GmbH, Altenberge with the Zetasizer Nano ZS by Malvern using the following parameters:

Measurement parameters:

30 Temperature: 25°C
Count Rate (kcps): 230.4
Cell Description: Disposable sizing cuvette

Attenuator: 7
 Measurement Position (mm): 4.65
 Duration Used (s): 20
 Light source: Standard laser (633 nm)

5

Samples parameters: (particle size)

Sample volume 1 ml
 Record Number: 28
 Material RI: 1.38
 Viscosity (cP): 0.8872
 Material Absorption: 0.100
 Dispersant Name: Water
 Dispersant RI: 1.330

10

15 The samples were measured at 25°C and disposable sizing cuvettes were used for DLS measurement.

Examples

20 Example 1: Inhibition of 5 α -reductase

To determine the ability of finasteride to inhibit 5 α -reductase type II and consequently the transformation from testosterone to dihydrotestosterone the following *in vitro* experiment was conducted.

25

Single Dose: At day 0 a cell culture was incubated. At day 1 a solution of 100 nM of finasteride in DMSO was applied once to the cell culture. The inhibition of 5 α -reductase was determined at days 2, 3, 4, 7 and 8.

30 Vehicle (negative control): At day 0 a cell culture was incubated. At days 1 to 8 the vehicle (DMSO) was applied to the cell culture. The inhibition of 5 α -reductase was determined at days 2, 3, 4, 7 and 8.

Positive control: At day 0 a cell culture was incubated. At days 1 to 8 a solution of 100 nM finasteride in DMSO was applied to the cell culture. The inhibition of 5 α -reductase was determined at days 2, 3, 4, 7 and 8.

- 5 The 5 α -reductase inhibitions (enzyme inhibition) of the corresponding administrations are shown in Figure 1.

As can be seen from Figure 1 by a daily application of finasteride the 5 α -reductase is completely inhibited as long the administration is carried out. However, even a
10 single dose administration of finasteride leads to a long-lasting inhibition of 5 α -reductase. About 50% of the enzyme is still inhibited at day 4. Thus, the irreversible binding of finasteride to of 5 α -reductase type II could be demonstrated.

15 **Example 2: Frequency of the administration and inhibition of 5 α -reductase at different sites of the body**

Topical formulations containing 100 nM finasteride are administered on the skin (scalp) with the following frequencies.

20

Example 2A:

As can be seen from Example 15 α -reductase is inhibited permanently by finasteride and the inhibition even lasts after the compound is eliminated from the body. However, new molecules of the enzyme are synthesized in few days, wherein
25 said enzymes are taking over the function of blocked enzyme molecules. A topical formulation containing 100 nM finasteride is administered on the skin (scalp) once daily. The concentration of finasteride and the 5 α -reductase inhibition in the skin and in testis (which is considered a major organ responsible for undesired side effects) are determined and shown in Figure 2. In spite of the dilution effect after
30 the topical application of 100 nM of finasteride an amount of about 1 nM finasteride is still present in the testis. As can be seen from the lower part of Figure 2 the reductase activity in the skin is preferably inhibited such that the

conversion from testosterone to dihydrotestosterone is prevented or at least advantageously reduced. However, as can be seen from the upper part of Figure 2 the reductase activity in the testis is also significantly affected by the daily topical administration of finasteride at the skin (scalp). In fact, the reductase activity in the testis is significantly reduced upon repetitive daily applications. As indicated above the testis is considered a major organ responsible for the described undesired side effects of finasteride.

Example 2B:

A topical formulation containing 100 nM finasteride is administered on the skin (scalp) every 3 days. The concentration of finasteride and the 5 α -reductase inhibition in the skin and in testis are determined and shown in Figure 3. Due to the dilution effect after the topical application of 100 nM of finasteride an amount of about 1 nM finasteride is even present in the testis. As can be seen from the lower part of Figure 3 the reductase activity in the skin is preferably inhibited such that the conversion from testosterone to dihydrotestosterone is prevented or at least advantageously reduced. Further, as can be seen from the upper part of Figure 3 the reductase activity in the testis is slightly affected by the topical administration of finasteride at the skin (scalp) every third day. In fact, the reductase activity in the testis is slightly reduced to a certain level but a further application does not further reduce the reductase activity since the imposed interval allows new molecules to be synthesized in the testis before the next application, in contrast to example 2A above. Thus, here a balanced combination of gradient (skin vs. testis) and treatment interval results in therapeutic benefit such as maintaining therapeutic effect by reduced undesirable side-effects.

Taking the above results into account it becomes clear that administration of finasteride every three days results in an advantage in the treatment of androgenetic alopecia since it further prevents or advantageously reduces the undesirable side effects known from a conventional administration.

Example 3: Cocrystal of Finasteride and 3-Hydroxybenzoic acid

Finasteride (2.3 g; 6.2 mmol) and 3-hydroxybenzoic acid (0.86 g; 6.2 mmol) were dissolved in methanol (2 ml) under stirring at 50°C resulting in a clear solution.

- 5 Under stirring, isopropyl acetate (2 ml) was added and the almost clear solution was left at ambient temperature overnight, resulting in a thick white precipitate. The sample was left for maturation (eight hours heat/cool cycle between 23°C/50°C) for 48 hours. To the sample seeds of the corresponding cocrystal were added and the mixture was left at room temperature under stirring. The mixture
- 10 was filtered under suction, washed with cold isopropyl acetate (3 ml) and dried at 40°C in vacuum oven (20 mbar) to yield 1.88 g (59.5%) of finasteride-3-hydroxybenzoic acid cocrystal.

Table 1: XRPD of Example 3

15

Angle (2-Theta°)	Intensity (%)	Angle (2-Theta°)	Intensity (%)
7.1	40.8	18.3	100
8.2	7.5	19.3	75.1
8.7	95.4	19.6	14.8
9.0	8.5	20.9	13.5
10.6	16.5	21.3	6.6
10.8	26.9	21.8	3.8
11.4	2.3	22.7	5.4
12.0	33.5	22.9	5.0
13.3	5.5	23.2	10.6
13.5	9.3	24.3	38.3
15.6	25.0	25.1	4.1
15.9	71.6	25.3	7.9
16.4	31.1	25.7	13.6
16.8	4.3	26.1	7.1
17.5	25.4	26.4	3.7
17.9	16.4		

Example 4: Cocrystal of Finasteride and 2,4-Dihydroxybenzoic Acid

Finasteride (2.3 g; 6.2 mmol) and 2,4-dihydroxybenzoic acid (0.95 g; 6.2 mmol) were added to methanol (2 ml) under stirring at 23°C, wherein a thick white suspension was obtained. Under further stirring, isopropyl acetate (2 ml) was added and the mixture was filtered under suction, washed with cold isopropyl acetate (3 ml) and dried at 23°C in a vacuum oven (20 mbar) to yield 2.05 g (63%) of finasteride 2,4-dihydroxybenzoic acid cocrystal.

10 Table 2: XRPD of Example 4

Angle (2-Theta°)	Intensity (%)	Angle (2-Theta°)	Intensity (%)	Angle (2-Theta°)	Intensity (%)
8.1	5.9	19.4	100	28.7	4.4
10.7	16.7	19.8	75.1	29.4	11.8
10.9	5.9	20.4	14.8	29.9	6.1
11.6	4.6	21.7	13.5	30.2	4.2
13.5	4.3	22.9	6.6	30.7	5.5
13.9	11.0	23.0	3.8	31.0	2.9
14.2	18.7	23.3	5.4	31.4	3.5
14.6	19.4	24.4	5.0	32.4	3.2
14.8	28.7	24.6	10.6	32.9	2.9
16.0	20.8	25.4	38.3	33.1	2.9
16.3	62.6	25.5	4.1	33.5	5.6
16.9	100.0	26.0	7.9	34.1	4.3
17.5	6.5	26.5	13.6	36.0	6.6
18.0	10.4	27.2	7.1	36.6	5.6
18.3	28.0	28.1	3.7		

The cocrystals according to Examples 3 and 4 and optionally further additives as described above can for example be dissolved in a solvent as described above to form a solution to be administered as a liquid topical formulation.

Alternatively, the cocrystals according to Examples 3 and 4 and optionally further additives as described above can for example be added to an ointment base to form a semi-solid formulation to be administered as a semi-solid topical formulation.

5 Example 5: Preparation of an emulsion

At 23°C finasteride (0.25 g) was added to ethanol (30.0 g) and the mixture was stirred at 23°C until the finasteride was dissolved at visual inspection. PEG-5-oleyl-ether (15.0 g) was added and the resulting mixture was stirred until dissolution. Octamethyltrisiloxane (3.0 g) was added and the resulting mixture was stirred until dissolution. Finally, purified water (51.75 g) was added and the resulting mixture was stirred until dissolution. The obtained formulation was a clear and colorless liquid emulsion and has the following composition:

15	Finasteride	0.25 g (0.25 wt.%)
	Ethanol (96%)	30.0 g (30.0 wt.%)
	PEG-5-oleyl-ether	15.0 g (15.0 wt.%)
	Octamethyltrisiloxane	3.0 g (3.0 wt.%)
	Purified water	51.75 g (51.75 wt.%)

20 Particle size: The Z-average of the intensity weighted particle size distribution of the present emulsion was determined by Dynamic Light Scattering (DLS) with the Zetasizer Nano ZS as described in the analytical section. The determination was carried out twice. The following results were obtained:

25	Emulsion	Z-average [nm]	PDI
	1 st Determination	29.81	0.093
	2 nd Determination	30.58	0.086

As can be seen the Z-average is about 30 nm and the PDI (poly dispersity index) is smaller than 0.1, indicating a homogenous distribution of the particles in the emulsion.

The emulsion can be administered as a topical formulation. Alternatively the emulsion can be transferred to a foam as described above and the resulting foam can be administered as a topical formulation.

Claims

1. Finasteride for use in the treatment of androgenetic alopecia, wherein finasteride is administered as a topical formulation once every 3 to 10 days.
2. Finasteride for use in the treatment according to claim 1, wherein the finasteride is administered once every 5 to 8 days.
3. Finasteride for use in the treatment according to claim 1 or 2, wherein the finasteride is administered in an amount of $0.2 \mu\text{g}/\text{cm}^2$ to $20 \mu\text{g}/\text{cm}^2$.
4. Finasteride for use in the treatment according to any one of claims 1 to 3, wherein the finasteride is contained in the formulation in a concentration of 0.025 to 1.00 wt.%.
5. Finasteride for use in the treatment according to any one of claims 1 to 4, wherein the formulation is a liquid formulation.
6. Finasteride for use in the treatment according to claim 5, wherein the liquid formulation is an emulsion or a solution.
7. Finasteride for use in the treatment according to claim 6, wherein the emulsion is a micro-emulsion.
8. Finasteride for use in the treatment according claims 6 or 7, wherein the emulsion comprises 20 to 40 wt.% organic solvent.
9. Finasteride for use in the treatment according to claim 8, wherein the emulsion further comprises 5 to 25 wt.% non-ionic emulsifier and/or 1.0 to 7.0 wt.% of a siloxane having 2 to 5 silicon atoms.

10. Finasteride for use in the treatment according to any one of claims 1 to 4, wherein the formulation is a semi-solid formulation.
11. Finasteride for use in the treatment according to claim 10, wherein the semi-liquid formulation is a crème, an ointment or a gel.
12. Finasteride for use in the treatment according to claim 10 or 11, wherein the semi-liquid formulation contains a cocrystal comprising finasteride.

Figures

Figure 1: 5 α -reductase type II inhibition (100 nM 24 hrs)

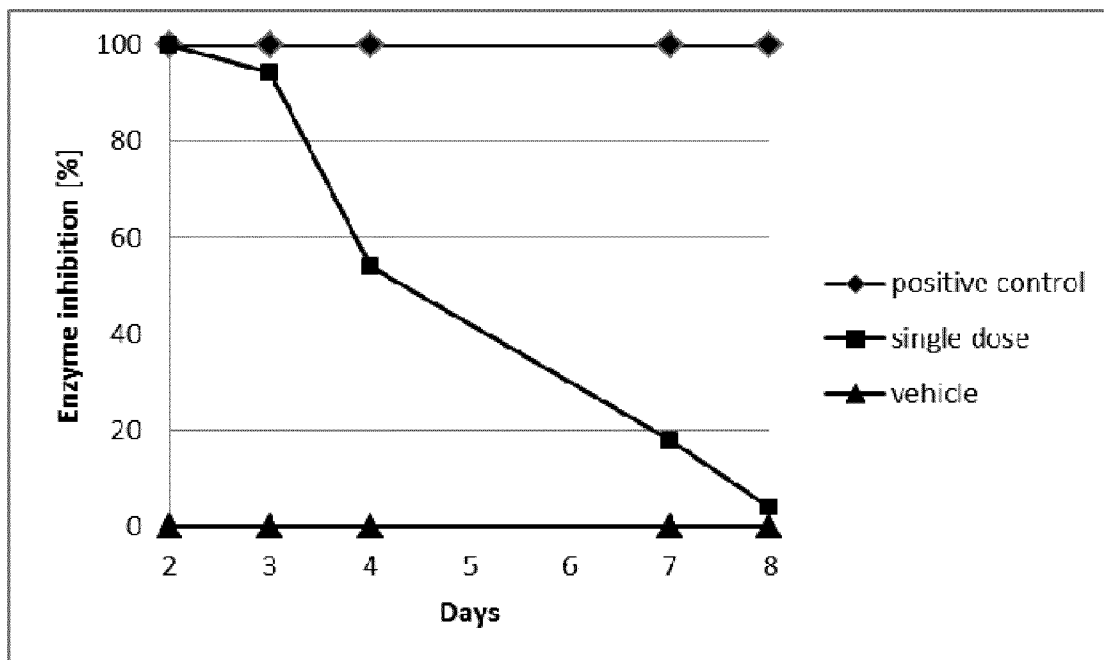


Figure 2

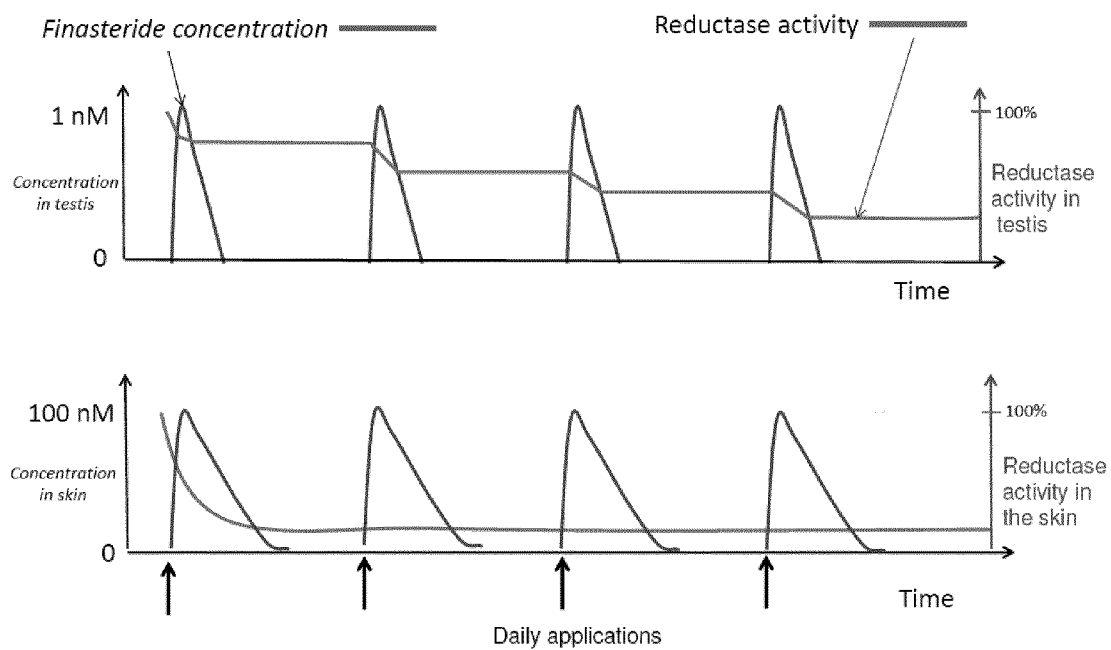
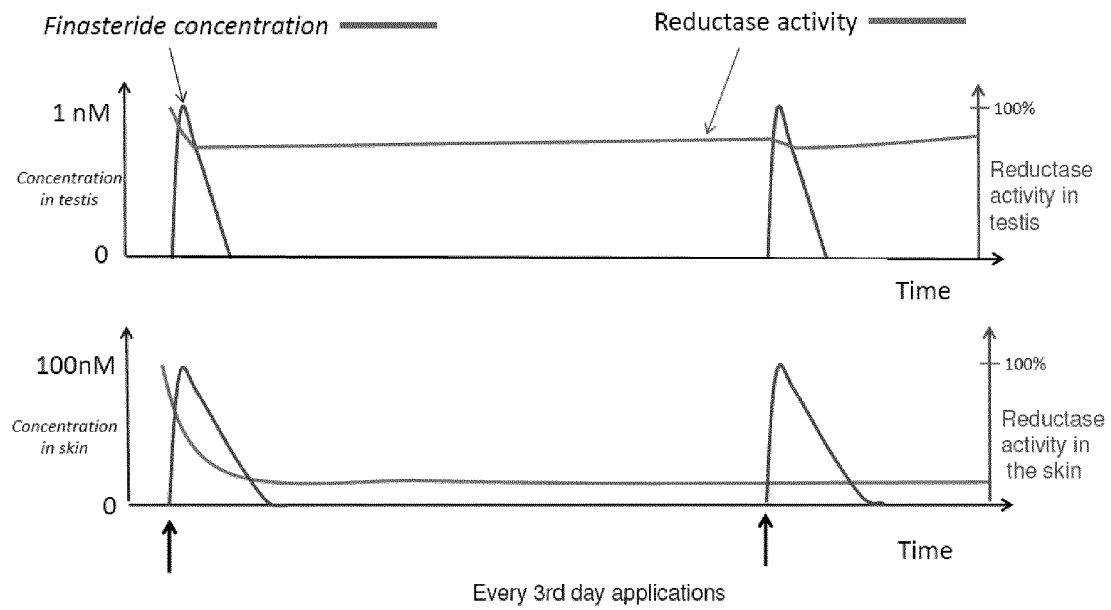


Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/064771

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/58 A61K9/00 A61K9/107 A61K9/08 A61P17/14
A61Q7/00 A61K8/06

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61Q A61P

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

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

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CASERINI MAURIZIO ET AL: "Effects of a novel finasteride 0.25% topical solution on scalp and serum dihydrotestosterone in healthy men with androgenetic alopecia", INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, DUSTRI-VERLAG, DEISENHOFEN-MUENCHEN, DE, vol. 54, no. 1, 31 December 2015 (2015-12-31), pages 19-27, XP009503569, ISSN: 0946-1965, DOI: 10.5414/CP202467 page 23 - page 25	1-12
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 February 2018

Date of mailing of the international search report

13/03/2018

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/064771

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

PCT/EP2017/064771

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