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Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

07-52636

21. EXPEDIENTE No.

54. TÍTULO Uso de Andrógenos para reducir la
probabilidad de adquirir o retardar el envejeci-
miento de la piel

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE Endorecherche Inc.

DOMICILIO Quebec, Canada

74. APODERADO Dña Maria Rodriguez D'Almeida

22. BOGOTÁ, D. C., May 25/07

SS



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PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)	Nombre: ENDORECHERCHE, INC.		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
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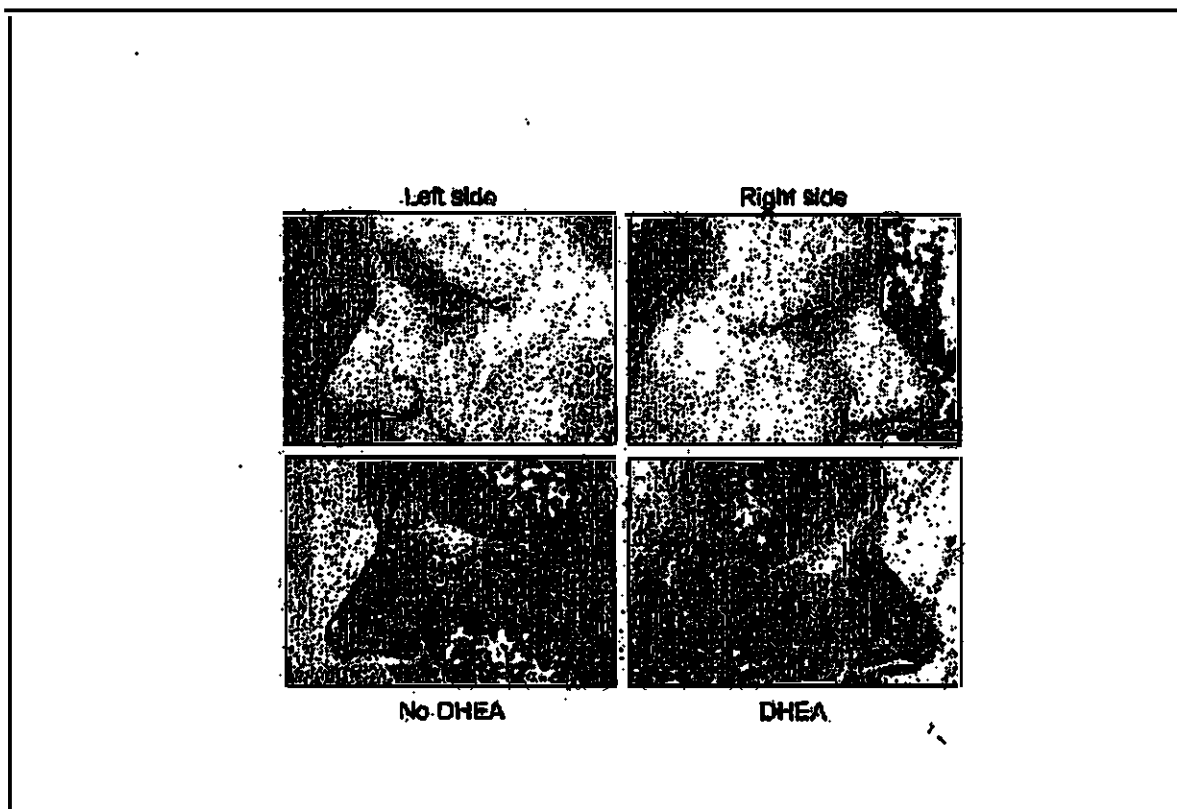
10)

ANEXOS

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- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Reporte internacional de búsqueda
 2. Opinión escrita

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

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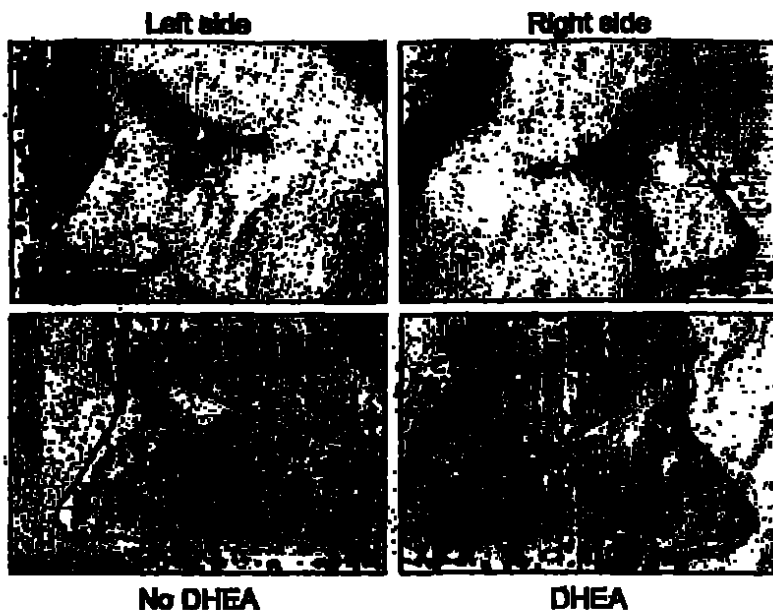
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF ANDROGENS TO REDUCE THE LIKELIHOOD OF ACQUIRING OR TO TREAT SKIN AGING



(57) Abstract: Novel methods of treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, particularly skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite, and formation of wrinkles, in susceptible warm-blooded animals including humans involving administration of an androgen or/and a sex steroid precursor. Pharmaceutical compositions for delivery of active ingredient(s) useful to the invention are also disclosed.

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USE OF ANDROGENS TO REDUCE THE LIKELIHOOD OF ACQUIRING OR TO TREAT SKIN AGING

FIELD OF THE INVENTION

[0001] The present invention relates to a method for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, comprising administering an effective amount of androgens or sex steroid precursors and prodrugs thereof to susceptible warm-blooded animals, including humans. In particular, the invention includes administering androgenic compounds or a precursor of sex steroids selected from the group consisting of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androst-5-ene-3 β ,17 β -diol (5-diol), androstenedione, testosterone, DHT, androstenedione and androstane-3 α , 17- β diol or prodrug, compounds transformed to any of these in vivo. The invention also relates to topical or oral pharmaceutical compositions for practicing the foregoing method.

BACKGROUND OF THE RELATED ART

[0002] The almost exclusive focus on the role of ovarian estrogens in women has removed the attention from the dramatic 70% fall in circulating DHEA which already occurs between the ages of 20 to 30 and 50 to 60 years (Migeon et al., 1957, JCEM, 17: 1051-1062; Vermeulen and Verdonck, 1976, JCEM, 42: 247-253; Vermeulen et al., 1982, JCEM, 54: 187-191; Orentreich et al., 1984, JCEM 59: 551-555; Bélanger et al., 1994, JCEM, 79: 1086-1090; Labrie et al., 1997, Labrie et al., 1997, JCEM, 82: 2396-2402). Since DHEA is

transformed to both androgens and estrogens in peripheral tissues, such a fall in serum DHEA and DHEA-S shows why women at menopause are not only lacking estrogens but have also been progressively deprived of androgens for a few years.

[0003] The marked reduction in the formation of DHEA-S by the adrenals during aging (Migeon et al., 1957, JCEM, 17: 1051-1062; Vermeulen and Verdonck, 1976, JCEM, 42: 247-253; Vermeulen et al., 1982, JCEM, 54: 187-191; Orentreich et al., 1984, JCEM 59: 551-555; Bélanger et al., 1994, JCEM, 79: 1086-1090) results in a dramatic fall in the tissue-specific formation of androgens and estrogens in peripheral target tissues, a situation that has been proposed to be associated with age-related diseases including insulin resistance (Coleman et al., 1982, Diabetes, 31: 830-833; Schriock et al., 1988, JCEM, 66: 1329-1331) and obesity (Nestler et al., 1988, JCEM, 66:57-61; MacEwen and Kurzman, 1988, J Nutrit, 121: S51-S55; Tchernof et al., 1995, Tchernof et al., 1995, Diabetes Care, 18: 292-299). Moreover, much attention has been given to the benefits of DHEA administered to postmenopausal women, especially on the bone, sebaceous glands, vagina and well being after oral (Morales et al., 1994, JCEM, 78: 1360-1367; Baulieu et al., 2000, Proc Natl Acad Sci USA, 87: 4279-4284) as well as percutaneous (Diamond et al., 1996, J Endocrinol, 150: S43-S50; Labrie et al., 1997, JCEM, 82: 3498-3505) administration of the precursor steroid.

[0004] The data showing the presence of relatively high levels of androgens in normal women strongly suggest that the androgens play a major but so-far unrecognized physiological role in women. In fact, the 44.5% fall which occurs in serum DHEA from 20-30 years of age to the age of 40 to 50 years in women could well explain the early bone loss and the increased FSH/LH ratio which precede the detectable decrease in ovarian steroidogenesis in perimenopausal women. In fact, serum FSH increases in

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premenopausal women even before serum E₂ shows a decrease (Grodin et al., 1973, JCEM, 36: 207-214). On the other hand, age-related bone loss has been reported to begin during the fourth decade while changes in bone turnover have also been found before menopause (Riggs et al., 1981, J Clin Invest, 67: 328-335; Mazess et al., 1982, Clinic Orthop, 165: 239-252; Johnston et al., 1985, JCEM, 61: 905-911). In agreement with these findings, bone density was lower at all sites examined in women classified as perimenopausal compared to premenopausal (Steinberg et al., 1989, JCEM, 69: 533-539).

[0005] Until recently, due to assay difficulties, only a limited number of circulating adrenal and gonadal steroids had been measured during advancing age, especially in women where the impact of androgens and estrogens of adrenal origin is of particular importance (Labrie et al., 1991, Mol Cell Endocrinol, 78: C113-C118). It is thus quite remarkable that most of the important decline in circulating DHEA, DHEA-S, androst-5-ene-diol-3 β , 17 β -diol (5-diol), 5-diol-G, androstenedione (4-dione) as well as the conjugated metabolites of androgens, namely androsterone-glucuronide (ADT-G) and androstane-3 α , 17 β -diol glucuronide (3 α -diol-G), occurs between the age ranges of 20-30 and 50-60 years while relatively small changes occur after the age of 60 years. It is thus important to notice that in the 50-60 year-old age group, serum DHEA has already decreased by 70% from the 20-30 year-old peak values (Labrie et al., 1997, JCEM, 82: 2396-2402). Such data suggest that androgenic hormone replacement therapy should start early, taking into account the marked decrease in androgens which occurs relatively early during aging in women.

[0006] As well demonstrated in our previous studies, supplementation with physiological amounts of exogenous DHEA permits the biosynthesis of androgens and estrogens only in the appropriate target tissues which contain the required and tissue-specific steroidogenic enzymes. The active

androgens and estrogens thus synthesized in specific peripheral tissues exert their action in the same cells that are responsible for their formation and very little leakage of the active steroids occurs into the circulation. In fact, as mentioned above, the most striking effects of DHEA administration are seen on the circulating levels of the glucuronide derivatives of the metabolites of DHT, namely ADT-G and 3 α -diol-G, these metabolites being produced locally in the peripheral intracrine tissues which possess the appropriate steroidogenic enzymes to synthesize DHT from the adrenal precursors DHEA and DHEA-S (Labrie et al., 1991, *Mol Cell Endocrinol*, 78: C113-C118; Labrie et al. 1996, *J Endocrinol*, 150: S107-S118). This local biosynthesis and action of androgens in target tissues eliminates the exposure of other tissues to active androgens and thus minimizes the risks of undesirable masculinizing or other androgen-related side effects. The same applies to estrogens although we feel that a reliable parameter of total estrogen secretion (comparable to the glucuronides for androgens) is not yet available.

[0007] DHEA has been shown to have important effects on the skin of aged individuals, the most salient of which is an increase in sebum production (Labrie et al., 1997, *JCEM*, 82: 3498-3505). This has been shown in a number of studies performed in women, particularly those > 70 years old who are physiologically hyposeborrheic and thus found an improvement of their skin with DHEA administration. The DHEA-induced increase in sebum production observed in our study is probably due to the fact that the sebaceous glands contain all the steroidogenic enzymes necessary to catalyze the transformation of DHEA into the androgen DHT, and that this androgen is the main stimulator of sebaceous gland activity (Labrie et al., 2000, *Horm Res*, 54: 218-219; Labrie et al., 2003, *End Rev*, 24: 152-182).

[0008] Apart from sebum production, other beneficial effects of DHEA on the skin have been noticed. To date, evaluation of the dermatological

aspects of DHEA administration have only been performed with some details in one study in which male and female subjects between the ages of 60 and 79 years were orally administered 50 mg of DHEA, once daily for 1 year. In that study, (Baulieu et al., 2000, Proc Natl Acad Sci USA, 97: 4279-4284) were evaluated skin hydration, skin pigmentation and skin thickness. Skin surface hydration significantly increased for the whole DHEA-treated population examined after 12 months of treatment. Skin surface hydration is considered a real benefit for the skin, especially in aged individuals since in these subjects the dryness makes the skin rough. DHEA also significantly decreased facial skin pigmentation (yellowness) for the whole population. This decrease was more pronounced in women > 70 years who are more concerned by age-related pigment changes. The two other components of skin colour remained stable during the duration of the study (i.e. lightness and redness).

[0009] In US 5,843,932, a method for treating skin atrophy or of inhibiting loss of collagen or connective tissue by administration of DHEA; DHEA-S or compounds converted in vivo to either of the foregoing is disclosed.

SUMMARY OF THE INVENTION

[0010] It is an object of the present invention to provide effective methods of treatment of skin diseases due to age-related androgen deficiency.

[0011] It is another object of the present invention to provide effective methods of treatment of skin diseases due to age-related sex-steroid precursor deficiency.

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[0012] It is another object to provide methods of reducing the risk of acquiring the above problems.

[0013] In one embodiment, the invention pertains to a method of treating or reducing the risk of acquiring skin atrophy, comprising administering to a patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs thereof.

[0014] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of collagen, comprising administering to patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs of thereof.

[0015] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of elastic fibers, administering to patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs of thereof.

[0016] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of elastic fibers, administering to patient in need of such treatment or reduction of risk an effective amount of sex steroid precursor or prodrugs of thereof.

[0017] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of connective tissue, comprising administering to patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs of thereof.

[0018] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring cellulite, comprising administering

to patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs thereof.

[0019] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring formation of wrinkles, comprising administering to patient in need of such treatment or reduction of risk an effective amount of androgens or prodrugs of thereof.

[0020] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring cellulite, comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S) and androst-5-ene-3 β ,17 β -diol (5-diol), in a subject or patient in need of said treatment or said steroid precursor.

[0021] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring formation of wrinkles, comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S) and androst-5-ene-3 β ,17 β -diol (5-diol), in a subject or patient in need of said treatment or said steroid precursor.

[0022] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of elastic fibers, comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S) and androst-5-ene-3 β ,17 β -diol (5-diol), in a subject or patient in need of said treatment or said steroid precursor.

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[0023] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring skin atrophy, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

[0024] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring loss of collagen, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

[0025] In another embodiment, the invention pertains to a method of treating or reducing the risk of loss of elastic fibers, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

[0026] In another embodiment, the invention pertains to a method of treating or reducing the risk of loss of connective tissue, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

[0027] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring wrinkles, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

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[0028] In another embodiment, the invention pertains to a method of treating or reducing the risk of acquiring cellulite, comprising administering androstenedione, androstenedione, testosterone, dihydrotestosterone, 5 α -androstane-3 α ,17 β -diol or compounds transformed into these, in a subject or patient in need of said treatment.

[0029] In another aspect, the invention provides topical pharmaceutical compositions containing the androgens together with pharmaceutically acceptable diluents or carriers.

[0030] In one embodiment, the precursor is DHEA.

[0031] In another embodiment, the androgen is testosterone or its derivatives.

[0032] As used herein, an androgen is a compound (or one of its metabolites) having a K_i value for the human androgen receptor of less than about $2 \times 10^{-8} M$ and an androgen receptor-mediated inhibitory effect on the growth of human breast cancer ZR-75-1 cells which reaches half-maximal value at a concentration below 10 nanomoles per liter or a compound (or one of its metabolites) which positively responds to the screening method described in the US provisional application entitled "Method for determination of anabolic activity" filed on August 30, 2004, application 60/606,174.

[0033] A patient in need of treatment or of reducing the risk of onset of a given disease is one who has either been diagnosed with such disease or one who is susceptible to acquiring such disease.

[0034] Except where otherwise stated, the preferred dosage of the active compounds (concentrations and modes of administration) of the invention is identical for both therapeutic and prophylactic purposes. The dosage for each active component discussed herein is the same regardless of the disease being treated (or of the disease whose likelihood of onset is being reduced).

[0035] Except when otherwise noted or where apparent from context, dosages herein refer to weight of active compounds unaffected by pharmaceutical excipients, diluents, carriers or other ingredients, although such additional ingredients are desirably included, as shown in the examples herein. Any dosage form, specially topical formulations (gel, lotion, cream, ointment or the like) commonly used in the pharmaceutical industry is appropriate for use herein, and the terms "excipient", "diluent", or "carrier" include such nonactive ingredients as are typically included, together with active ingredients in such dosage forms in the industry. For example, typical cream, penetrating agent, preservatives, or the like may be included for topical formulations.

[0036] All of the active ingredients used in any of the therapies discussed herein may be formulated in pharmaceutical compositions which also include one or more of the other active ingredients. Alternatively, they may each be administered separately but sufficiently simultaneous in time so that a patient eventually has elevated blood levels or otherwise enjoys the benefits of each of the active ingredients (or strategies) simultaneously. In some preferred embodiments of the invention, for example, one or more active ingredients are to be formulated in a single pharmaceutical composition.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0037] Figure 1 shows the comparison between male and female mouse dorsal skin. (A) Paraffin sections of mouse dorsal skin stained with hematoxylin and eosin. a) In the intact male, all hair follicles are in the telogen phase and located in the dermis, which is bordered by a thin layer of hypodermis. b) In the intact female, all hair follicles are also in the telogen phase, while the hypodermis is thicker in comparison to the male, and the dermis is narrower. c) After GDX, the hair follicles of the male are in late anagen. d) In the GDX female, all the hair follicles are in anagen. Epidermis (E), dermis (D), hypodermis (H), panniculus carnosus (PC) and hair follicles (HF). Scale bar = 100 μ m. (B) Comparison between male and female total skin thickness as well as the thickness of each skin layer (epidermis, dermis and hypodermis) in intact and GDX animals and in GDX animals treated with DHT, E₂ or DHEA. Values are presented as means $\pm$ SEM. * p <0.05 vs. GDX male control; ** p <0.01 vs. GDX female control (Duncan-Kramer multiple-range-test).

[0038] Figure 2 shows the expression of androgen receptor (AR) in the epidermis of mouse dorsal skin. AR was found to be exclusively localized in the nuclei. a) in the intact male, most of epidermal nuclei are labeled. b) in the intact female, most of epidermal nuclei are labeled but the labeling intensity is less than in the male. Three weeks after GDX, no labeling could be detected in the GDX males (c) nor in the GDX females (d). When GDX male (e) and female (f) mice were treated with DHT, strong AR labeling was observed in most of the nuclei of epidermal cells. When GDX males (g) and females (h) received E₂, weak AR labeling was detected in some nuclei. Similar to DHT treatment, when GDX males (i) and females (j) received DHEA, a strong labeling was detected in most of the epidermal nuclei. Scale bar = 20 μ m.

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[0039] Figure 3 and figure 4 show a comparison of the face skin treated with DHEA (right side of the face) or untreated (left side of the face). Three-hundred microliters (0.3ml) of the emulsion, containing DHEA were applied on the forehead and on the right side of the face during 13 weeks.

DETAILED DESCRIPTION OF THE INVENTION

[0040] The present invention shows that a major effect of androgens was seen on dermal thickness. In fact, collagen and elastic fibers are known to be the main component of the dermis that provides a major support for skin resistance, including a possible role in the formation of wrinkles. An increase in dermal thickness was observed after DHT and DHEA treatment in GDX females, (Fig 1) while, under all experimental conditions, the dermis is thicker in males, thus possibly explaining the lack of effect of androgens in the male during a 3-week treatment period. Striking gender differences are seen in the hypodermis of intact animals, thus providing further similarities with human skin (Hattori et al, 1993) and suggesting that DHEA and androgens could be beneficial for the reducing the risk of acquiring or treating cellulite.

[0041] Using the mouse as a model, the present invention clearly establishes morphological differences between males and females in the different mouse skin layers and appendages. Moreover, the specific and differential role of androgens and estrogens at different sites has been identified while providing evidence for an action of DHEA mediated by androgens in the dermis and estrogens in the epidermis.

[0042] Active ingredient for topical application is preferably present at from 0.05% to 20% by weight relative to the total weight of the

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pharmaceutical composition, more preferably between 0.1 and 10% DHEA or 5-diol and between 0.1% and 3% for an androgen. Alternatively, the active ingredient may be placed into a transdermal patch having structures known in the art, for example, structures such as those set forth in E.P. Patent No.0279982.

[0043] When formulated as an ointment, lotion, gel or cream or the like, the active compound is admixed with a suitable carrier which is compatible with human skin or mucosa. Suitable carriers are known in the art and include but are not limited to Klucel HF and Glaxal base. Some are commercially available, e.g., Glaxal base available from Glaxal Canada Limited Company. Other suitable vehicles can be found in Koller and Buri, S.T.P. Pharma 3(2), 115-124, 1987. The carrier is preferably one in which the active ingredient(s) is (are) soluble at ambient temperature at the concentration of active ingredient that is used. The carrier should have sufficient viscosity to maintain the steroid on a localized area of skin or mucosa to which the composition has been applied, without running or evaporating for a time period sufficient to permit substantial penetration of the precursor or androgen through the localized area of skin or mucosa to cause a desirable clinical effect. The carrier is typically a mixture of several components, e.g. pharmaceutically acceptable solvents and a thickening agent. A mixture of organic and inorganic solvents can aid hydrophylic and lipophylic solubility, e.g. water and an alcohol such as ethanol and propylene glycol.

[0044] Preferred sex steroid precursors are dehydroepiandrosterone (DHEA) (available from Diosynth Inc., Chicago, Illinois, USA), 5-androsten-3 β ,17 β -diol (available from Steraloida, Wilton, New Hampshire USA).

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[0045] One other preferred sex steroid precursor is 4-androstene-3,17-dione, available from Sigma-Aldrich Canada Ltd, Oakvill, Ontario, Canada.

[0046] One preferred androgen of the invention is Stanolone (5 α -androstane-17 β -ol-3-one, DHT), available from Sigma-Aldrich Canada Ltd, Oakvill, Ontario, Canada.

[0047] Another preferred androgen is AndroGel a gel containing 1% of testosterone in alcohol, water, Carbopol 980 NF, isopropyl myristate and 0.1 M sodium hydroxide, and available from Solvay Pharma, Markham, Ontario, Canada

[0048] One preferred androgen for systemic action is Androderm, a patch containing 12.2 mg or 24.3 mg of testosterone, available from Laboratoires Paladin Inc., Montréal, Québec, Canada.

[0049] Other esters of testosterone (testosterone undecanoate, available from Organon Canada Ltd., Scarborough, Ontario, Canada, under the name andriol, testosterone enanthate, available from Theramed Corporation, Mississauga, Ontario, Canada under the name Delatestryl, testosterone cypionate available from Pfizer Canada, Kirland, Canada under the name Depo-testosterone (cypionate) or from Sabex, 2002 Inc., Boucherville, Qc, Canada under the name testosterone cypionate injection USP) and derivatives (i.e. nandrolone (19-nor testosterone) and esters (nandrolone decanoate available from Organo Canada, Ltd. Scarborough Ontario Canada under the name Deca-Durabolin), methyltestosterone available from sigma-Aldrich Canada Ltd., Oakvill, Ontario, Canada are also preferred.

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[0050] It is also preferred that the androgen are 5 α -androsterane-3 α , 17 β -diol and 5 α -androsterane-3,17-dione, both available from Sigma-Aldrich Canada Ltd., Oakville, Ontario, Canada.

[0051] It is preferred that the sex steroid precursor or the androgen is formulated as an alcoholic gel containing 1.0 to 10% of caprylic-capric triglyceride (Neobee M-5); 10 to 20% of hexylene glycol; 2.0 to 10% of diethyleneglycol monomethyl ether (Transutol); 2.0 to 10% of Cyclomethicone (Dow Corning 345); 1.0 to 2% of benzyl alcohol and 1.0 to 5.0% of hydroxypropylcellulose (Klucel HF).

[0052] It is also preferred that the sex steroid precursor or the androgen is formulated as a cream containing 2.0 to 4.0% of Laurylmethicone copolyol, 5.0 to 7.0% Cyclomethicone, 2.0 to 4.0% of mineral oil, 6.0 to 8.0% of Cetearyl isononate, 0.5 to 1.5% of Emulgin B₂, 0.01 to 0.1% of butylated hydroxytoluene, 49.0 to 60.0% of Propylene Glycol, 10 to 20% of water, 0.5 to 1.5% of Magnesium sulphate, 4.0 to 6.0% of ethanol and 0.1 to 3.0% of sex steroid precursor or androgen.

[0053] It is also preferred that the sex steroid precursor or the androgen is formulated as a cream containing 0.1 to 10% of sex steroid precursor or androgen, 10 to 25% of Emulsifying Wax, 5 to 20% of Light mineral oil, 0.5 to 2.0% of Benzyl alcohol, 20 to 40 % of Ethanol 95% and 20 to 40 % of water.

[0054] It is also preferred that the sex steroid precursor or the androgen is formulated as a cream containing 0.1 to 10% of sex steroid precursor or androgen, 2 to 10 % of Cetyl alcohol, 5 to 10% Cetyl Esters Wax, 0.25 to 0.5 % of Phenylethyl alcohol, 5 to 10 % of White Wax, 20 to 40 % of water, 20 to 40 % of Glycerol, 2.0 to 10.0% of Mineral oil, 1.0 to 5.0% of

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Sodium Lauryl sulfate, 3.0 to 6.0% of Glyceryl monostearate, 3.0 to 6.0% of Propyl glycol monostearate, and 1 to 5.0% of Methyl stearate.

[0055] It is also preferred that the sex steroid precursor or the androgen is formulated for oral administration as a capsule containing 10 to 50 mg of sex steroid precursor or androgen derivative.

[0056] The carrier may also include various additives commonly used in ointments and lotions and well known in the cosmetic and medical arts. For example, fragrances, antioxidants, perfumes, gelling agents, thickening agents such as carboxymethylcellulose, surfactants, stabilizers, emollients, coloring agents and other similar agents may be present.

[0057] Preferably, the attending clinician will, especially at the beginning of treatment, monitor an individual patient's overall response and serum levels of DHEA or androgen and, especially, monitor the patient's overall response to treatment, adjusting dosages as necessary where a given patients' metabolism or reaction to treatment is atypical.

[0058] Typical dose for topical administration of sex steroid precursor or androgen is 5 mg to 200 mg of active ingredient per day, per 50 kg of body weight, preferably 20 to 60 mg per day.

If oral administration is chosen, 10 to 100 mg active ingredient should be administered once daily per 50 kg of body weight.

EXAMPLES OF EFFECTIVENESS OF THE PRESENT INVENTION

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Example 1

Materials and Methods

ANIMALS AND TREATMENTS

[0059] Fifty six adult male and female C57BL6 mice 13-15 weeks of age were obtained from Harlan Laboratory (Indiana, USA). Mice were randomly distributed into 4 groups of 7 animals per group as follows: (1) intact control; (2) GDX control; (3) GDX+DHT (0.1mg/mouse); (4) GDX+DHEA (6.25 mg/mouse). On day one of the study, bilateral GDX was performed as described (Castro, 1974 and Fleischman, 1981) in all animals except those of the first group which were sham-operated. Starting from the second day after GDX and for three weeks, DHEA is daily administrated orally as a suspension in 0.4% methylcellulose and 5% ethanol to the animals of the appropriate groups. Animals of intact and GDX control groups were treated with the vehicle alone during the same period. Six hours after the last treatment, all animals were sacrificed.

[0060] The oral doses of DHEA were selected based upon previous published studies (Labrie et al, 1996; Labrie et al, 2003b). Thus, the selected physiological doses completely reversed the GDX-induced atrophy of hormone-sensitive organs and led to organ weights similar to those found in intact animals. Since DHT is known to be poorly active by the oral route, it was injected subcutaneously. To determine the DHT dose, a preliminary dose-range study was performed (see supplementary online material, online Table S1).

Tissue processing

[0061] After shaving the long hair, the dorsal skin was excised, flattened and immediately immersed in 10% buffered formalin. A sample

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was embedded in paraffin blocks from which 4µm sections were cut and routinely stained. The other part of the skin was used for the whole mount technique as described (Badertscher JA, 1940, Stain Technol, 15: 29-30).

Skin thickness analysis

[0062] Under the light microscope, measurements were performed using the IMAGE-PRO PLUS (Media Cybernetics, USA). Twenty-five readings were scored from each skin layer of each animal. The epidermal thickness was measured from stratum basale to stratum granulosum (excluding stratum corneum), whereas the dermal thickness was the distance between the epidermis and the hypodermis. Finally, the hypodermal thickness was measured as the distance between the dermis and the panniculus carnosus.

Immunohistochemistry

[0063] Paraffin sections were deparaffinized and rehydrated. Endogenous peroxidase activity was eliminated by preincubation in 3% H₂O₂ in methanol for 30 min. A microwave retrieval technique using citrate buffer was applied (Tacha et Chen, 1994), and non-specific binding sites were neutralized with 10% goat serum. The sections were then incubated for 60 min at room temperature with mouse anti-Ki-67 antibody clone MIB-5 (1:60) (Dako Diagnostic, CA, USA) or for 90 min at room temperature with rabbit anti-androgen receptor (AR) antibody (1:300) (N-20; Santa Cruz Biotechnology, Inc., CA, USA). Zymed SP kit (San Francisco, CA, USA) and Vectastain Elite ABC Kit (Vector Laboratories, Inc. Burlingame, CA, USA) were used for AR, and Ki-67 antibodies, respectively. Under microscope monitoring, diaminobenzidine was used as the chromogen. For the evaluation of Ki-67, the labeling index of 400 cells was calculated from each animal.

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Statistical analysis

[0064] Data were expressed as means $\pm$ S.E.M. The statistical significance was determined according to the multiple range test of Duncan-Kramer (Kramer CY, 1956, Biometrics, 12: 307-310).

Results

[0065] Morphological examination of dorsal skin of 16-to 18-week-old male and female mice reveals that gender differences in the global thickness of the skin and in the proportions of the different skin layers are clearly seen (Figs 1A and 1B). In fact, the major difference is that the dermis in the male is much thicker than in the female while the epidermis and hypodermis are thicker in the female, thus resulting in total skin which is 40% thicker in the male.

Epidermis

[0066] The epidermis of intact females is approximately 40% thicker than in males ($p < 0.01$). Three weeks after GDX, the epidermal thickness of females decreased by 40% ($p < 0.01$) while, a 13% increase was observed after DHEA treatment ($p < 0.05$).

[0067] As indicated by the number of Ki-67-positive basal cells, cell proliferation was found to be higher in intact females (11.8 ± 0.7 vs 9.3 ± 0.4 , $p < 0.05$), thus indicating a gender difference. Furthermore, 3 weeks after GDX, the level of cell proliferation decreased in females by 27% (8.6 ± 0.7 , $p < 0.01$), a value similar to that observed in intact males. AR immunostaining intensity was found to be slightly higher in intact males than females (Figs 2a, 2b). Three weeks after GDX, AR expression decreased in male epidermal cells to a level similar to that of females (Figs 2c, 2d). When GDX animals

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received DHT or DHEA, a strong AR expression was observed in both males and females (Figs 2e, 2i, 2f, 2j).

Dermis

[0068] In intact animals, the dermis was 190% thicker in the male compared to the female ($p<0.01$). After GDX, the female dermal thickness increased by 22% ($p<0.05$) while the 7% decrease in the male was not statistically significant. Only in GDX females, DHT and DHEA treatments significantly increased dermal thickness by 47% ($p<0.01$) and 19% ($p<0.05$), respectively.

Hypodermis

[0069] The hypodermis in the intact female was about 11-fold thicker than in the male ($p<0.01$). As seen in Figure 1B, after GDX, hypodermal thickness increased in both male and female mice ($p<0.01$) while treatment with DHT, E₂ or DHEA markedly decreased hypodermal thickness in GDX animals of both sexes ($p<0.01$). These findings are a good indication that treatment with DHT, E₂ or DHEA is efficient for the treatment of cellulite.

Table I

	Epidermis				Dermis				Hypodermis			
	♂		♀		♂		♀		♂		♀	
	T (µm)	%	T (µm)	%	T (µm)	%	T (µm)	%	T (µm)	%	T (µm)	%
Intact	9.4 ± 0.3	1.8	13.3 ± 0.4**	3.6	500 ± 10.2	94.9	171 ± 13.3*	46	18 ± 1.5*	3.3	187 ± 1.5**	50.4
GDX	9.4 ± 0.2	1.7	9.3 ± 0.2	1.6	463 ± 21.3	84.1	209 ± 10.4	35	78 ± 5.8	14.2	378 ± 3.9	63.4
GDX+DHT	10 ± 0.2	2.1	9.6 ± 0.2	2.5	451 ± 24.1	93	307 ± 13.3**	79.5	24 ± 1.9*	4.9	70 ± 4.6**	18
GDX+DHRA	8.9 ± 0.3	1.7	10.5 ± 0.3*	3.2	486 ± 28.7	92.8	249 ± 11.8*	75.8	29 ± 6.2*	5.5	69 ± 4.5**	21

Table 1. Gender differences in the relative proportions of the different skin layers. Values are presented as means ± SEM. **, $p < 0.01$, experimental versus GDX male; **, $p < 0.01$, experimental versus GDX female; *, $p < 0.05$, experimental versus GDX female (Duncan-Kramer multiple-range-test). T : Thickness (µm); % : Proportion of each skin layer.

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Example 2
Protocol ERC-202

Study Design

[0070] This study is a randomized double-blind placebo-controlled trial of 15 subjects per arm. The study was divided into two phases, a screening period and a treatment period of 13 weeks.

Subjects and treatment

[0071] After written informed consent was obtained, and women were found eligible, each subject was randomized to receive either a 0.0% (placebo), a 0.1%, a 0.3%, a 1% or a 2% DHEA emulsion twice a day in the morning and evening.

[0072] Daily, before breakfast, and after supper, for 13 weeks, subjects received 3.0 ml of one of the five emulsions.

[0073] All subjects were be instructed to apply the study treatment on the face (right side) and forehead, upper chest, back of hands, back of arms, external face of thighs and legs twice daily (in the morning between 06:00 and 09:30h and in the evening between 18:00 and 21:30h) during 13 weeks. The first application of the study treatment was carried out at the investigational site where instructions were provided to the subjects on how to apply the topical emulsion. Three-hundred microliters (0.3ml) of the emulsion were applied on the forehead and face (right side), 0.3 ml per back of arm and back of hand (0.3 ml x2), 0.3ml on the upper chest, 0.6 ml per thigh (0.6 ml x2) and 0.3 ml per leg (0.3 ml x2) for a total dose of 3.0 ml of DHEA emulsion twice daily.

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PHARMACEUTICAL COMPOSITION EXAMPLES

[0074] Set forth below, by way of example and not of limitation, are several topical pharmaceutical compositions utilizing preferred active sex steroid precursor DHRA, preferred androgens. The concentration of active ingredient may be varied over a wide range as discussed herein. The amounts and types of other ingredients that may be included are well known in the art.

Example A**Topical cream**

Ingredient	Weight % (by weight of total composition)
DHRA	1.0
Emulsifying Wax, NF	18.0
Light mineral oil, NF	12.0
Benzyl alcohol	1.0
Ethanol 95% USP	34.0
Purified water, USP	34.0

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Example B**Topical cream****Cream 0.1% DHEA (Formulation No 0759-0435)**

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	6.0
Marcol 82	3.0
Cetearyl isononate (Cetiol SN)	7.0
Emulgin B2	1.0
B.H.T	0.1
Propylene Glycol	58.4
DHEA, GMP	0.1
Water, USP	15.4
Magnesium sulfate, 7 H ₂ O	1.0
Absolute ethanol USP	5.0
Total:	100.0

Example C.**Topical cream****Cream 0.3% DHEA (Formulation No 0759-0435)**

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	6.0
Marcol 82	3.0
Cetearyl isononate (Cetiol SN)	7.0
Emulgin B2	1.0
B.H.T	0.1
Propylene Glycol	58.4
DHEA, GMP	0.3
Water, USP	15.2
Magnesium sulfate, 7 H ₂ O	1.0
Absolute ethanol USP	5.0
Total:	100.0

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Example D**Topical cream****Cream 0.3% DHEA (Formulation No 0759-0484)**

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	10.0
Primol 352	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Emulglin B2	1.0
B.H.T	0.1
Propylene Glycol	49.60
DHEA, GMP	0.3
Water, USP	20.00
Magnesium sulfate, 7 H₂O	1.0
Absolute ethanol USP	5.0
Total:	100.0

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Example E**Topical cream****Cream 1.0% DHRA (Formulation No 0759-0435)**

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	6.0
Marcol 82	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Eumulgol B2	1.0
BHT	0.1
Propylene Glycol	58.4
DHRA, GMP	1.0
Water, USP	14.5
Magnesium sulfate, 7 H ₂ O	1.0
Absolute ethanol USP	5.0
Total:	100.0

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Example F

Topical cream

Cream 1.5% DHEA (Formulation No 484-12-1.5%)

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	5.0
Primol 352	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Emulglin B2	1.0
B.H.T	0.090
Propylene Glycol	45.41
ethanol USP	14.0
DHEA, GMP	1.5
Water, USP	14.0
Magnesium sulfate, 7 H ₂ O	0.65
ethanol USP	5.35
Total:	100.0

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Example G

Topical cream

Cream 1.5% DHEA (Formulation No 435-3-1.5%)

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	6.0
Primol 352	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Bumulgin B2	1.0
B.H.T	0.090
Propylene Glycol	58.41
DHEA, GMP	1.5
Water, USP	14.0
Magnesium sulfate, 7 H ₂ O	1.0
ethanol USP	5.0
Total:	100.0

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Example H
Topical cream

Cream 1.5% DHEA (Formulation No 47-1.5%)

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone	5.0
Mineral oil	3.0
2-ethylhexyl stearate	10.0
Cutina E24	1.0
B.H.T	0.090
Propylene Glycol	45.51
ethanol USP	10.0
DHEA, GMP	1.5
Water, USP	15.0
Magnesium sulfate, 7 H ₂ O	0.65
ethanol USP	5.25
Total:	100.0

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Example I
Topical cream

Cream 2.0% DHEA (Formulation No 0759-0435)

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	6.0
Marcol 82	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Bumulgln B2	1.0
B.H.T	0.1
Propylene Glycol	58.4
DHEA, GMP	2.0
Water, USP	13.5
Magnesium sulfate, 7 H₂O	1.0
Absolute ethanol USP	5.0
Total:	100.0

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Example J
Topical cream

Cream 0.3% Testosterone

Ingredient	Weight % (by weight of total composition)
Laurylmethicone copolyol (DC Emulsifier 10)	3.0
Cyclomethicone (Mirasil CM5)	10.0
Primol 352	3.0
Cetearyl isononanoate (Cetiol SN)	7.0
Emulglin B2	1.0
B.H.T	0.1
Propylene Glycol	49.60
Testosterone GMP	0.3
Water, USP	20.00
Magnesium sulfate, 7 H ₂ O	1.0
Absolute ethanol USP	5.0
Total:	100.0

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Example K

Topical cream

Cream 0.3% DHEA

Ingredient	Weight % (by weight of total composition)
Cetyl alcohol	8.0
Mineral oil	7.0
Cetyl Esters Wax	4.0
White Wax	6.0
Glyceryl monostearate,	4.0
Propyl glycol monostearate	2.0
Methyl stearate	1.0
Phenylethyl alcohol	0.5
Glycerol	44.70
DHEA GMP	0.30
Water, USP	21.50
Sodium Lauryl Sulfate	1.00
Total:	100.0

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Example I
Topical cream

Cream 0.3% DHT

Ingredient	Weight % (by weight of total composition)
Cetyl alcohol	8.0
Mineral oil	7.0
Cetyl Esters Wax	4.0
White Wax	6.0
Glyceryl monostearate,	4.0
Propyl glycol monostearate	2.0
Methyl stearate	1.0
Phenylethyl alcohol	0.5
Glycerol	44.70
DHT GMP	0.30
Water, USP	21.50
Sodium Lauryl Sulfate	1.00
Total:	100.0

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Example M
Topical cream

Cream 0.3% Testosterone

Ingredient	Weight % (by weight of total composition)
Cetyl alcohol	8.0
Mineral oil	7.0
Cetyl Esters Wax	4.0
White Wax	6.0
Glyceryl monostearate,	4.0
Propyl glycol monostearate	2.0
Methyl stearate	1.0
Phenylethyl alcohol	0.5
Glycerol	44.70
Testosterone GMP	0.30
Water, USP	21.50
Sodium Lauryl Sulfate	1.00
Total:	100.0

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Example N

Topical gel

Gel 10.0% DHEA

Ingredient	Weight % (by weight of total composition)
DHEA	10.0
Caprylic-capric Triglyceride (Neobee M-5)	5.0
Hexylene Glycol NF	15.0
Transcutol (diethyleneglycol monomethyl ether)	5.0
Benzyl alcohol	2.0
Cyclomethicone (Dow corning 345)	5.0
Ethanol (absolute) USP	56.0
Hydroxypropylcellulose (1500 cps) (KLUCCEL)	2.0
Total :	100.0

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Example O

Topical gel

Gel 20% DHT

Ingredient	Weight % (by weight of total composition)
Dihydrotestosterone	2.0
Caprylic-capric Triglyceride (Neobee M-5)	5.0
Hexylene Glycol NF	15.0
Transcutol (diethyleneglycol monomethyl ether)	5.0
Benzyl alcohol	2.0
Cyclomethicone (Dow corning 345)	5.0
Ethanol (absolute) USP	64.0
Hydroxypropylcellulose (1500 cps) (KLUCEL)	2.0
Total :	100.0

Example P
Oral Capsules

Capsule 50 mg DHEA

Ingredient	mg/capsule
	Strength: 50 mg
DHEA (micronized)	50.0
Cellulose, Microcrystalline (AVICEL 302)	248.5
Magnesium Stearate	1.50
Total	300.0

Example Q
Oral Capsules

Capsule 25 mg DHEA

Ingredient	mg/capsule
	Strength: 25 mg
DHEA (micronized) (House standard)	25.0
Cellulose, Microcrystalline (AVICEL 302) (USP)	273.5
Magnesium Stearate (NF)	1.50
Total	300.0

[0075] The invention has been described in terms of preferred embodiments and examples, but is not limited thereby. Those of skill in the art will readily recognize the broader applicability and scope of the invention which is limited only by the patent claims herein.

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What is claimed is:

1. A method for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of androgens or prodrugs of thereof.
 2. A method of claim 1 wherein these skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite, and wrinkles.
 3. The method of claim 1 wherein the androgen is selected from the group consisting of testosterone (4-androstene-17 β -ol-3-one), dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs of thereof.
 4. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene-3 β ,17 β -diol and prodrugs of thereof.
 5. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one androgen selected from the group consisting of testosterone (4-androstene-17 β -ol-3-one), dihydrotestosterone (5 α -androstane-17 β -ol-3-one),
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androstenedione (4-androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs of thereof.

6. The method of claims 4, wherein sex steroid precursors are administered topically.

7. A method for treating or reducing the likelihood of acquiring skin atrophy, loss of collagen, comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one androgen selected from the group consisting of testosterone (4-androstene-17 β -ol-3-one), dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs of thereof.

8. The method of claim 4 wherein sex steroid precursors are administered orally.

9. The method of claim 1, 5 or 7 wherein androgens or prodrugs of thereof are administered topically.

10. The method of claim 1, 5 or 7 wherein androgens or prodrugs of thereof are administered orally.

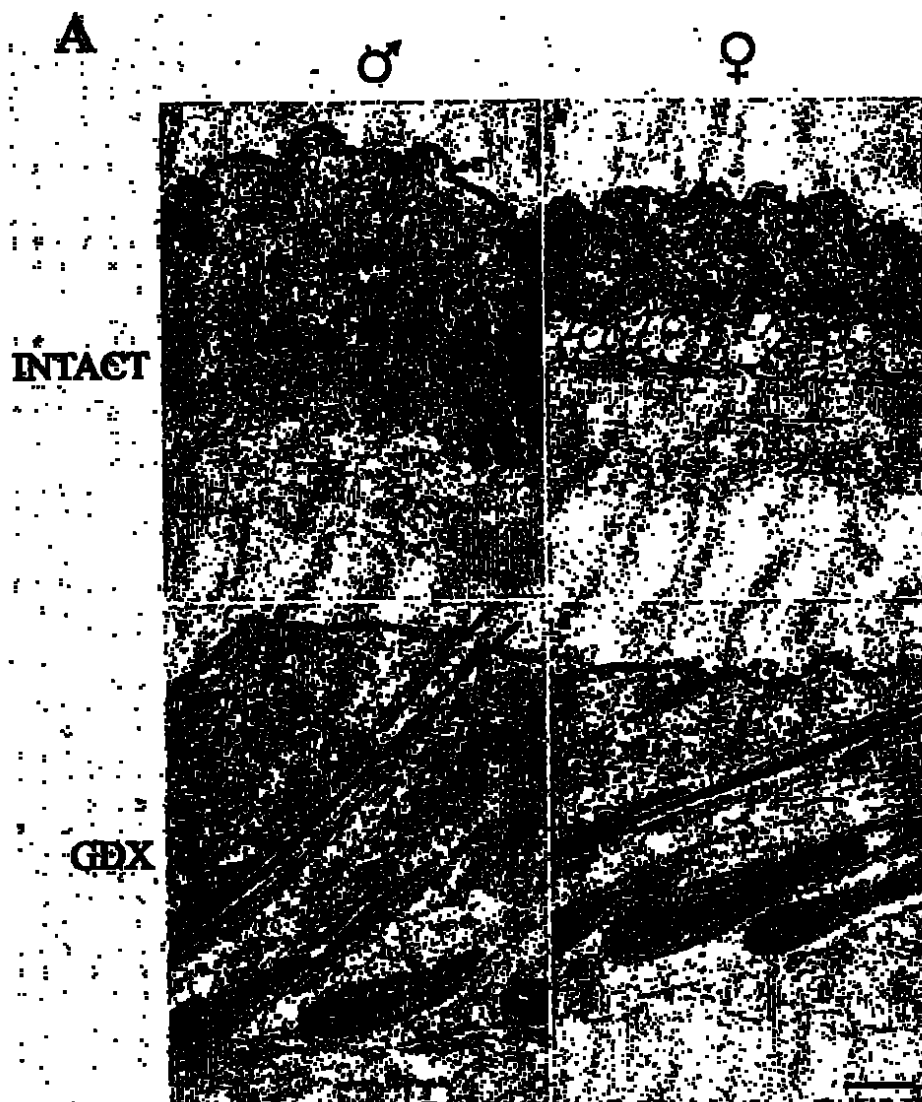
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11. Use of an effective amount of androgens or prodrugs thereof in the manufacture of a medicament for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency.
12. The use of claim 11, wherein the skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite and wrinkles.
13. The use of claim 1, wherein the androgen is selected from the group consisting of testosterone (4-androstene-17 β -ol-3-one), dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione ((4-androstene-3, 17dione), androstenedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof.
14. An effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene 3 β , 17 β -diol and prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.
15. An effective amount of at one least androgen selected from the group consisting of (4-androstene-17 β -ol-3-one), dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3, 17dione), androstenedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.
16. A topical composition for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient comprising an effective amount of at least one androgen selected from the group consisting of (4-androstene-17 β -ol-3-

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FIGURE 1



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FIGURE 1

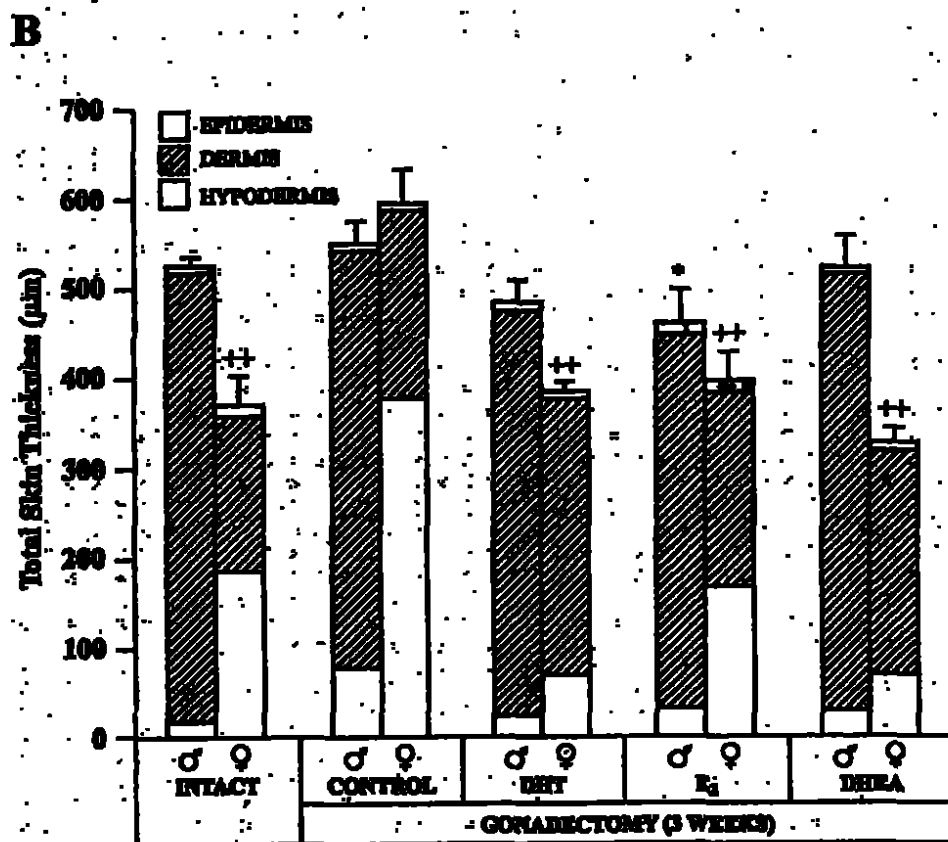
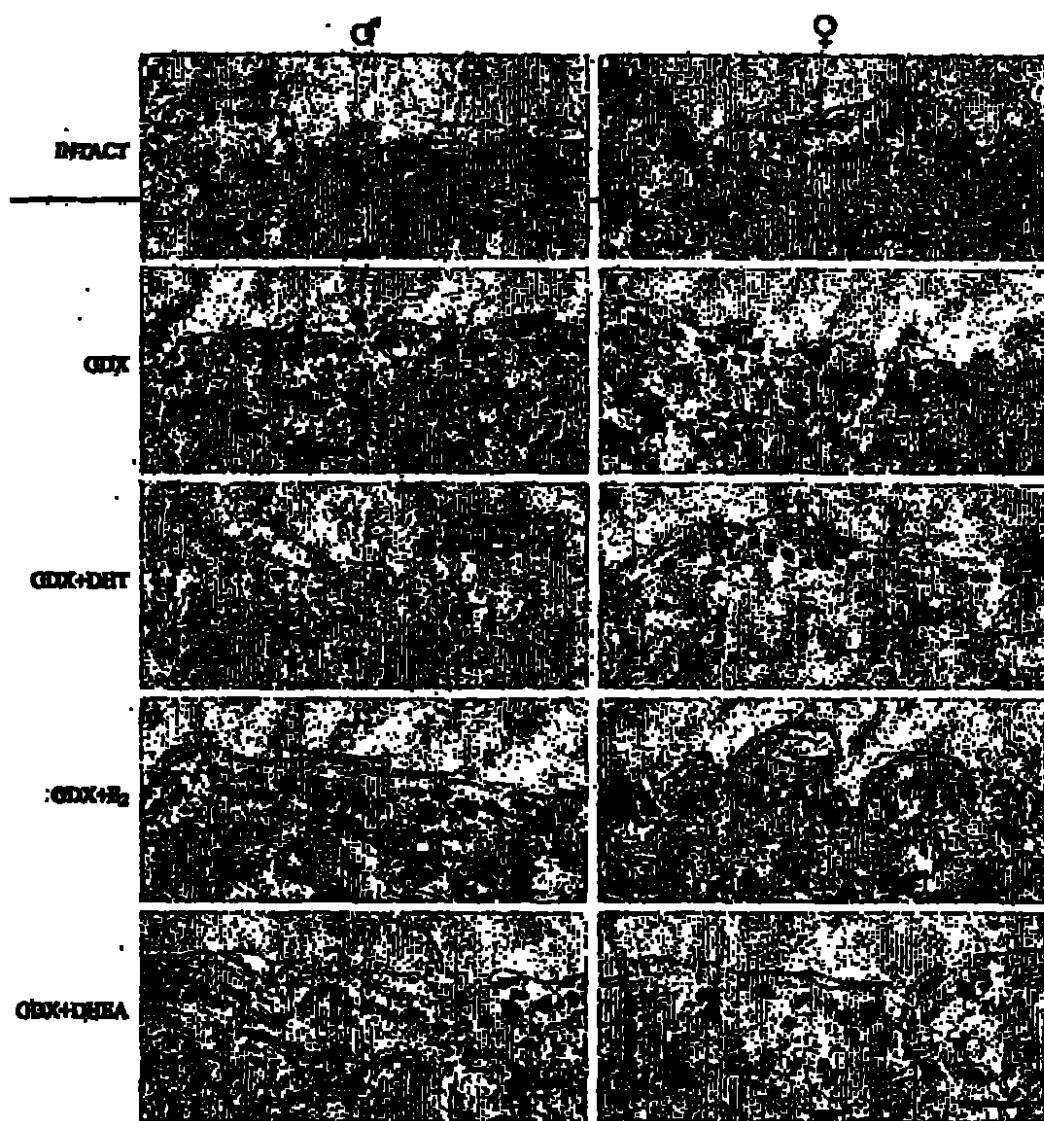


FIGURE 2



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FIGURE 3

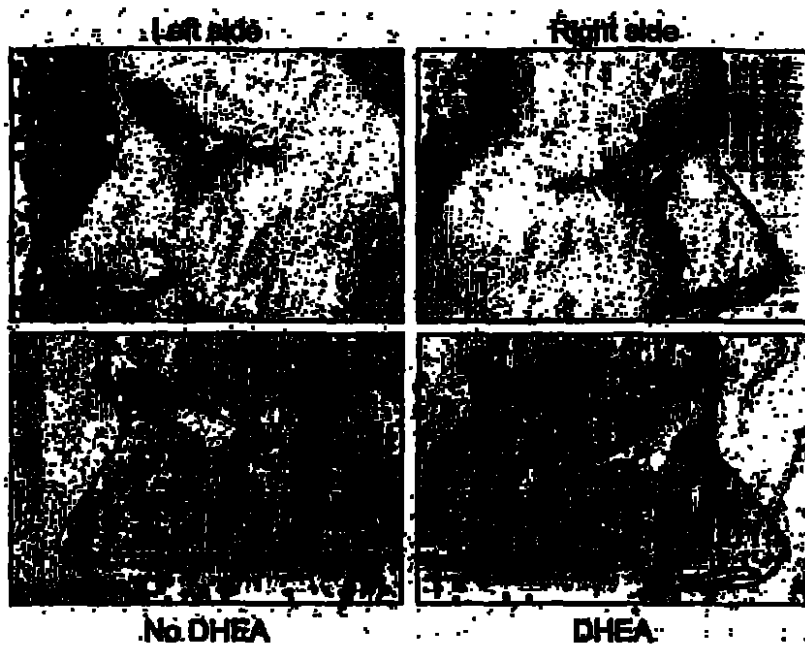


SUBSTITUTE SHEET (RULE 26)

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FIGURE 4



SUBSTITUTE SHEET (RULE 26)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001652

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/568 (2006.01), A61P 17/00 (2006.01), A61Q 19/08 (2006.01), A61Q 19/06 (2006.01)

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)

IPC(7): A61K 31/568, A61P 17/00, A61K 7/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(7): A61K

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

Delphion, USPTO, Espacenet, Pubmed, Scopus, Internet, Canadian Patent db.

Keywords: DHEA, testosterone, skin atrophy, collagen, androgen*, androgen deficiency.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IL 157355D A (DIKSTEIN) 28-03-2004, full document. & WO 2005/030159 A	1-3, 5, 7, 9-15
X	US 5,843,932 B (LABRIE) 01-12-1998, full document.	1-15
X	WO 97/10255 A (KUBERNICK et al.) 20-03-1997	1-15
X	BEULIEU, R. E. et al., Dihydroplandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue, PNAS, 11-04-2000, vol. 97(8), pages 4279-4284.	1-15

[] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:	* Documents published after the international filing date or priority date and not in compliance with the requirements set forth in paragraph 1 of the Rules of the Patent Cooperation Treaty
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"B" earlier application or patent not published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered in view of one or more other prior documents, such combination being obvious to a person skilled in the art
"L" document which may show doubt on priority date or which is cited to establish the publication date of another citation or other special reason (see specification)	"Z" document of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"T" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 February 2006 (14-02-2006)

Date of mailing of the international search report

14 February 2006 (14-02-2006)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer

James Martyn (819) 953-0761

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2003/001652

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim Nos.: 1-10
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-10, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 1-10.
2. ☒ Claim Nos.: 16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 16 is incomplete.
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2005/001652

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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USO DE ANDRÓGENOS PARA REDUCIR LA PROBABILIDAD DE ADQUIRIR
O TRATAR EL ENVEJECIMIENTO DE LA PIEL

CAMPO DE LA INVENCION

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La presente invención se refiere a un método para tratar o reducir la probabilidad de adquirir enfermedades de la piel debido a la deficiencia del andrógeno relacionada con la edad, que comprende administrar una

10 cantidad efectiva de andrógenos o precursores esteroides sexuales y profármacos de los mismos en animales de sangre caliente susceptibles, que incluye a los humanos. En particular, la invención incluye administrar compuestos androgénicos o un precursor esteroides sexuales

15 seleccionados del grupo que consiste en dehidroepiandrosterona (DHEA), sulfato de dehidroepiandrosterona (DHEA-S), y androst-5-en-3 β ,17 β -diol (5-diol), androstendiona, testosterona, DHT, androstandiona y androstan-3 α , 17- β diol o profármaco,

20 compuestos transformados a cualquiera de éstos en vivo. La invención también se refiere a las composiciones farmacéuticas tópicas u orales para practicar el método anterior.

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ANTECEDENTES DE LA INVENCION

El enfoque casi exclusivo en la función de estrógenos ováricos en las mujeres ha quitado la atención de la dramática caída del 70% en el DHEA circulante lo cual ya ocurre entre las edades de 20 a 30 y 50 a 60 años (Migeon et al., 1957, JCEM, 17: 1051-1062; Vermeulen y Verdonck, 1976, JCEM, 42: 247-253; Vermeulen et al., 1982, JCEM, 54: 187-191; Orentreich et al., 1984, JCEM 59: 551-555; Bélanger et al., 1994, JCEM, 79: 1086-1090; Labrie et al., 1997, Labrie et al., 1997, JCEM, 82: 2396-2402). Ya que la DHEA se transforma tanto a andrógenos como a estrógenos en tejidos periféricos, tal caída en el suero DHEA y DHEA-S muestra por qué las mujeres en la menopausia no sólo carecen de estrógenos sino que también se han privado progresivamente de andrógenos durante algunos años.

La marcada reducción en la formación de DHEA-S por las glándulas suprarrenales durante el envejecimiento (Migeon et al., 1957, JCEM, 17: 1051-1062; Vermeulen y Verdonck, 1976, JCEM, 42: 247-253; Vermeulen et al., 1982, JCEM, 54: 187-191; Orentreich et al., 1984, JCEM 59: 551-555; Bélanger et al., 1994, JCEM, 79: 1086-1090) resulta en una caída dramática en la formación de tejido específico de andrógenos y estrógenos en los tejidos

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periféricos al objetivo, una situación que se propone está asociada con las enfermedades relacionadas con la edad que incluye la resistencia a la insulina (Coleman et al., 1982, diabetes, 31: 830-833; Schriock et al., 1988, JCEM, 66: 1329-1331) y obesidad (Nestler et al., 1988, JCEM, 66:57-61; MacEwen y Kurzman, 1988, J Nutrit, 121: S51-S55; Tchernof et al., 1995, Tchernof et al., 1995, Cuidados para la diabetes, 18: 292-299). Es más, se ha prestado mucha atención a los beneficios de DHEA administrada a las mujeres posmenopáusicas, especialmente en el bienestar de hueso, glándulas sebáceas, vagina y después la administración oral (Morales et al., 1994, JCEM, 78: 1360-1367; Baulieu et al., 2000, Proc Natl Acad Sci E.U.A., 87: 4279-4284) así como percutánea (Diamond et al., 1996, J Endocrinol, 150: S43-S50; Labrie et al., 1997, JCEM, 82: 3498-3505) del esteroide precursor.

Los datos muestran la presencia de niveles relativamente altos de andrógenos en mujeres considerablemente normales sugieren que los andrógenos desempeñan un papel fisiológico principal pero hasta ahora no reconocido en las mujeres. De hecho, la caída del 44.5% que ocurre en el suero DHEA desde los 20-30 años de edad a la edad de 40 a 50 años en las mujeres podría explicar bien la pérdida temprana de hueso y la proporción FSH/LH aumentada la cual precede a la disminución perceptible de

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esteroidogénesis ovárica en las mujeres del perimenopáusicas. De hecho, el suero FSH aumenta en las mujeres premenopáusicas incluso antes de que el suero E₂ muestre una disminución (Grodin et al., 1973, JCEM, 36: 207-214). Por otro lado, se reporta que la pérdida de hueso relacionada con la edad empieza durante la cuarta década mientras también se han encontrado cambios en la producción de hueso antes de la menopausia (Riggs et al., 1981, J Clin Invest, 67: 328-335; Mazess et al., 1982, - 10 Clinic Orthop, 165: 239-252; Johnston et al., 1985, JCEM, 61: 905-911). De Conformidad con estos resultados, la densidad ósea fue absolutamente más baja en sitios examinados en mujeres clasificadas como perimenopáusicas comparada con premenopáusicas (Steinberg et al., 1989, 15 JCEM, 69: 533-539).

Hasta hace poco, debido a dificultades de ensayo, únicamente se han medido un número limitado de esteroides de gónadas y suprarrenales circulantes durante edad avanzada, especialmente en mujeres dónde el impacto de 20 andrógenos y estrógenos de origen suprarrenal es de particular importancia (Labrie et al., 1991, Mol Cel Endocrinol, 78: C113-C118). Por lo tanto es bastante notable que la mayoría del declive importante en la DHEA, DHEA-S, androst-5-en-diol-3 β , 17 β -diol (5-diol), 5-diol-G, 25 androstendiona (4-diona) circulante así como los

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metabolitos conjugados de andrógenos, a saber androesterona-glucuronida (ADT-G) y androstano- 3α , 17β -diol glucuronida (3α -diol-G), ocurre entre los rangos de edad de 20-30 y 50-60 años mientras que los cambios 5 relativamente pequeños ocurren después de la edad de 60 años. Por lo tanto es importante notar que en el grupo etario de 50-60 años, el suero DHEA ya ha disminuido a 70% desde los valores pico de 20-30 años de edad (Labrie et al., 1997, JCEM, 82: 2396-2402). Tales datos sugieren que 10 la terapia de reemplazo de hormonas androgénicas debe empezar temprano, teniendo en cuenta la marcada disminución en andrógenos la cual ocurren relativamente temprano durante el envejecimiento de las mujeres.

También se demostró en nuestros estudios 15 anteriores, que la complementación con cantidades fisiológicas de DHEA exógenos permite la biosíntesis de andrógenos y estrógenos únicamente en los tejidos objetivo apropiados los cuales contienen enzimas esteroidogénicas requeridas y tejido específico. Los andrógenos activos y 20 estrógenos sintetizados por lo tanto en los tejidos periféricos específicos ejercen su acción en las mismas células que son responsables de su formación y ocurre una fuga muy pequeña de esteroides activos a la circulación. De hecho, como se menciona anteriormente, se ven los 25 efectos de choque de la administración de DHEA en los



niveles circulantes de los derivados de glucuronida de los metabolitos de DHT, a saber ADT-G y 3 α -diol-G, estos metabolitos se producen localmente en los tejidos intracrinicos periféricos que poseen las enzimas del esteroideogénicas apropiadas para sintetizar la DHT de los precursores suprarrenales DHEA y DHEA-S (Labrie et al., 1991, Mol Cell Endocrinol, 78: C113-C118; Labrie et al. 1996, J Endocrinol, 150: S107-S118). Esta biosíntesis local y acción de andrógenos en los tejidos objetivo eliminan la exposición de otros tejidos a andrógenos activos y por lo tanto minimizan los riesgos de masculinización indeseable u otros efectos colaterales relacionados con los andrógenos. Lo mismo aplica para los estrógenos aunque se cree que todavía no está disponible un parámetro confiable de secreción de estrógeno total (comparable a las glucuronidas para los andrógenos).

La DHEA ha mostrado tener efectos importantes en la piel de individuos de edad avanzada, el más sobresaliente el cual es un aumento en la producción de sebo (Labrie et al., 1997, JCEM, 82: 3498-3505). Esto se ha mostrado en varios estudios realizados en mujeres, particularmente en aquéllos > 70 años de edad quienes son fisiológicamente hipo-seborreicos y por lo tanto se encontró una mejora de su piel con administración de DHEA. La DHEA inducida aumenta la producción de sebo observado

en nuestro estudio es probablemente debido al hecho que las glándulas sebáceas contienen todas las enzimas esteroideogénicas necesarias para catalizar la transformación de DHEA en el andrógeno DHT, y este andrógeno es el estimulador principal de la actividad de la glándula sebácea (Labrie et al., 2000, Horm Res, 54: 218-219; Labrie et al., 2003, End Rev, 24: 152-182).

Aparte de la producción de sebo, se han notado otros efectos benéficos de DHEA en la piel. A la fecha, la evaluación de los aspectos dermatológicos de la administración de DHEA se ha realizado únicamente con algunos detalles en un estudio en el cual se administró oralmente 50 mg de DHEA a sujetos masculinos y femeninos entre las edades de 60 y 79 años, una vez por día durante 1 año. En ese estudio, (Baulieu et al., 2000, Proc Natl Acad Sci E.U.A., 97: 4279 - 4284) se evaluó hidratación de la piel, pigmentación de la piel y espesor de la piel. La hidratación de la superficie de la piel aumentó significativamente para toda la población examinada que se trató con DHEA después de 12 meses de tratamiento. La hidratación de la superficie de la piel se considera un beneficio real para la piel, sobre todo en individuos de edad avanzada ya que en estos individuos la resequedad vuelve la piel áspera. La DHEA también disminuyó significativamente la pigmentación de la piel facial

(amarillez) en toda la población. Esta disminución fue más pronunciada en mujeres > 70 años quienes se interesan más por los cambios de pigmento relacionados con la edad. Los otros dos componentes de color de la piel permanecieron estables durante la duración del estudio (es decir la luminosidad y rojez).

En la patente E.U.A. 5,843,932, se describe un método para tratar la atrofia de la piel o de inhibir la pérdida de colágeno o tejido conectivo por la administración de DHEA, DHEA-S o compuestos convertidos en vivo a cualquiera de los anteriores.

SUMARIO DE LA INVENCION

Es un objetivo de la presente invención proveer métodos efectivos para el tratamiento de enfermedades de la piel debido a la deficiencia del andrógeno relacionada con la edad.

Es otro objetivo de la presente invención proveer métodos efectivos para el tratamiento de la piel debido a la deficiencia del precursor esteroide sexual relacionado con la edad.

Es otro objetivo proveer métodos para reducir el riesgo de adquirir los problemas anteriores.

En una modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir atrofia de la piel, que comprende administrar una cantidad efectiva de andrógenos o profármacos de los mismos, a un
5 paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir pérdida de colágeno, que comprende administrar una cantidad
10 efectiva de andrógenos o profármacos de los mismos, a un paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir pérdida
15 de fibras elásticas, administrar una cantidad eficaz de andrógenos o profármacos de los mismos, a un paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir pérdida
20 de fibras elásticas, administrar una cantidad efectiva de precursor esteroide sexual o profármacos de los mismos, a un paciente con la necesidad de tal tratamiento o reducción de riesgo.

En otra modalidad, la invención pertenece a un
25 método para tratar o reducir el riesgo de adquirir pérdida

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de tejido conectivo, administrar una cantidad efectiva de andrógenos o profármacos de los mismos a un paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un
5 método para tratar o reducir el riesgo de adquirir celulitis, que comprende administrar una cantidad eficaz de andrógenos o profármacos de los mismos a un paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un
10 método para tratar o reducir el riesgo de adquirir formación de arrugas, administrar una cantidad efectiva de andrógenos o profármacos de los mismos a un paciente con necesidad de tal tratamiento o reducción del riesgo.

En otra modalidad, la invención pertenece a un
15 método para tratar o reducir el riesgo de adquirir celulitis, que comprende aumentar niveles de un precursor esteroide sexual seleccionado del grupo que consiste en dehidroepiandrosterona (DHEA), sulfato de dehidroepiandrosterona (DHEA-S), y androst-5-en-3 β ,17 β -
20 diol (5-diol), en un sujeto o paciente con la necesidad de dicho tratamiento o dicho precursor esteroide.

En otra modalidad, la invención pertenece a un
método para tratar o reducir el riesgo de adquirir formación de arrugas, que comprende aumentar niveles de un
25 precursor esteroide sexual seleccionado del grupo que

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consiste en dehidroepiandrosterona (DHEA), sulfato de dehidroepiandrosterona (DHEA-S), y androst-5-en-3 β ,17 β -diol (5-diol), en un sujeto o paciente con la necesidad de dicho tratamiento o dicho precursor esteroide.

5 En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir pérdida de fibras elásticas, que comprende que comprende aumentar niveles de un precursor esteroide sexual seleccionado del grupo que consiste en dehidroepiandrosterona (DHEA),
10 sulfato de dehidroepiandrosterona (DHEA-S), y androst-5-en-3 β ,17 β -diol (5-diol), en un sujeto o paciente con la necesidad de dicho tratamiento o dicho precursor esteroide.

En otra modalidad, la invención pertenece a un
15 método para tratar o reducir el riesgo de adquirir atrofia de la piel, que comprende administrar androstendiona, androstandiona, testosterona, dihidrotestosterona, 5 α -androstano-3 α , 17 β -diol o compuestos transformados en éstos, a un sujeto o paciente con necesidad de dicho
20 tratamiento.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir pérdida de colágeno, que comprende administrar androstendiona, androstandiona, testosterona, dihidrotestosterona, 5 α -
25 androstano-3 α , 17 β -diol o compuestos transformados en

éstos, a un sujeto o paciente con necesidad de dicho tratamiento.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de pérdida de
5 fibras elásticas, que comprende administrar androstendiona, androstandiona, testosterona, dihidrotestosterona, 5α -androstandio-3 α , 17β -diol o compuestos transformados en éstos, a un sujeto o paciente con necesidad de dicho tratamiento.

10 En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de pérdida de tejido conectivo, que comprende administrar androstendiona, androstandiona, testosterona, dihidrotestosterona, 5α -androstandio-3 α , 17β -diol o
15 compuestos transformados en éstos, a un sujeto o paciente con necesidad de dicho tratamiento.

En otra modalidad, la invención pertenece a un método para tratar o reducir el riesgo de adquirir arrugas, que comprende administrar androstendiona,
20 androstandiona, testosterona, dihidrotestosterona, 5α -androstandio-3 α , 17β -diol o compuestos transformados en éstos, a un sujeto o paciente con necesidad de dicho tratamiento.

En otra modalidad, la invención pertenece a un
25 método para tratar o reducir el riesgo de adquirir

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celulitis, que comprende administrar androstendiona, androstandiona, testosterona, dihidrotestosterona, 5 α -androstandiona, 17 β -diol o compuestos transformados en éstos, a un sujeto o paciente con necesidad de dicho

5 tratamiento.

En otro aspecto, la invención provee composiciones farmacéuticas tópicas que contienen los andrógenos junto con diluyentes o vehículos transmisores aceptables farmacéuticamente.

10 En una modalidad, el precursor es DHEA.

En otra modalidad, el andrógeno es testosterona o sus derivados.

Como se utiliza en la presente invención, un andrógeno es un compuesto (o uno de sus metabolitos) que

15 tiene un valor K_i para el receptor andrógeno humano por lo menos de aproximadamente $2 \times 10^{-6} M$ y un efecto inhibitorio mediante receptor andrógeno en el crecimiento de las células ZR-75-1 del cáncer de mama humano el cual alcanza el valor máximo-medio en una concentración por debajo de

20 10 nanomoles por litro o un compuesto (o uno de sus metabolitos) el cual responde positivamente al método de detección descrito en la solicitud provisional E.U.A. titulada "Método para la determinación de actividad anabólica" con fecha 30 de agosto de 2004, solicitud

25 60/606,174.

Un paciente con necesidad de tratamiento o de reducción de riesgo de ataque de una enfermedad dada es aquel que ha sido diagnosticado con tal enfermedad o aquel susceptible a adquirir tal enfermedad.

5 Excepto dónde se declare de otra forma, la dosificación preferida de los compuestos activos (concentraciones y modos de administración) de la invención es idéntica para propósitos terapéuticos y profilácticos. La dosificación para cada componente activo
10 discutido en la presente invención es el mismo sin tomar en cuenta la enfermedad de que se trate (o de la enfermedad cuya la probabilidad de ataque se reduce).

 Excepto cuando se haga notar de otra manera o donde quede claro por el contexto, las dosificaciones
15 referidas por la presente invención para el peso de compuestos activos no afectados por los excipientes farmacéuticos, diluyentes, vehículos transmisores u otros ingredientes, aunque tales ingredientes adicionales se incluyen deseablemente en la presente invención, como se
20 muestra en los ejemplos de la misma. Cualquier forma de dosificación, especialmente las fórmulas tópicas (gel, loción, crema, ungüento o similares) utilizadas normalmente en la industria farmacéutica son apropiadas para el uso en la presente invención, y los términos
25 "excipiente", "diluyente" o "vehículo transmisor" incluyen

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tales ingredientes no activos como se incluyen típicamente, junto con los ingredientes activos en tales formas de dosificación en la industria. Por ejemplo, se pueden incluir crema típica, agente penetrante, 5 preservativos, o similares para las fórmulas tópicas.

Todos los ingredientes activos utilizados en cualquiera de las terapias discutidas en la presente invención se pueden formular en composiciones farmacéuticas las cuales también incluyen uno o más de los 10 otros ingredientes activos. Alternativamente, cada uno se puede administrar por separado pero lo suficientemente simultáneos para que un paciente que eventualmente tenga niveles sanguíneos elevados o por otra parte que goce de los beneficios de cada uno de los ingredientes activos (o 15 estrategias) simultáneamente. En algunas modalidades preferidas de la invención, por ejemplo, uno o más ingredientes activos se formularán en una sola composición farmacéutica.

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BREVE DESCRIPCIÓN DE LAS FIGURAS

La figura 1A muestra la comparación entre la piel dorsal de un ratón macho y uno hembra. (A) secciones de parafina de la piel dorsal de un ratón manchó teñida con 25 hematoxilina y eosina. a) En el macho intacto, todos los

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folículos de pelo están en la fase telogen y se localizan en la dermis la cual colinda con una capa delgada de hipodermis. b) En la hembra intacta, todos los folículos de pelo están también en fase telogen, mientras que la 5 hipodermis es más gruesa comparada con la del macho, y la dermis es más angosta. c) Después de GDX, los folículos de pelo del macho están en la fase anagen. d) En la hembra GDX, todos los folículos de pelo están en la fase anagen. Epidermis (E), dermis (D), hipodermis (H), panniculus 10 carnosus (PC) y folículos de pelo (HF). Escala = 100 μ m. La figura 1B es una comparación entre el espesor de piel total del macho y de la hembra así como el espesor de cada capa de la piel (epidermis, dermis e hipodermis) en animales intactos y GDX y en animales GDX tratados con 15 DHT, E_2 o DHEA. Los valores se presentan como significa $\pm$ SEM. * $p < 0.05$ contra el control macho GDX; ** $p < 0.01$ contra el control hembra GDX (prueba de rango múltiple de Duncan-Kramer).

La figura 2 muestra la expresión de receptor 20 andrógeno (AR) en la epidermis de la piel dorsal del ratón. Se encontró que el AR se localiza exclusivamente en el núcleo) en el macho intacto, se etiqueta la mayoría de núcleos epidérmicos, b) en la hembra intacta, la mayoría de núcleos epidérmicos se etiqueta pero la intensidad del 25 etiquetado es menor que en el macho. Tres semanas después

de GDX, no se pudo detectar ningún etiquetado en los machos GDX (c) ni en las hembras GDX (d). Cuando los ratones macho (e) y hembra (f) GDX se trataron con DHT, se observó etiquetado AR considerable en la mayoría de los núcleos de células epidérmicas. Cuando machos (g) y hembras (h) GDX recibieron E_2 , se observó etiquetado AR débil en algunos núcleos. Similar al tratamiento de DHT, cuando los machos GDX (i) y hembras (j) recibieron DHEA, se observó un etiquetado considerable en la mayoría de los núcleos epidérmicos. Escala = 20 μ m.

La figura 3 y la figura 4 muestran una comparación de la piel de la cara tratada con DHEA (lado derecho de la cara) o sin tratar (lado izquierdo de la cara). Trescientos microlitros (0.3ml) de emulsión, que contiene DHEA se aplicaron en la frente y en el lado derecho de la cara durante 13 semanas.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención muestra que se vio un efecto mayor de andrógenos en el espesor dérmico. De hecho, se sabe que el colágeno y las fibras elásticas son el elemento principal de la dermis que provee un soporte mayor para la resistencia de la piel, que incluyen un posible papel en la formación de arrugas. Se observó un

aumento en el espesor dérmico después de DHT y de tratamiento de DHEA en las hembras GDX, (figura 1) mientras, bajo todas las condiciones experimentales, la dermis es más gruesa en los machos, lo que posiblemente explica la falta de efecto de andrógenos en el macho durante un período de tratamiento de 3 semanas. Se ven diferencias de género llamativas en la hipodermis de animales intactos, por lo que provee además similitudes con la piel humana (Hattori et al, 1993) y sugiere que el DHEA y los andrógenos podrían ser beneficiosos para reducir el riesgo de adquirir o tratar celulitis.

Utilizando el ratón como modelo, la presente invención establece claramente las diferencias morfológicas entre los machos y hembras en las diferentes capas de la piel y accesorias del ratón. Es más, se ha identificado la función específico y diferencial de los andrógenos y estrógenos en sitios diferentes lo que provee evidencia de una acción de la DHEA por medio de andrógenos en la dermis y estrógenos en la epidermis.

El ingrediente activo para aplicación tópica está preferentemente presente de 0.05% a 20% por peso con relación al peso total de la composición farmacéutica, más preferentemente entre 0.1 y 10% de DHEA o 5-diol y entre 0.1% y 3% para un andrógeno. Alternativamente, el ingrediente activo se puede colocar en un parche trans-

dermal que tiene estructuras conocidas en la técnica, por ejemplo, las estructuras tales como aquellas establecidas en la Patente E.P. No.0279982.

Cuando se fórmula como un ungüento, loción, gel o
5 crema o similares, el compuesto activo se mezcla con un
vehículo transmisor conveniente el cual es compatible con
mucosa o piel humana. Los vehículos transmisores
convenientemente se conocen en la técnica e incluyen pero no
se limitan a Klucel HF y base Glaxal. Por ejemplo, algunos
10 están comercialmente disponibles la base Glaxal está
disponible de Glaxal Canadá Limited Company. Se pueden
encontrarse otros vehículos transmisores convenientes en
Koller y Buri, S.T.P. Pharma 3(2), 115-124, 1987. El
vehículo transmisor es preferentemente uno que tenga
15 ingrediente(s) activo(s) solubles a temperatura ambiente
en la concentración de ingredientes activos que se
utiliza. El vehículo transmisor debe tener la viscosidad
suficiente para mantener el esteroide en una área
localizada de piel o mucosa en la cual se ha aplicado la
20 composición, sin correrse o evaporarse por un lapso
suficiente para permitir la penetración sustancial del
precursor o andrógeno a través del área localizada de piel
o mucosa para causar un efecto clínico deseable. El
vehículo transmisor típicamente es una mezcla de varios
25 componentes, por ejemplo, solventes farmacéuticamente

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aceptables y un agente espesante. Una mezcla de solventes orgánicos e inorgánicos pueden ayudar con la solubilidad hidrofílica y lipofílica, por ejemplo agua y alcohol como etanol y propilenglicol.

- 5 Los precursores esteroide sexuales preferidos son dehidroepiandrosterona (DHEA) (disponible de Diosynth Inc., Chicago, Illinois, E.U.A.), 5-androsten-3 β ,17 β -diol (disponible de Steraloids, Wilton, New Hampshire E.U.A.).

- Otro precursor esteroide sexual preferido tiene
10 4-androsten-3,17-diona, disponible de Sigma-Aldrich Canadá Ltd., Oakvill, Ontario, Canadá.

Un andrógeno preferido de la invención es estanolona (5 α -androstando-17 β -ol-3-ona, DHT), disponible de Sigma-Aldrich Canadá Ltd., Oakvill, Ontario, Canadá.

- 15 Otro andrógeno preferido es AndroGel un gel que contiene 1% de testosterona en alcohol, agua, Carbopol 980 NF, isopropil miristato y 0.1 hidróxido de sodio M, y disponible de Solvay Pharma, Markham, Ontario, Canadá.

- Un andrógeno preferido para acción sistémica es
20 Androderm, un parche que contiene 12,2 mg o 24.3 mg de testosterona, disponible de Laboratoires Paladín Inc., Montreal, Quebec, Canadá.

- Otros ésteres de testosterona (undecanoato de testosterona, disponible de Organon Canadá Ltd.,
25 Scarborough, Ontario, Canadá, bajo el nombre de andriol,

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enantato de testosterona, disponible de Theramed Corporation, Mississauga, Ontario, Canadá bajo el nombre de Delatestryl, cipionato de testosterona disponible de Pfizer Canadá, Kirland, Canadá bajo el nombre de Depo-
5 testosterona (cipionato) o de Sabex, 2002 Inc., Boucherville, Qc, Canadá bajo el nombre de inyección de cipionato de testosterona (USP) y derivados [es decir nandrolona (19-nor testosterona) y también se prefieren ésteres (decanoato de nandrolona disponible de Organo
10 Canadá, Ltd. Scarborough Ontario Canadá bajo el nombre de Deca-Durabolin), metiltestosterona disponible de Sigma-Aldrich Canadá Ltd., Oakvill, Ontario, Canadá.

También se prefiere que el andrógeno 5 α -androstan-3 α ,17 β -diol y 5 α -androstan-3,17-diona, ambos
15 disponibles de Sigma-Aldrich Canadá Ltd., Oakvill, Ontario, Canadá.

Se prefiere que el precursor esteroide sexual o el andrógeno se formulen como un gel de alcohol que contiene 1.0 a 10% de triglicérido caprílico-cáprico
20 (Neobee M-5); de 10 a 20% de glicol hexileno; de 2.0 a 10% dietilenglicol monometil éter (Transutol); de 2.0 a 10% de Ciclometicona (Dow Corning 345); de 1.0 a 2% de alcohol bencílico y de 1.0 a 5.0% de hidroxipropilcelulosa (Klucel HF).

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También se prefiere que el precursor esteroide sexual o el andrógeno se formule como una crema que contiene de 2.0 a 4.0% de copoliol Laurilmeticona, de 5.0 a 7.0% Ciclometicona, de 2.0 a 4.0% de aceite mineral, de 5 6.0 a 8.0% de isononoato Cetearil, de 0.5 a 1.5% de Eumulgin B₂, de 0.01 a 0.1% de hidroxitolueno butilado, de 49.0 a 60.0% Propilenglicol, 10 a 20% de agua, de 0.5 a 1.5% de sulfato de Magnesio, de 4.0 a 6.0% de etanol y de 0.1 a 3.0% de precursor esteroide sexual o andrógeno.

10 También se prefiere que el precursor esteroide sexual o el andrógeno se formule como una crema que contiene de 0.1 a 10% de precursor esteroide sexual o andrógeno, de 10 a 25% de Cera emulsificadora, de 5 a 20% de Aceite de mineral ligero, de 0.5 a 2.0% de alcohol 15 bencílico, de 20 a 40% de Etanol al 95% y de 20 a 40% de agua.

También se prefiere que el precursor esteroide sexual o el andrógeno se formule como una crema que contiene de 0.1 a 10% de precursor esteroide sexual o 20 andrógeno, de 2 a 10% de alcohol cetílico, de 5 a 10% Cera de ésteres de cétilo, de 0.25 a 0.5% de alcohol de Feniletíl, de 5 a 10% de Cera blanca, de 20 a 40% de agua, de 20 a 40% de Glicerol, de 2.0 a 10.0% de Aceite mineral, de 1.0 a 5.0% de Sulfato láurico de sodio, de 3.0 a 6.0%

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de Monoestearato glicerilo, de 3.0 a 6.0% de Monoestearato de glicol propilo, y de 1 a 5.0% de Estearato de metilo.

También se prefiere que el precursor esteroide sexual o el andrógeno se formule para administración oral
5 como una cápsula que contiene de 10 a 50 mg de precursor esteroide sexual o derivado de andrógeno.

El vehículo transmisor normalmente también puede incluir varios aditivos utilizados en ungüentos y lociones y bien conocidas en las técnicas cosméticas y médicas. Por
10 ejemplo, pueden estar presentes fragancias, antioxidantes, perfumes, agentes gelificantes, agentes espesores tal como carboximetilcelulosa, agentes tensioactivos, estabilizadores, emolientes, agentes colorantes y otros agentes similares.

Preferentemente, el médico que atiende
15 supervisara, especialmente al principio de tratamiento, la respuesta general de un paciente individual y los niveles de suero DHEA o andrógeno y, sobre todo, supervisar la respuesta general del paciente al tratamiento, las
20 dosificaciones de ajuste como requisito dónde el metabolismo de un paciente dado o la reacción al tratamiento son atípicos.

La dosis típica administración tópica de precursor esteroide sexual o andrógeno es de 5 mgs a 200

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mgs de ingrediente activo por día, por cada 50 kgs de peso corporal, preferentemente de 20 a 60 mgs por día.

Si se selecciona administración oral se debe administrar de 10 a 100 mg del ingrediente activo una vez por día por cada 50 kg de peso del cuerpo.

EJEMPLOS

EJEMPLO 1

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Materiales y métodos

Animales y tratamientos

Se obtuvieron cincuenta y seis ratones machos y hembras C57BL6 adulto de 13-15 semanas de edad de Harlan Laboratory (Indiana, E.U.A.). Los ratones se distribuyeron al azar en 4 grupos de 7 animales por grupo de la siguiente manera: (1) control intacto; (2) control GDX; (3) GDX+DHT (0.1mg/ratón); (4) GDX+DHEA (6.25mg/ratón). En el día uno del estudio, se realizó GDX bilateral como se describe (Castro, 1974 y Fleischman, 1981) en todos los animales excepto aquéllos del primer grupo con operación simulada. A partir del segundo día después de GDX y durante tres semanas, se administra DHEA de forma oral diariamente como suspensión en 0.4% metilcelulosa y 5% etanol a los animales de los grupos apropiados. Se

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trataron los animales de los grupos de control intacto y GDX solamente con el vehículo durante el mismo periodo. Seis horas después del último tratamiento, todos los animales se sacrificaron.

5 Las dosis orales de DHEA se seleccionaron con base en los estudios anteriores publicados (Labrie et al, 1996; Labrie et al, 2003b). Por lo tanto, las dosis fisiológicas seleccionadas invirtieron completamente la atrofia inducida por GDX de los órganos sensibles a
10 hormonas y llevaron al peso del órgano similar al encontrado en los animales intactos. Ya que se sabe que la DHT es pobremente activo por ruta oral, se inyectó hipodérmicamente. Para determinar la dosis de DHT, se realizó un estudio dosis-rango preliminar (ver material
15 suplementario en línea, Tabla en línea S1).

Procesamiento del tejido

Después de rasurar el pelo largo, se cortó la piel dorsal, se aplanó y se sumergió inmediatamente en
20 solución con pH regulado en formalina al 10%. Se incluyó una muestra en bloques de parafina las cuales se cortaron y tiñeron rutinariamente secciones de 4µm. La otra parte de la piel se utilizó para la técnica completa de montaje como se describe (Badertscher JA, 1940, tinte Technol, 15:
25 29-30).

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Análisis del espesor de la piel

Bajo la luz del microscopio, se realizaron
5 medidas utilizando IMAGE-PRO PLUS (Media Cybernetics,
E.U.A.). Se anotaron veinticinco lecturas de cada capa de
la piel de cada animal. Se midió el espesor epidérmico de
la capa basal a la capa granulosa (excluyendo la capa
córnea), considerando que el espesor dérmico es la
10 distancia entre la epidermis y la hipodermis. Finalmente,
se midió el espesor hipodérmico como la distancia entre la
dermis y el pániculo carnososo.

Inmunohistoquímica

15 Se desparafinaron y re-hidrataron las secciones
de parafina. Se eliminó la actividad peroxidasa endógena
por preincubación en 3% de H_2O_2 en metanol por 30 min. Se
aplicó una técnica de recuperación por microonda que
utiliza regulador de pH de citrato (Tacha et Chen, 1994),
20 y se neutralizaron los sitios de unión no específicos con
suero de cabra al 10%. Se incubaron entonces las secciones
por 60 min. a temperatura ambiente con clon MIB-5 de
anticuerpo de anti-Ki-67 ratón (1:60) (Dako Diagnostic,
CA, E.U.A.) o por 90 min. a temperatura ambiente con
25 receptor antiandrógeno de conejo anticuerpo (AR) (1:300)

(N-20; Santa Cruz Biotechnology, Inc., CA, E.U.A.). Se utilizarón kit Zymed SP (San Francisco, CA, E.U.A.) y kit Vectastain Elite ABC (Vector Laboratories, Inc., Burlingame, CA, E.U.A.) para AR, y anticuerpos Ki-67, respectivamente. En la supervisión bajo el microscopio, el se utilizó diaminobenzidina como cromógen. Para la evaluación de Ki-67, se calculo el índice de etiquetado de 400 células de cada animal.

10 Análisis estadístico

Se expresaron los datos como significa + S.E.M.. La importancia estadística se determino según la prueba de rango múltiple de Duncan-Kramer (Kramer CY, 1956, Biometrics, 12: 307-310).

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Los resultados

El examen morfológico de piel dorsal de ratones macho y hembra de 16 a 18 semanas de edad revela que se ven claramente las diferencias de género en el espesor general de la piel y en las proporciones de las diferentes capas de la piel (figuras 1A y 1B). De hecho, la mayor diferencia es que la dermis en el macho es mucho más gruesa que en la hembra mientras que la epidermis e hipodermis son más gruesas en la hembra, lo que resulta

por lo tanto en el total de la piel que es 40% más gruesa en el macho.

Epidermis

5 La epidermis de las hembras intactas es aproximadamente 40% más gruesa que en los machos ($p < 0.01$). Tres semanas después de GDX, el espesor epidérmico de las hembras disminuyó por en un 40% ($p < 0.01$) mientras que, se observó un 13% aumento después del tratamiento de DHEA
10 ($p < 0.05$).

 Como se indicó por el número de células basales positivas Ki-67, se encontró que la proliferación celular es superior en las hembras intactas (11.8 ± 0.7 contra 9.3 ± 0.4 , $p < 0.05$), lo que indica una diferencia de género.
15 Además, 3 semanas después de GDX, el nivel de proliferación celular disminuyó en las hembras a 27% (8.6 ± 0.7 , $p < 0.01$), se observó un valor similar en los machos intactos. Se encontró que la intensidad de inmunidad AR es ligeramente superior en los machos intactos que en las
20 hembras (figuras 2a, 2b). Tres semanas después de GDX, la expresión AR disminuyó en las células epidérmicas del macho, a un nivel similar al de las hembras (figuras 2c, 2d). Cuando los animales GDX recibieron DHT o DHEA, se observó una expresión AR considerable tanto en machos como
25 en hembras (figuras 2e, 2i, 2f, 2j).

d

Dermis

En los animales intactos, la dermis fue 190% más gruesa en el macho comparado con la hembra ($p < 0.01$). Después de GDX, aumentó el espesor dérmico de la hembra a 22% ($p < 0.05$) mientras que no fue estadísticamente significativa la disminución del 7% en el macho. Únicamente en las hembras GDX, los tratamientos DHT y DHEA significativamente aumentaron el espesor dérmico en un 47% ($p < 0.01$) y 19% ($p < 0.05$), respectivamente.

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Hipodermis

La hipodermis en la hembra intacta fue aproximadamente de 11 pliegues más gruesa que en el macho ($p < 0.01$). Como se ve en la figura 1B, después de GDX, el espesor hipodérmico tanto en los ratones macho y hembras ($p < 0.01$) mientras están en tratamiento con DHT, E_2 o DHEA disminuyó notablemente el espesor de ipodérmico en los animales GDX de ambos sexos ($p < 0.01$). Estos resultados son buena indicación de que el tratamiento con DHT, E_2 o DHEA es eficaz para el tratamiento de celulitis.

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d

TABLA 1

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	Epidermis				Dermis				Hipodermis			
	♂		♀		♂		♀		♂		♀	
	T	%	T	%	T	%	T	%	T	%	T	%
Intacto	9.4±0.3	1.8	9.4±0.4 ⁺⁺	3.6	500±10.2	94.9	171±13.3 ⁺	46	18±1.5 ⁺⁺	3.3	187±1.5 ⁺⁺	50.4
GDX	9.4±0.2	1.7	9.3±0.2	1.6	463±21.3	84.1	209±10.4	35	78±5.8	14.2	378±3.9	63.4
GDX+DHT	10±0.2	2.1	9.6±0.2	205	451±24.1	93	307±13.3 ⁺⁺	79.5	24±1.9 ⁺⁺	4.9	70±4.6 ⁺⁺	18
GDX+DHEA	8.9±0.3	1.7	10.5±0.3 ⁺	3.2	486±28.7	92.8	249±11.8	75.8	29±6.2 ⁺⁺	5.5	69±4.5 ⁺⁺	21

Tabla 1.- Diferencias de género en proporciones relativas de las diferentes capas de la piel. Se presentan los valores como significan + SEM.**, p<0.01, experimental contra macho GDX; ++, p<0.01, experimental contra hembra GDX; +, p<0.05, experimental contra hembra GDX (prueba de rango múltiple de Duncan-Kramer). T: Espesor (µm); %: Proporción de cada capa de la piel.

ef

EJEMPLO 2**Protocolo ERC-202****Plan de estudio**

5 Este estudio es un ensayo de placebo-controlado a doble ciego aleatorizado de 15 sujetos por brazo. El estudio se dividió en dos fases, un período de detección y un período de tratamiento de 13 semanas.

10 **Sujetos y tratamiento**

Después de que se obtuvo del consentimiento informado por escrito, y se encontraron mujeres elegibles, cada sujeto recibió de manera aleatorizada ya sea un 0.0% (placebo), un 0.1%, un 0.3%, un 1% o una 2% de emulsión de DHEA dos veces por día en la mañana y tarde.

Diariamente, antes del desayuno, y después de la cena, durante 13 semanas, los sujetos recibieron 3.0 ml de una de las cinco emulsiones.

Se instruyó a todos los sujetos, para como
20 aplicar el tratamiento del estudio en la cara (lado derecho) y frente, tórax superior, dorso de manos, dorso de brazos, cara externa de muslos y piernas, dos veces diariamente (en la mañana entre las 06:00 y las 09:30 hrs. y en la tarde entre las 18:00 y las 21:30 hrs.) durante 13
25 semanas. La primera aplicación del tratamiento del estudio

se llevó a cabo en el sitio de la investigación dónde se instruyó a los sujetos de cómo aplicar la emulsión tópica. Se aplicaron trescientos micro-litros (0.3ml) de emulsión en la frente y cara (lado derecho), 0.3 ml por dorso de 5 brazo y dorso de mano (0.3 ml x2), 0.3ml en el tórax superior, 0.6 ml por muslo (0.6 ml x2) y 0.3 ml por pierna (0.3 ml x2) para una dosis total de 3.0 ml de emulsión de DHEA dos veces diariamente.

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EJEMPLOS DE LA COMPOSICIÓN FARMACÉUTICA

Como se establece a continuación a modo de ejemplo y no de limitación, son varias composiciones farmacéuticas tópicas que utilizan el precursor esteroide 15 sexual activo preferido DHEA, andrógenos preferidos. Se puede variar la concentración del ingrediente activo en una amplia gama como se discutió en la presente invención. Las cantidades y tipos de otros ingredientes que se pueden incluir se conocen bien en la técnica.

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EJEMPLO A

Crema tópica

	Ingrediente	% Peso (en peso de la composición total)
5	DHEA	1.0
	Cera Emulsificante, NF	18.0
	Aceite mineral ligero, NF	12.0
	Alcohol benzílico	1.0
	Etanol 95% USP	34.0
10	Agua purificada, USP	34.0

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EJEMPLO BCrema tópica

Crema 0.1% DHEA (Fórmula No 0759-0435)

5	Ingrediente	% Peso (en peso de la composición total)
	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	6.0
10	Marcol 82	3.0
	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
15	Propilen Glicol	58.4
	DHEA, GMP	0.1
	Agua, USP	15.4
	Sulfato de Magnesio, 7 H2O	1.0
20	Etanol absoluto USP	5.0
	Total:	100.0

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EJEMPLO CCrema tópica

Crema 0.1% DHEA (Fórmula No 0759-0435)

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	6.0
10	Marcol 82	3.0
	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
15	Propilen Glicol	58.4
	DHEA, GMP	0.3
	Agua, USP	15.2
	Sulfato de Magnesio, 7 H2O	1.0
20	Etanol absoluto USP	5.0
	Total:	100.0

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EJEMPLO DCrema tópica

Crema 0.3% DHEA (Fórmula No 0759-0484)

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	10.
	Primol 352	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
	Propilen Glicol	49.60
15	DHEA, GMP	0.3
	Agua, USP	20.00
	Sulfato de Magnesio, 7 H2O	1.0
	Etanol absoluto USP	5.0
20	Total:	100.0

EJEMPLO ECrema tópica

Crema 1.0% DHEA (Fórmula No 0759-0435)

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	6.0
	Marcol 82	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
	Propilen Glicol	58.4
15	DHEA, GMP	1.0
	Agua, USP	14.5
	Sulfato de Magnesio, 7 H2O	1.0
	Etanol absoluto USP	5.0
20	Total:	100.0

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EJEMPLO F**Crema tópica****Crema 1.5% DHEA (Fórmula No 484-12-1.5%)**

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	5.0
	Primol 352	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.090
	Propilen Glicol	45.41
15	Etanol USP	14.0
	DHEA, GMP	1.5
	Agua, USP	14.0
	Sulfato de magnesio, 7 H2O	0.65
20	Etanol USP	5.35
	Total:	100.0

EJEMPLO G**Crema tópica****Crema 1.5% DHEA (Fórmula No 435-3-1.5%)**

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	6.0
	Primol 352	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	1.0
	Propilen Glicol	58.41
15	DHEA, GMP	1.5
	Agua, USP	14.0
	Sulfato de Magnesio, 7 H2O	1.0
	Etanol USP	5.0
20	Total:	100.0

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EJEMPLO H**Crema tópica****Crema 1.5% DHEA (Fórmula No 47-1.5%)**

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasol CM5)	5.0
	Aceite mineral	3.0
10	2-etilhexil estearato	10.0
	Cutina E24	1.0
	B.H.T	0.090
	Propilen Glicol	45.51
	DHEA, GMP	1.5
15	Agua, USP	15.0
	Sulfato de Magnesio, 7 H2O	0.65
	Etanol USP	5.25
20	Total:	100.0

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EJEMPLO I**Crema tópica****Crema 2.0% DHEA (Fórmula No 0759-0435)**

	Ingrediente	g Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasil CM5)	6.0
	Marcol 82	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
	Propilen Glicol	58.4
15	DHEA, GMP	2.0
	Agua, USP	13.5
	Sulfato de Magnesio, 7 H2O	1.0
	Etanol absoluto USP	5.0
20	Total:	100.0

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EJEMPLO J

Capsula de gelatina

Crema 0.3% Testosterona

	Ingrediente	% Peso (en peso de la composición total)
5	Laurilmeticona copoliol (DC Emulsificante 10)	3.0
	Ciclometicona (Mirasil CM5)	10.0
	Primol 352	3.0
10	Cetearil isononato (Cetiol SN)	7.0
	Eumulgin B2	1.0
	B.H.T	0.1
	Propilen Glicol	49.60
15	Testosterona GMP	0.3
	Agua, USP	20.00
	Sulfato de Magnesio, 7 H2O	1.0
	Etanol absoluto USP	5.0
20	Total:	100.0

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EJEMPLO K**Crema tópica****Crema 0.3% DHEA**

	Ingrediente	% Peso (en peso de la composición total)
5	Alcohol Cetil	8.0
	Aceite mineral	7.0
	Cera Cetil Éster	4.0
	Cera blanca	6.0
10	Gliceril de monoestearato,	4.0
	Propil Glicol de monoestearato	2.0
	Estearato de metil	1.0
	Alcohol peniletil	0.5
15	Glicerol	44.70
	DHEA GMP	0.30
	Agua, USP	21.50
	Sulfato de Sodio Lauril	1.0
20	Total:	100.0

EJEMPLO LCrema tópicaCrema 0.3% DHT

	Ingrediente	% Peso (en peso de la composición total)
5	Alcohol Cetil	8.0
	Aceite mineral	7.0
	Cera Cetil Éster	4.0
	Cera blanca	6.0
10	Gliceril de monoestearato,	4.0
	Propil Glicol de monoestearato	2.0
	Estearato de metil	1.0
	Alcohol peniletil	0.5
15	Glicerol	44.70
	DHEA GMP	0.30
	Agua, USP	21.50
	Sulfato de Sodio Lauril	1.0
20	Total:	100.0

EJEMPLO M**Crema tópica****Crema 0.3% Testosterona**

	Ingrediente	% Peso (en peso de la composición total)
5	Alcohol Cetil	8.0
	Aceite mineral	7.0
	Cera Cetil Éster	4.0
	Cera blanca	6.0
10	Gliceril de monoestearato,	4.0
	Propil Glicol de monoestearato	2.0
	Estearato de metil	1.0
15	Alcohol peniletil	0.5
	Glicerol	44.70
	Testosterona GMP	0.30
	Agua, USP	21.50
	Sulfato de Sodio Lauril	1.0
20	Total:	100.0

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EJEMPLO NCrema tópicaGel 10.0% DHEA

	Ingrediente	% Peso (en peso de la composición total)
5	DHEA	10.0
	Capril- capricho Triglicérido (Neobee M-5)	5.0
	Hexilen glicol NF	15.0
10	Transcutol (dietilenglicol monometil éter)	5.0
	Alcohol Bencílico	2.0
	Ciclometicona (Dow Corning 345)	5.0
15	Etanol (absoluto) USP	56.0
	Hidroxipropilcelulosa (150 cps) (KLUCEL)	2.0
	Total:	100.0

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EJEMPLO OGel tópicoGel 2.0% DHT

Ingrediente	g Peso (en peso de la composición total)
Ditidrotestosterona	2.0
Capril- capricho Triglicérido (Neobee M-5)	5.0
Hexilen glicol NF	15.0
Transcutol (dietilenglicol monometil éter)	5.0
Alcohol Bencílico	2.0
Ciclometicona (Dow Corning 345)	5.0
Etanol (absoluto) USP	64.0
Hidroxipropilcelulosa (150 cps) (KLUCEL)	2.0
Total:	100.0

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EJEMPLO P

Capsulas orales

Capsulas 50 mg DHEA

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Ingrediente	Mg/capsula
	Grosor: 50 mg
DHEA (microionizado)	50.0
Celulosa microcristalina (AVICEL 302)	248.5
Estearato de magnesio	1.50
Total	300.0

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EJEMPLO Q

Capsulas orales

Capsulas 25 mg DHEA

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Ingrediente	Mg/capsula
	Grosor: 50 mg
DHEA (microionizado) (Estándar local)	25.0
Celulosa microcristalina (AVICEL 302) (USP)	273.5
Estearato de magnesio	1.50
Total	300.0

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La invención se ha descrito en términos de las modalidades preferidas y ejemplos, pero no se limita. Aquéllos expertos en la técnica reconocerán una más amplia aplicabilidad y alcance de la invención la cual se limita
5 únicamente por las reivindicaciones de patente de la misma.

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NOVEDAD DE LA INVENCION

Habiendo descrito el presente invento, se considera como una novedad y, por lo tanto, se reclama
5 como prioridad lo contenido en las siguientes:

REIVINDICACIONES

1.- Un método para tratar o reducir la
10 probabilidad de adquirir enfermedades de la piel debido a la deficiencia del andrógeno relacionadas con la edad, que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de andrógenos o profármacos del mismo.

15 2.- El método de conformidad con la reivindicación 1, caracterizado porque estas enfermedades de la piel se seleccionan del grupo que consiste de atrofia de piel, pérdida de colágeno, pérdida de fibras elásticas, pérdida de tejido conectivo, celulitis, y
20 arrugas.

3.- El método de conformidad con la reivindicación 1, caracterizado porque el andrógeno se seleccionan del grupo que consiste de testosterona (4-androstan-17 β -ol-3-ona), dihidrotestosterona (5 α -
25 androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-

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diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

4.- Un método para tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de
5 fibras elásticas que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un precursor esteroide sexual seleccionado del grupo que consiste de dehidroepiandrosterona, sulfato de
10 dehidroepiandrosterona, 5-androsten-3 β ,17 β -diol o profármacos del mismo.

5.- Un método para tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas que comprende administrar al paciente con
15 necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un andrógeno que se selecciona del grupo que consiste de testosterona (4-androstan-17 β -ol-3-ona), dihidrotestosterona (5 α -androsten-17 β -ol-3-ona),
20 androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

6.- El método de conformidad con la reivindicación 4, caracterizado porque los precursores
25 esteroide sexual se administran tópicamente.

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7.- Un método para tratar o reducir la probabilidad de adquirir atrofia de la piel, pérdida de colágeno, que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un andrógeno que se selecciona del grupo que consiste de testosterona (4-androstan-17 β -ol-3-ona), dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

8.- El método de conformidad con la reivindicación 4, caracterizado porque los precursores esteroide sexual se administran oralmente.

9.- El método de conformidad con las reivindicaciones 1, 5 o 7, caracterizado porque los andrógenos o profármacos del mismo se administran tópicamente.

10.- El método de conformidad con las reivindicaciones 1, 5 o 7, caracterizado porque los andrógenos o profármacos del mismo se administran oralmente.

11.- El uso de una cantidad efectiva de andrógenos o profármacos del mismo en la fabricación de un medicamento para tratar o reducir la probabilidad de

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adquirir enfermedades de la piel debido a la deficiencia del andrógeno relacionadas con la edad.

12.- El uso de conformidad con la reivindicación 11, en donde las enfermedades de la piel se seleccionan del grupo que consiste de atrofia de la piel, pérdida de colágeno, pérdida de fibras elásticas, pérdida de tejido conectivo, celulitis y arrugas.

13.- El uso de conformidad con la reivindicación 1, en donde el andrógeno se seleccionan del grupo que consiste de testosterona (4-androstan-17 β -ol-3-ona), dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

14.- Una cantidad efectiva por lo menos de un precursor esteroide sexual que se selecciona del grupo que consiste de dehidroepiandrosterona, sulfato de dehidroepiandrosterona, 5-androsten-3 β ,17 β -diol o profármacos del mismo para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente.

15.- Una cantidad efectiva por lo menos de un andrógeno que se selecciona del grupo que consiste de (4-androsten-17 β -ol-3-ona), dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-

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diona), androstandiona (5α -androsten-3,17-diona), 5α -androsten- 3α ,17 β -diol o profármacos del mismo para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente.

- 5 16.- Una composición tópica para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente por lo menos de un andrógeno que se selecciona del grupo que consiste de (4-androsten-17 β -ol-3-

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RESUMEN DE LA INVENCION

Métodos novedosos para tratar o reducir la probabilidad de adquirir enfermedades de la piel debido a deficiencias del andrógeno relacionadas con la edad, particularmente atrofia de la piel, pérdida de colágeno, pérdida de fibras elásticas, pérdida de tejido conectivo, celulitis y formación de arrugas, en animales de sangre caliente susceptibles, que incluye a los seres humanos; que involucran la administración de un andrógeno y/o un precursor esteroide sexual. También se describen composiciones farmacéuticas para el suministro de ingrediente(s) activo(s) útiles para la invención.

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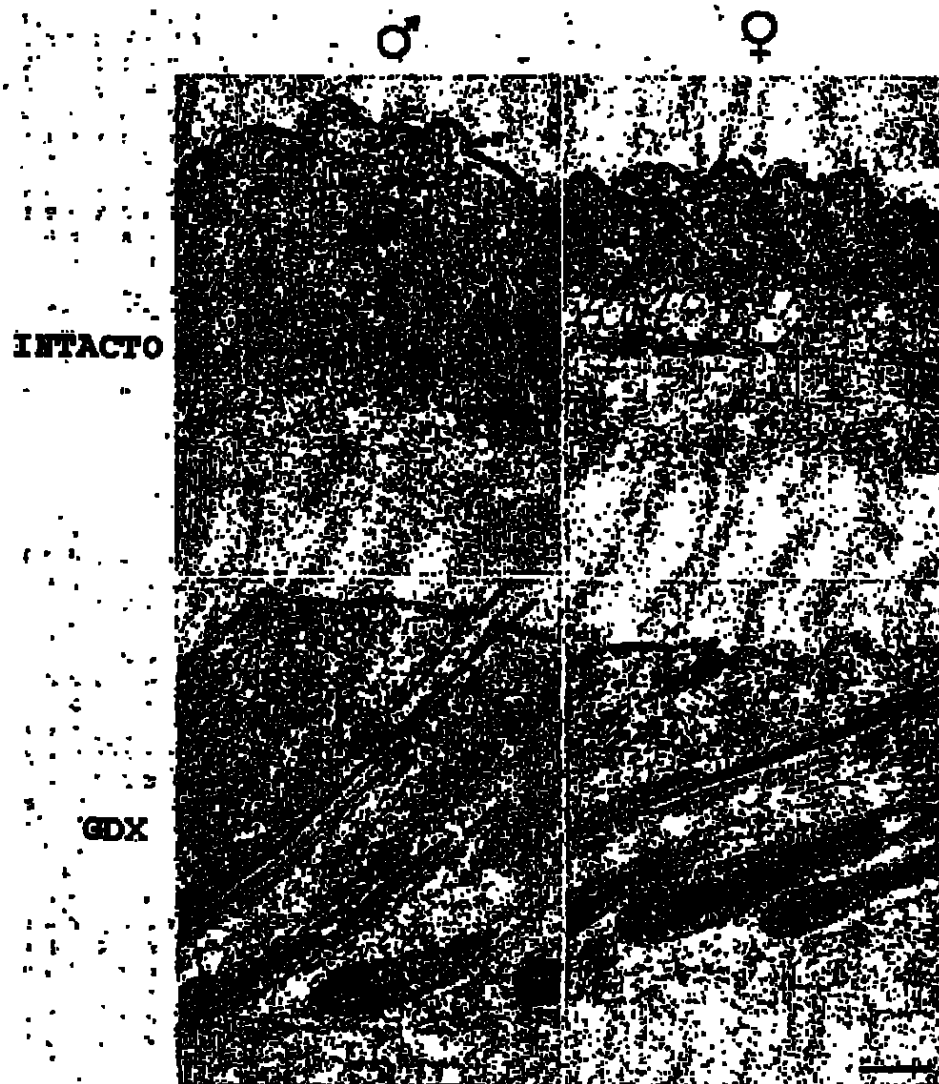


FIGURA 1A

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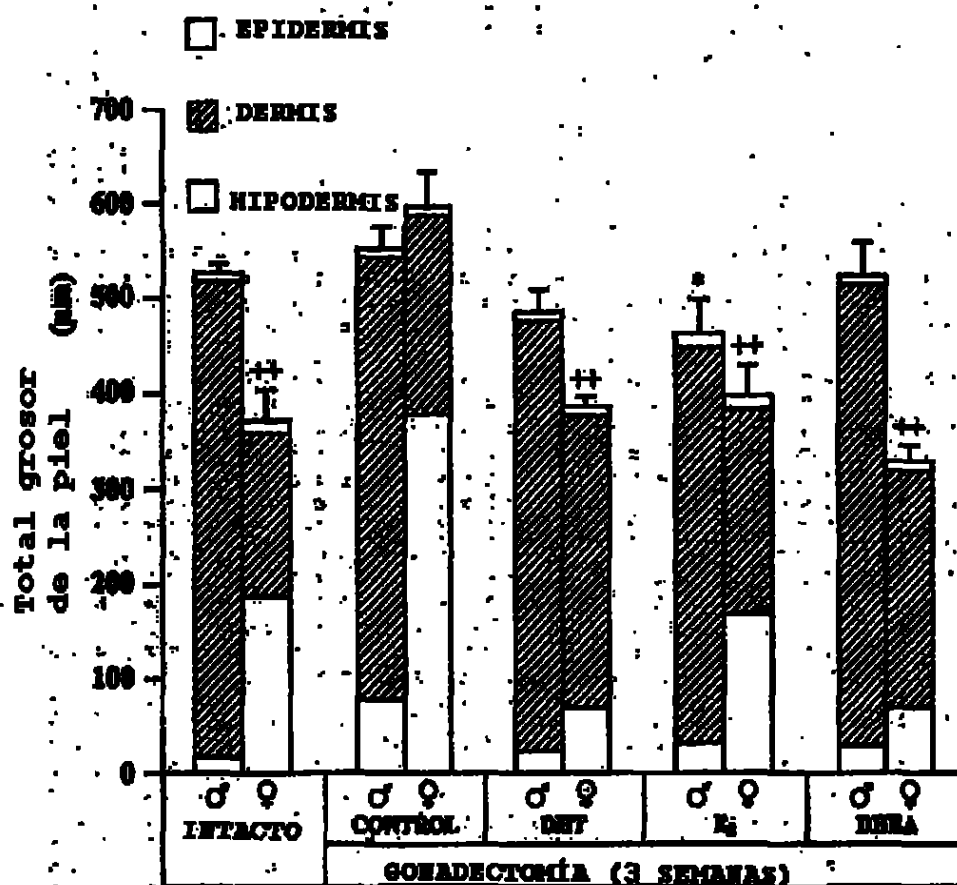


FIGURA 1B

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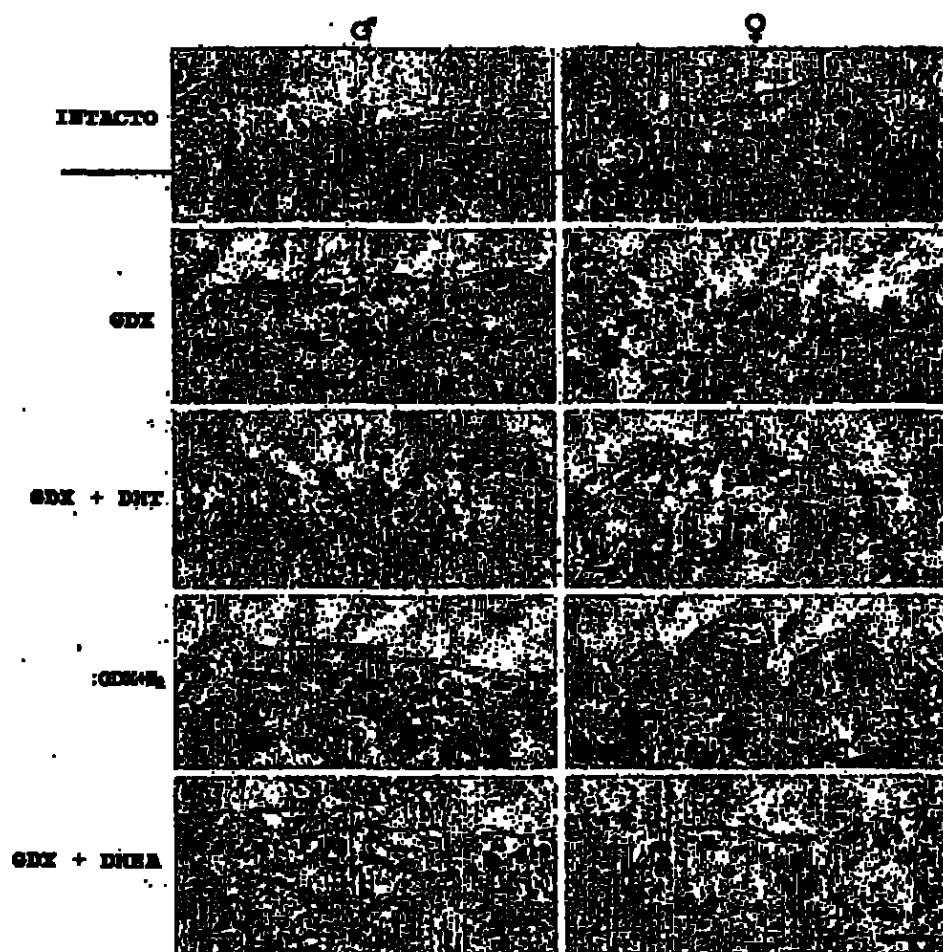


FIGURA 2

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DHEA



NO
DHEA



FIGURA 3

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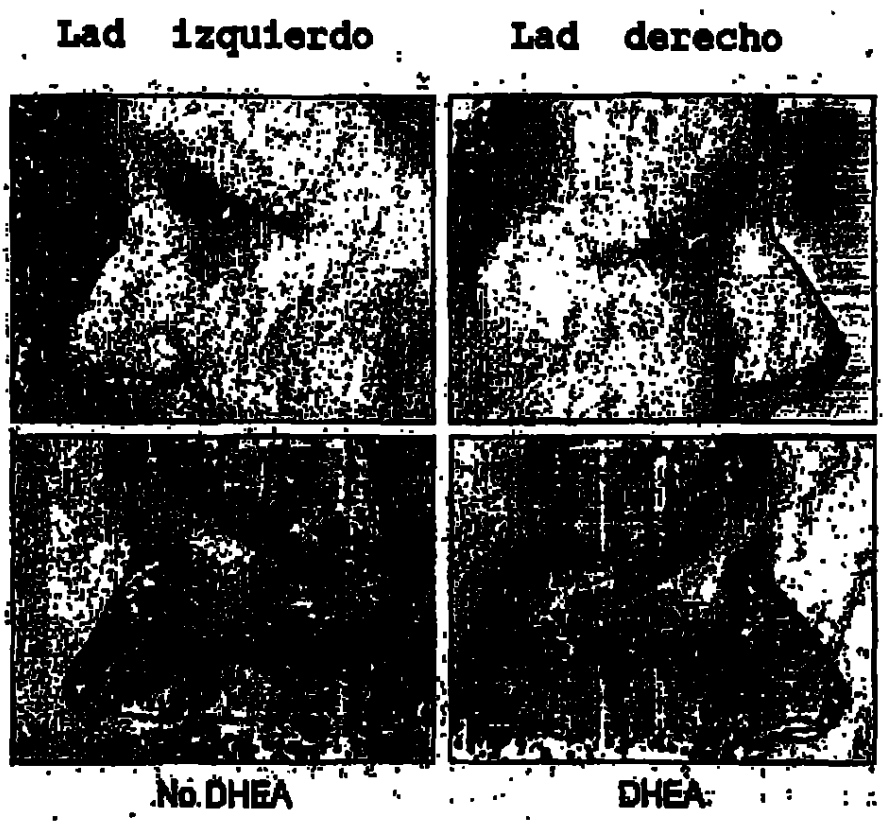


FIGURA 4

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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To: MARKS & CLERK Box 957 Station B OTTAWA, Ontario Canada, K1P 5S7		PCT NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty) (PCT Rule 71.1)	
Applicant's or agent's file reference 18696-PCT		Date of mailing (day/month/year) 22 February 2007 (22-02-2007)	
International application No. PCT/CA2005/001652		International filing date (day/month/year) 31 October 2005 (31-10-2005)	
Priority date (day/month/year) 01 November 2004 (01-11-2004)		IMPORTANT NOTIFICATION	
Applicant ENDORECHERCHE, INC. ET AL			
1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application. 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices. 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices. 4. REMINDER The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301). Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the <i>PCT Applicant's Guide</i>. The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.			
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476		Authorized officer Gisèle Faubert 819-997-6254	

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 18696-PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/CA2005/001652	International filing date (day/month/year) 31 October 2005 (31-10-2005)	Priority date (day/month/year) 01 November 2004 (01-11-2004)
International Patent Classification (IPC) or national classification and IPC IPC: A61K 31/568 (2006.01), A61P 17/00 (2006.01), A61Q 19/06 (2006.01), A61Q 19/08 (2006.01)		
Applicant ENDORECHERCHE, INC. ET AL		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>2</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>2</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions). 4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application		
Date of submission of the demand 17 May 2006 (17-05-2006)	Date of completion of this report 22 February 2007 (22-02-2007)	
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer James Martyn 819-953-0761	

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Box No. I Basis of the report

1. With regard to the language, this report is based on:
- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):
- ☐ the international application as originally filed/furnished
- ☒ the description:
- ☐ pages 1-37 as originally filed/furnished
- ☐ pages* received by this Authority on _____
- ☐ pages* received by this Authority on _____
- ☒ the claims:
- ☐ pages as originally filed/furnished
- ☐ pages* as amended (together with any statement) under Article 19
- ☒ pages* 38-40 claims 1 to 14 received by this Authority on 03-01-2007
- ☐ pages* received by this Authority on _____
- ☒ the drawings:
- ☒ pages 1/4 - 4/4 as originally filed/furnished
- ☐ pages* received by this Authority on _____
- ☐ pages* received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-9

because:

☒ the said international application, or the said claims Nos. 1-9

relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 1-9 are directed to a method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by this Authority. Regardless, this Authority has established a written opinion based on the alleged effect or purpose/use of the product defined in claims 1-9.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	<u>4-5</u>	YES
	Claims	<u>1-3, 6-14</u>	NO
Inventive step (IS)	Claims	<u>none</u>	YES
	Claims	<u>1-14</u>	NO
Industrial applicability (IA)	Claims	<u>1-14</u>	YES
	Claims	<u>none</u>	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents not cited in the International Search Report:

D1 COLLINS, 'Soy molecule could help skin, hair woes'. News for the College of Biology and Agriculture [online] 22-03-2004 [retrieved on 12-10-2006]. Retrieved from the internet: <http://bioagnews.byu.edu/newrelease.aspx?id=94>

D2 'Get rid of cellulite'. [online] 06-04-2004 (date obtained from <http://web.archive.org>) [retrieved 12-10-2006]. Retrieved from <http://www.strochmarka.com/cellulite.html>

D3 'The Delano Report' [online] 15-10-2004 (date obtained from <http://web.archive.org>) [retrieved 11-10-2006]. Retrieved from <http://www.delano.com/Articles/DHEA.html>

D4 HERTOEGHE, 'Minimizing Obesity with Hormone Replacement Therapy' Chapter 8 of "Anti-Aging Medical Therapeutics, Vol 5" [online] 2003. Retrieved from http://www.worldhealth.net/pdf/bookstore/therm5_ch8.pdf

With regard to novelty:

The instant application comprises methods of treating androgen deficiency related conditions of the skin by administration of androgens; specifically, methods of treating skin diseases due to age-related androgen deficiency with dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs, as well as methods of treating acquiring wrinkles and cellulite or loss of elastic fibres with dehydroepiandrosterone (DHEA or Prasterone), dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs.

D1 states "the DHT molecule regulates both male and female pattern baldness, and affects facial hair growth and skin health, too, apparently by stimulating procollagens, which help get rid of wrinkles." D1 is novelty destroying for claims 1-2, 6, 8-14.

D2 states "if you have a 'very' feminine figure, pear shaped, or are over 35 you may be more prone to cellulite than most as the fatty toxins accumulate around the feminine hips and thighs more rapidly in this case be sure to keep your hormones balanced. Try or DHEA caps for a more balanced figure." D2 is novelty destroying for claims 3, 7 and 12.

D3 lists "typical claims made for DHEA". Under the subheading skin it states "improves thickness, color, wrinkles, elasticity, collagen, puffiness under the eyes. D3 is novelty destroying for claims 3, 7 and 12.

Claims 1-3, 6-14 lack novelty, and therefore do not comply with Articles 33(2) PCT.

With regard to inventive step:

D4, page 69, under heading Cellulite, states "a low DHEA level may also favour cellulite accumulation". It is known that DHEA supplementation, applied topically or taken internally, increases DHEA levels, therefore, supplementation with DHEA will reduce cellulite accumulation. Claims 3, 7 and 12 possess no inventive step over D4.

Continued in Supplemental box.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

The specification as filed teaches methods of treating androgen deficiency related conditions of the skin by administration of androgens; specifically, methods of treating skin diseases due to age-related androgen deficiency with dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs, as well as methods of treating acquiring wrinkles and cellulite or loss of elastic fibres with dehydroepiandrosterone (DHEA or Prasterone), dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs. It is noted that only experimental results for DHEA, DHT and testosterone have been disclosed. It is therefore assumed that the utility for androstenedione, androstenedione and prodrugs has been soundly predicted from these results. The fact that the utility of DHEA, DHT and testosterone is anticipated by D1-D4 results in a lack of inventive step for the use of androstenedione, androstenedione and prodrugs for reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency. Claims 4 and 5 therefore lack inventive step.

Claims 1-14 lack inventive step and therefore do not comply with Articles 33(3) PCT.

With regard to industrial applicability:

Claims 1-14 possess industrial applicability and therefore comply with Article 33(4) PCT.

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Claims

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1. A method for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, comprising administering to patient in need of such treatment or in need of reduction of risk, an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs thereof.
2. A method of claim 1 wherein these skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite, and wrinkles.
3. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene- 3 β ,17 β -diol and prodrugs thereof.
4. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of androstenedione (4- androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs thereof.

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AMENDED SHEET

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5. The method of claims 3, wherein the sex steroid precursors or prodrugs thereof are administered topically. 120
6. A method for treating or reducing the likelihood of acquiring skin atrophy, loss of collagen, comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs thereof.
7. The method of claim 3, wherein the sex steroid precursors or prodrugs thereof are administered orally.
8. The method of claim 1, 4 or 6 wherein the compounds or prodrugs thereof are administered topically.
9. The method of claim 1 or 5 wherein the compounds or prodrugs thereof are administered orally.
10. Use of an effective amount of an effective amount of compounds selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof in the manufacture of a medicament for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency.

08 JANUARY 2007 09.01

11. The use of claim 10, wherein the skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite and wrinkles.

12. An effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene 3 β , 17 β -diol and prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.

13. An effective amount of at one least compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.

14. A topical composition for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient comprising an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione ((4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof, and a pharmaceutically acceptable carrier.

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AMENDED SHEET

REIVINDICACIONES

1.- Un método para tratar o reducir la probabilidad de adquirir enfermedades de la piel debido a la deficiencia del andrógeno relacionadas con la edad, que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva por lo menos un compuesto que se selecciona del grupo que consiste de dihidrotestosterona (5α -androsten- 17β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5α -androsten-3,17-diona), 5α -androsten- 3α , 17β -diol o profármacos del mismo.

2.- El método de conformidad con la reivindicación 1, caracterizado porque estas enfermedades de la piel se seleccionan del grupo que consiste de atrofia de piel, pérdida de colágeno, pérdida de fibras elásticas, pérdida de tejido conectivo, celulitis, y arrugas.

3.- Un método para tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un precursor esteroide sexual

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seleccionado del grupo que consiste de dehidroepiandrosterona, sulfato de dehidroepiandrosterona, 5-androsten-3 β ,17 β -diol o profármacos del mismo.

4.- Un método para tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un compuesto que se selecciona del grupo que consiste de androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

5.- El método de conformidad con la reivindicación 3, caracterizado porque los precursores esteroide sexual se administran tópicamente.

6.- Un método para tratar o reducir la probabilidad de adquirir atrofia de la piel, pérdida de colágeno, que comprende administrar al paciente con necesidad de tal tratamiento o con necesidad de reducción de riesgo, una cantidad efectiva de por lo menos un compuesto que se selecciona del grupo que consiste de dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -

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androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo.

7.- El método de conformidad con la reivindicación 3, caracterizado porque los precursores esteroide sexual se administran oralmente.

8.- El método de conformidad con las reivindicaciones 1, 4 o 6, caracterizado porque los compuestos o profármacos del mismo se administran tópicamente.

9.- El método de conformidad con las reivindicaciones 1, 4 o 6, caracterizado porque los compuestos o profármacos del mismo se administran oralmente.

10.- El uso de una cantidad efectiva de compuestos o profármacos del mismo que se seleccionan del grupo que consiste de dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo en la fabricación de un medicamento para tratar o reducir la probabilidad de adquirir enfermedades de la piel debido a la deficiencia del andrógeno relacionada con la edad.

11.- El uso de conformidad con la reivindicación 10, en donde las enfermedades de la piel se seleccionan del grupo que consiste de atrofia de la piel, pérdida de colágeno, pérdida de

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fibras elásticas, pérdida de tejido conectivo, celulitis y arrugas.

12.- Una cantidad efectiva por lo menos de un precursor esteroide sexual que se selecciona del grupo que consiste de dehidroepiandrosterona, sulfato de dehidroepiandrosterona, 5-androsten-3 β ,17 β -diol o profármacos del mismo para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente.

13.- Una cantidad efectiva por lo menos de un compuesto que se selecciona del grupo que consiste de (4-androsten-17 β -ol-3-ona), dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-diona), 5 α -androsten-3 α ,17 β -diol o profármacos del mismo para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente.

14.- Una composición tópica para el uso al tratar o reducir la probabilidad de adquirir arrugas y celulitis o pérdida de fibras elásticas en un paciente por lo menos de un andrógeno que se selecciona del grupo que consiste de dihidrotestosterona (5 α -androsten-17 β -ol-3-ona), androstendiona (4-androsten-3,17-diona), androstandiona (5 α -androsten-3,17-

diona), 5α -androsten- $3\alpha,17\beta$ -diol o profármacos del mismo y un vehículo transmisor aceptable farmacéuticamente.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MARKS & CLERK
Box 957
Station B
OTTAWA, Ontario
Canada, K1P 5S7

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing 14 February 2006 (14-02-2006)
(day/month/year)

Applicant's or agent's file reference
18696-PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/CA2005/001652

International filing date 31 October 2005 (31-10-2005)
(day/month/year)

Applicant
ENDORECHERCHE, INC. ET AL

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19 :

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46) :

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that :

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for the international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer
Jean-Luc Robert (819) 953-0756

Form PCT/ISA/220 (October 2005)

(See notes on accompanying sheet)

NOTES TO FROM PCT/ISA/220

These Notes are intended to give instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)) :

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter :

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1b4(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43b4.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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PATENT COOPERATION TREATY
PCT
INTERNATIONAL SEARCH REPORT
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 18696-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No. PCT/CA2005/001652	International filing date (day/month/year) 31 October 2005 (31-10-2005)	(Earliest) Priority date (day/month/year) 01 November 2004 (01-11-2004)
Applicant ENDORECHERCHE, INC. ET AL		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I

2. ☒ Certain claims were found unsearchable (see Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows :

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 4

☒ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 1-10

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 1-10, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 1-10.

2. ☒ Claim Nos. : 16

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

Claim 16 is incomplete.

3. ☐ Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/568 (2006.01), A61P 17/00 (2006.01), A61Q 19/08 (2006.01), A61Q 19/06 (2006.01)

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)

IPC(7): A61K 31/568, A61P 17/00, A61K 7/48

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

IPC(7): A61K

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

Delphion, USPTO, Espacenet, PubMed, Scopus, Internet, Canadian Patent db.

Keywords: DHEA, testosterone, skin atrophy, collagen, androgen*, androgen deficiency.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IL 157535D A (DIKSTEIN) 28-03-2004, full document. & WO 2005/030159 A	1-3, 5, 7, 9-15.
X	US 5,843,932 B (LABRIE) 01-12-1998, full document.	1-15
X	WO 97/10255 A (GUBERNICK et al.) 20-03-1997	1-15
X	BEULIEU, E. E. et al., Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue, PNAS, 11-04-2000, vol. 97(8), pages 4279-4284.	1-15

☐ 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

"Z" document member of the same patent family

Date of the actual completion of the international search

14 February 2006 (14-02-2006)

Date of mailing of the international search report

14 February 2006 (14-02-2006)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer

James Martyn (819) 953-0761

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2005/001652

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
IL157535D	28-03-2004	WO2005030159 A1	07-04-2005

US5843832	AT275957 T		15-10-2004
	AU886120 B2		05-02-1998
	AU5388494 A		28-07-1994
	AL5855794 A		15-08-1994
	CA2154161 A1		04-08-1994
	CN1100541C C		05-02-2003
	CN1439873 A		03-09-2003
	CZ9501585 A3		13-12-1995
	DE89433894D D1		21-10-2004
	DE89433894T T2		22-09-2005
	DK680327T T3		03-01-2005
	EP0880327 A1		08-11-1995
	EP1382340 A1		21-01-2004
	ES2227523T T3		01-04-2005
	FI953017 A		19-08-1995
	HU73241 A2		29-07-1998
	IL108371D D0		12-04-1994
	JP3441730B2 B2		02-09-2003
	NO3140678 B1		27-01-2003
	NO3148568 B1		28-04-2003
	NO3158808 B1		13-10-2003
	NO952417 A		18-06-1995
	NO20003546 A		18-06-1995
	NO20024189 A		16-08-1995
	NZ250712 A		28-11-1998
	NZ512334 A		27-05-2005
	PT680327T T		31-12-2004
	SK77985 A3		09-04-1997
	US5728688 A		17-03-1998
	US5776823 A		07-07-1998
	US5780480 A		14-07-1998
	US5788347 A		25-08-1998
	US5807849 A		15-09-1998
	US5824671 A		20-10-1998
	US5837700 A		17-11-1998
	US5854229 A		29-12-1998
	US5872114 A		16-02-1999
	US5822700 A		13-07-1999
	US5848434 A		07-09-1999
	US5855455 A		21-09-1999
	WO9416709 A2		04-08-1994
	ZA9400372 A		19-07-1995

WO9710255	20-03-1997	AT195527T T	15-09-2000
		AU712977 B2	18-11-1999
		AU8988898 A	01-04-1997
		CA2231781 A1	20-03-1997
		DE89808888D D1	21-09-2000
		DE89808888T T2	15-03-2001
		EP0878391 A1	11-11-1998
		ES2151180T T3	16-12-2000
		HK1015794 A1	12-01-2001
		IL123837 A	12-03-2003
		US5738537 A	07-04-1998
		US8025347 A	15-02-2000
		US8284750 B1	04-09-2001
		ZA9807704 A	27-05-1997

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
MARKS & CLERK
Box 957
Station B
OTTAWA, Ontario
Canada, K1P 5S7

Date of mailing 14 February 2006 (14-02-2006)
(day/month/year)

Applicant's or agent's file reference
18696-PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CA2005/001652

International filing date (day/month/year)
31 October 2005 (31-10-2005)

Priority date (day/month/year)
01 November 2004 (01-11-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC: A61K 31/568 (2006.01), A61P 17/00 (2006.01), A61Q 19/08 (2006.01), A61Q 19/06 (2006.01)

Applicant
ENDORECHERCHE, INC. ET AL

1. This opinion contains indications relating to the following items :

- | | |
|--|--|
| ☒ Box No. I | Basis of the opinion |
| ☐ Box No. II | Priority |
| ☒ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ Box No. VI | Certain documents cited |
| ☐ Box No. VII | Certain defects in the international application |
| ☒ Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Date of completion of this opinion
14 February 2006 (14-02-2006)

Authorized officer
James Martyn (819) 953-0761

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form
- ☐ furnished subsequently to this Authority for the purposes of search.

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in this subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claim Nos. 1-10 and 16

because:

☒ the said international application, or the said claim Nos. 1-10 relate to the following subject matter which does not require an international search (*specify*):

Claims 1-10, directed to a method for treatment of the human or animal body by surgery or therapy, is/are not required to be searched nor is a written opinion required by this Authority. Regardless, this Authority has established a written opinion based on the alleged effects or purposes/uses of the product defined in claims 1-10.

☒ the description, claims or drawings (*indicate particular elements below*) or said claim Nos. 16 are so unclear that no meaningful opinion could be formed (*specify*):

Claim 16 appears to be incomplete.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>None</u>	YES
	Claims <u>1-15</u>	NO
Inventive step (IS)	Claims <u>None</u>	YES
	Claims <u>1-15</u>	NO
Industrial applicability (IA)	Claims <u>1-15</u>	YES
	Claims <u>None</u>	NO

2. Citations and explanations :

Reference is made to the following documents:

D1 IL 157535D A (DIKSTEIN) 28-03-2004, full document. Reference will be made to WO 2005/030159 A for English translation.

D2 US 5,843,932 B (LABRIE) 01-12-1998, full document.

D3 WO 97/10255 A (GUBERNICK et al.) 20-03-1997

D4 BEULIEU, E. E. et al., Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue, PNAS, 11-04-2000, vol. 97(8), pages 4279-4284.

With regard to novelty and inventive step:

The instant application comprises methods of treating androgen deficiency related conditions by administration of androgens as well as uses of androgens in the manufacture of a medicament. The specifically claimed androgens are dehydroepiandrosterone, testosterone, dehydrotestosterone androstenedione, androstenedione and prodrugs. It is worth noting that dehydroepiandrosterone is converted into all claimed androgens within the human body and therefore dehydroepiandrosterone is considered to be a prodrug of androgens. It is also noted that loss of collagen, loss of elastic fibers, loss of connective tissue and wrinkles may be collectively grouped as skin atrophy. D1 teaches the use of testosterone esters for the treatment of skin aging. The summary of invention of D1, page 2, lines 2-4, states "androgen containing topical preparations that decrease atrophy of the skin due to aging or external factors, such as photoaging, or prolonged corticosteroid treatment have been found by the present invention". D2, D3 and D4 all teach the use of DHEA for the treatment of skin atrophy. D1-4 are novelty destroying for claims 1-15.

Claims 1-15 lack novelty, and therefore also lack inventive step, and do not comply with Articles 33(2) or 33(3) PCT.

With regard to industrial applicability:

Claims 1-15 possess industrial applicability and therefore comply with Article 33(4) PCT.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim 16 appears to be incomplete and does not comply with Article 6 of the PCT.

The statement found on page 37, paragraph [0075] of the description does not comply with Article 6 of the PCT. This is a general statement which implies that the extent of protection may be expanded in some vague and imprecise way.

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To:
MARKS & CLERK
Box 957
Station B
OTTAWA, Ontario
Canada, K1P 5S7

Date of mailing
(day/month/year) **25 October 2006 (25-10-2006)**

REPLY DUE within TWO months/days from
the above date of mailing

Priority date (day/month/year)
01 November 2004 (01-11-2004)

Applicant
ENDORECHERCHE, INC. ET AL

1. ☒ [X] The written opinion established by the International Searching Authority:
☒ [X] is ☐ [] is not
considered to be a written opinion of the International Preliminary Examining Authority.
2. This second (first, etc.) opinion contains indications relating to the following items:
- | | |
|--|--|
| ☒ [X] Box No. I | Basis of the opinion |
| ☐ [] Box No. II | Priority |
| ☒ [X] Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ [] Box No. IV | Lack of unity of invention |
| ☒ [X] Box No. V | Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ [] Box No. VI | Certain documents cited |
| ☐ [] Box No. VII | Certain defects in the international application |
| ☒ [X] Box No. VIII | Certain observations on the international application |
3. The applicant is hereby invited to reply to this opinion.
When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
Also For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bix. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
- If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: **01 March 2007 (01-03-2007)**

James Martyn (819) 953-0761

WRITTEN OPINION OF THE
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/CA2005/001652

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this opinion has been established on the basis of (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

- ☐ the international application as originally filed/furnished
- ☒ the description:
- | | |
|------------|-------------------------------|
| pages 1-37 | as originally filed/furnished |
| pages | received by this Authority on |
| pages | received by this Authority on |
- ☒ the claims:
- | | |
|-------------|---|
| pages | as originally filed/furnished |
| pages | as amended (together with any statement) under Article 19 |
| pages 38-40 | received by this Authority on 02-10-2006 |
| pages | received by this Authority on |
- ☒ the drawings:
- | | |
|-----------------|-------------------------------|
| pages 1/4 - 4/4 | as originally filed/furnished |
| pages | received by this Authority on |
| pages | received by this Authority on |
- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (specify):
- ☐ any table(s) related to the sequence listing (specify):

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (specify):
- ☐ any table(s) related to the sequence listing (specify):

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**WRITTEN OPINION OF THE
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

International application No.
PCT/CA2005/001652

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-9

because:

☒ the said international application, or the said claims Nos. 1-9
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 1-9 are directed to a method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by this Authority. Regardless, this Authority has established a written opinion based on the alleged effect or purpose/use of the product defined in claims 1-9.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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**WRITTEN OPINION OF THE
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

International application No.
PCT/CA2005/001652

Box No. V Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims ~~none~~	YES
	Claims 1-14	NO
Inventive step (IS)	Claims ~~none~~	YES
	Claims 1-14	NO
Industrial applicability (IA)	Claims 1-14	YES
	Claims ~~none~~	NO

2. Citations and explanations:

Reference is made to the following documents:

- D1 COLLINS, 'Soy molecule could help skin, hair woes'. News for the College of Biology and Agriculture [online] 22-03-2004 [retrieved on 12-10-2006]. Retrieved from the internet: <http://bioagnews.bya.edu/newrelease.aspx?id=94>
D2 'Get rid of cellulite'. [online] 06-04-2004 (date obtained from <http://web.archive.org>) [retrieved 12-10-2006]. Retrieved from <http://www.strochmarika.com/cellulite.html>
D3 'The Delano Report' [online] 15-10-2004 (date obtained from <http://web.archive.org>) [retrieved 11-10-2006]. Retrieved from <http://www.delano.com/Articles/DHEA.html>
D4 HERTOOGHE, 'Minimizing Obesity with Hormone Replacement Therapy' Chapter 8 of 'Anti-Aging Medical Therapeutics, Vol 5' [online] 2003. Retrieved from http://www.worldhealth.net/pdf/bookstore/thera5_ch8.pdf

With regard to novelty:

The instant application comprises methods of treating androgen deficiency related conditions of the skin by administration of androgens; specifically, methods of treating skin diseases due to age-related androgen deficiency with dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs, as well as methods of treating acquiring wrinkles and cellulite or loss of elastic fibres with dehydroepiandrosterone (DHEA or Prasterone), dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs.

D1 states "the DHT molecule regulates both male and female pattern baldness, and affects facial hair growth and skin health, too, apparently by stimulating procollagens, which help get rid of wrinkles." D 1 is novelty destroying for claims 1-2, 4, 6, 8-14.

D2 states "if you have a 'very' feminine figure, pear shaped, or are over 35 you may be more prone to cellulite than most as the fatty toxins accumulate around the feminine hips and thighs more rapidly in this case be sure to keep your hormones balanced. Try or DHEA caps for a more balanced figure." D2 is novelty destroying for claims 3, 7 and 9.

D3 lists "typical claims made for DHEA". Under the subheading skin it states "improves thickness, color, wrinkles, elasticity, collagen, puffiness under the eyes. D3 is novelty destroying for claims 3, 7 and 9.

Claims 1-4, 6-14 lack novelty, and therefore do not comply with Articles 33(2) PCT.

With regard to inventive step:

D4, page 69, under heading Cellulite, states "a low DHEA level may also favour cellulite accumulation". It is known that DHEA supplementation, applied topically or taken internally, increases DHEA levels, therefore, supplementation with DHEA will reduce cellulite accumulation. Claims 3, 5, 7 and 9 possess no inventive step over D4.

Continued in Supplemental box.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 9 is unclear and does not comply with Article 6 of the PCT. The double inclusion of any element renders the claims indefinite. The following expression has already been defined previously in the claims and should therefore be referred to using a definite article. Claim 7, to which claim 9 depends, is also contains the expression administered orally.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: V

The specification as filed teaches methods of treating androgen deficiency related conditions of the skin by administration of androgens; specifically, methods of treating skin diseases due to age-related androgen deficiency with dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs, as well as methods of treating acquiring wrinkles and cellulite or loss of elastic fibres with dehydroepiandrosterone (DHEA or Prasterone), dehydrotestosterone (DHT) androstenedione, androstenedione and prodrugs. It is noted that only experimental results for DHEA, DHT and testosterone have been disclosed. It is therefore assumed that the utility for androstenedione, androstenedione and prodrugs is based on these findings. The fact that the utility of DHEA, DHT and testosterone is anticipated by D1-D4 results in a lack of inventive step for the use of androstenedione, androstenedione and prodrugs for reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency.

Claims 1-14 lack inventive step and therefore do not comply with Articles 33(3) PCT.

With regard to industrial applicability:

Claims 1-14 possess industrial applicability and therefore comply with Article 33(4) PCT.

MARKS & CLERK

Canada

Patent & Trademark Agents

Our ref: 18696-PCT
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January 08, 2007

Commissioner of Patents
Canadian Patent Office
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IN THE MATTER OF INTERNATIONAL APPLICATION NO. PCT/CA2005/001652

APPLICANT: Endorecherche, Inc.
SERIAL NO.: PCT/CA2005/001652
FILING DATE: 31-October-2005
TITLE: Use of Androgens to Reduce the Likelihood of Acquiring or to
Treat Skin Aging
OUR FILE NO.: 18696-PCT

Dear Sir:

In response to the Written Opinion dated October 25, 2006, we are submitting the following remarks and observations:

IN THE CLAIMS:

Please withdraw the claims 1 to 14 at present on file in favour of a new set of claims 1 to 14 (pages 38, 39 and 40) attached herewith.

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REMARKS:

The applicants have amended the claims to take care of the formal objections.

With respect to the prior art objections, the applicants point out that Document D2 is a web site selling herbal and similar products, particularly DHEA. Effectively, DHEA is mentioned in this document but not for the treatment of cellulite. It says only "Try our DHEA caps for a more balanced figure" with no reference to cellulite. As described, the treatment of cellulite or "Directions for Cellulite Removal" is made of a Collagen Cocktail with vitamins, a foaming seaweed wash, a vitamin C spray and a daily Lotion. There is no indication that the formulations contain DHEA.

Document D3, The Delano Report, reports typical claims made for DHEA. Effectively, elasticity of skin is discussed. Applicant is not claiming an effect on elasticity which could well be explained by an effect limited to the epidermis or dermis. Instead, applicants' claims specify a method of treating "loss of elastic fibers" which is more specific and more scientific than the general term of "elasticity" which could have nothing to do with a specific effect on elastic fibers. "Elasticity" could be due to an effect on other cell components.

Document D4 (T. Hertoghe, Anti-Aging Medical, Therapeutics, volume 5, 2003) on page 69 speaks of cellulite. It notes that low DHEA levels and cellulite may co-exist, but does not suggest a cause and effect relationship. It mentions that when obese men were treated, their levels of plasma DHEA sulfate increased. However, this document does not mention that DHEA treatment may be useful for cellulite. Low DHEA levels and cellulite do not show or even suggest that there could be more than a non causative temporal relationship. A causal relationship is not demonstrated nor indicated.

In view of the above amendments and comments, it is believed that the Examiner should be in a position to issue a favourable opinion, and such action is respectfully requested.

Respectfully submitted,

Richard J. Mitchell
RJM/pm
Encl.

146

Claims

1. A method for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, comprising administering to patient in need of such treatment or in need of reduction of risk, an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5α -androstane- 17β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstanedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17β -diol and prodrugs thereof.
2. A method of claim 1 wherein these skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite, and wrinkles.
3. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene- 3β , 17β -diol and prodrugs thereof.
4. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of androstenedione (4- androstene-3,17-dione), androstanedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17β -diol and prodrugs thereof.

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5. The method of claims 3, wherein the sex steroid precursors or prodrugs thereof are administered topically.
6. A method for treating or reducing the likelihood of acquiring skin atrophy, loss of collagen, comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol and prodrugs thereof.
7. The method of claim 3, wherein the sex steroid precursors or prodrugs thereof are administered orally.
8. The method of claim 1, 4 or 6 wherein the compounds or prodrugs thereof are administered topically.
9. The method of claim 1 or 5 wherein the compounds or prodrugs thereof are administered orally.
10. Use of an effective amount of an effective amount of compounds selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstenedione (5 α -androstane-3,17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof in the manufacture of a medicament for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency.

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11. The use of claim 10, wherein the skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite and wrinkles.
12. An effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene 3 β , 17 β -diol and prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.
13. An effective amount of at one least compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.
14. A topical composition for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient comprising an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione ((4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof, and a pharmaceutically acceptable carrier.

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Our ref: 18696PCT

Your Ref: * * * * *

October 2, 2006

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IN THE MATTER OF INTERNATIONAL APPLICATION NO. PCT/CA2005/001652

(
●
APPLICANT: ENDORECHERCHE, INC. et al
SERIAL NO.: PCT/CA2005/001652
FILING DATE: 31-October-2005
TITLE: Use of Androgens to Reduce the Likelihood of Acquiring or to
Treat Skin Aging

AMENDMENT UNDER ARTICLE 34

(
●
Dear Sir:

Pursuant to the Demand submitted on May 16, 2006, we are respectfully submitting herewith the following amendments and remarks.

IN THE CLAIMS:

Please withdraw the claims at present on file in favour of a new set of claims 1 to 14 attached herewith.

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REMARKS:

By their amendments, the applicants have restricted the invention to compounds selected from the group specifically now set forth in Claim 1. It will now be noted that Claim 1 refers to at least one compound selected from the recited group, and that testosterone has been excluded.

Firstly, the Examiner is asked to note that there is a fundamental difference between the administration of DHEA and the administration of androgens as testosterone or dihydrotestosterone and their derivatives. This point is explained in paragraph [006] of the specification. In addition, the Examiner should be aware that there is an important difference between prodrugs and precursors. The art considers "prodrugs" to be biologically inactive compounds which are converted to biologically active drugs in the body (see definition of the prodrug concept in A textbook of Drug Design and Developments edited by P. Krogsgaard-Larsen and H. Bundgaard, Harwood academic publishers, 1991, pages 114-115 (copy attached).

DEHA is a biologically active precursor which is converted into androgens or estrogens or both in specific cells while not being converted into androgens or estrogens in other cells where it exerts no activity. DHEA is a natural steroid that is biologically active and is a natural precursor to androgens; it is not in itself an androgen prodrug. Thus, Claim 1 for example, does not cover DHEA.

Claim 3 on the other hand recites DHEA, but this claim is directed to a method of treatment for wrinkles and cellulite,

While the Examiner is silent with regard to cellulitis, he considers wrinkles and loss of elastic fibers under the skin as skin atrophy, presumably by reference to D1, pages 3 lines 12 to 13, wherein it is stated that "the term "treatment" refers to ameliorating, preventing or improving at least one parameter associated with atrophy and aging of the skin such as decrease of wrinkles (number, severity, area) improved conality, increased skin layers, improvements of naturally reduced during aging such collagen GAGs etc."

However, in reality, wrinkles are more related to skin aging than skin atrophy. Reference D2 only teaches the treatment of skin atrophy, collagen and connective tissue. D3 teaches only the use of esters of DHEA and D4 teaches only sebum production, skin hydration, pigmentation, and epidermal thickness. In the applicant's submission, contrary to the Examiner's position, documents D1 to D4 do not teach a method of reducing the likelihood requiring wrinkles etc. as more particularly set forth in Claim 3, for example.

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It is thus believed that the claims, as amended, should now be in a condition for the Examiner to issue a favourable opinion.

Respectfully submitted,

Richard J. Mitchell
RJM/pm
Encl.

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Claims

1. A method for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency, comprising administering to patient in need of such treatment or in need of reduction of risk, an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5α -androstane- 17β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstanedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17β -diol or prodrugs thereof.
2. A method of claim 1 wherein these skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite, and wrinkles.
3. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene- 3β , 17β -diol and prodrugs thereof.
4. A method for treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5α -androstane- 17β -ol-3-one), androstenedione (4- androstene-3,17-dione), androstanedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17-diol and prodrugs thereof.

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5. The method of claims 3, wherein sex steroid precursors are administered topically.
6. A method for treating or reducing the likelihood of acquiring skin atrophy, loss of collagen, comprising administering to patient in need of such treatment or in need of reduction of risk an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5α -androstane- 17β -ol-3-one), androstenedione (4-androstene-3,17-dione), androstenedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17-diol and prodrugs thereof.
7. The method of claim 3, wherein sex steroid precursors are administered orally.
8. The method of claim 1, 4 or 6 wherein the compounds or prodrugs of thereof are administered topically.
9. The method of claim 1, 5 or 7 wherein the compounds or prodrugs of thereof are administered orally.
10. Use of an effective amount of an effective amount of compounds selected from the group consisting of dihydrotestosterone (5α -androstane- 17β -ol-3-one), androstenedione (4 androstene-3,17-dione), androstenedione (5α -androstane-3,17-dione), 5α -androstane- 3α , 17β -diol or prodrugs thereof in the manufacture of a medicament for treating or reducing the likelihood of acquiring skin diseases due to age-related androgen deficiency.
11. The use of claim 10, wherein the skin diseases are selected from the group consisting of skin atrophy, loss of collagen, loss of elastic fibers, loss of connective tissue, cellulite and wrinkles.

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12. An effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, 5-androstene 3 β , 17 β -diol and prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.

13. An effective amount of at one least compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient.

14. A topical composition for use in treating or reducing the likelihood of acquiring wrinkles and cellulite or loss of elastic fibers in a patient comprising an effective amount of at least one compound selected from the group consisting of dihydrotestosterone (5 α -androstane-17 β -ol-3-one), androstenedione (4-androstene-3, 17dione), androstanedione (5 α -androstane-3, 17-dione), 5 α -androstane-3 α , 17 β -diol or prodrugs thereof, and a pharmaceutically acceptable carrier.

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A Textbook of DRUG DESIGN and DEVELOPMENT

Edited by

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5.1 DEFINITION OF THE PRODRUG CONCEPT

During the past 20 years it has become more obvious that the commonly used processes of delivering therapeutic agents to the sites of their action within the body are generally inefficient and unreliable. Optimization of drug delivery and consequently improvement in drug efficacy implies an efficient and selective delivery and transport of a drug substance to its site of action. Recognition of the importance of drug delivery for the therapeutic indices of many types of drugs has been followed by a large increase in research activities in this area, and much attention has been focused on approaches which aim at enhancing the efficacy and reducing the toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

Prodrug design comprises an area of drug research that is concerned with the optimization of drug delivery. A prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule.

A molecule with optimal structural configuration and physico-chemical properties for eliciting the desired therapeutic response at its target site does not necessarily possess the best molecular form and properties for its delivery to its point of ultimate action. Usually, only a minor fraction of doses administered reach the target area and since most agents interact with non-target sites as well, an inefficient delivery may result in undesirable side-effects. This fact of differences in transport and *in situ* effect characteristics for many drug molecules is the basic reason why bioreversible chemical derivatization of drugs, i.e. prodrug formation, is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved.

Prodrug research matured as a branch of pharmaceutical research during the 1970s. Over the past decade this chemical approach to optimization of drug delivery has undergone considerable expansion, largely as a result of an increased awareness and understanding of the physico-chemical factors that effect the efficacy of drug

delivery and action. Several drugs are now used clinically in the form of prodrugs, and as the prodrug approach is becoming an integral part of the new drug design process one may expect that the new drugs in many cases will appear as prodrugs.

The term "prodrug" or "pro-agent" was first used by A. Albert in 1958 to describe compounds which undergo biotransformation prior to eliciting a pharmacological effect. Although terms such as drug latentiation, bioreversible derivatives, congeners and biolabile drug-carrier conjugates have been used synonymously with the term "prodrug", the latter is now the standardized term to describe pharmacologically inactive chemical derivatives of a drug molecule that require a transformation within the body in order to release the active drug.

Prodrugs are designed to overcome pharmacologically and/or pharmacokinetically based problems associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug. The prodrug approach can be illustrated as shown in Figure 5.1. The usefulness of a drug molecule is limited by its suboptimal physico-chemical properties, e.g. it shows poor biomembrane permeability. By attachment of a pro-moiety to the molecule or otherwise modifying the compound, a prodrug is formed that overcomes the barrier for the drug's usefulness. Once past the barrier, the prodrug is reverted to the parent compound by a post-barrier enzymatic or non-enzymatic process. Prodrug formation can thus be considered as conferring a transient chemical cover to alter or eliminate undesirable properties of the parent drug molecule.

A number of barriers may limit the clinical usefulness of a drug. In the pharmaceutical phases, i.e. the incorporation of a potential drug entity into a practically useful drug delivery system or dosage form, the barriers may be represented by formulation problems due to the physico-chemical properties of the drug, such as poor water solubility, and by aesthetic properties of the drug, such as taste and tissue irritation.

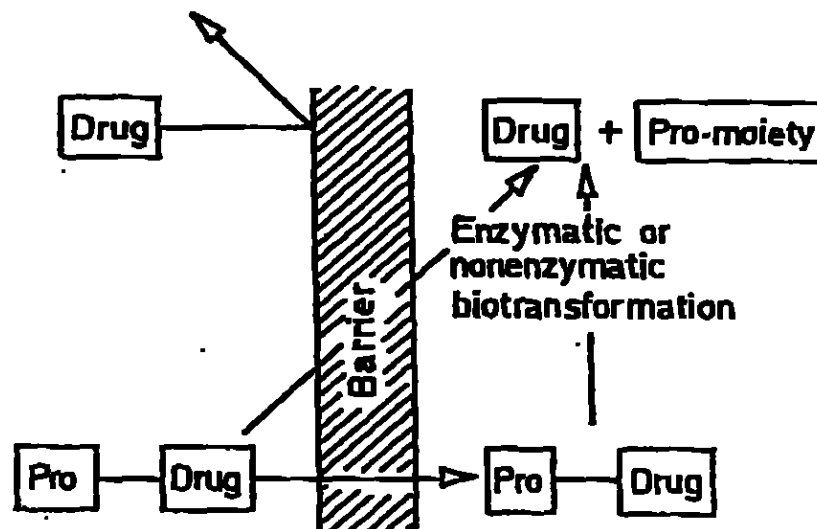


Figure 5.1. Schematic illustration of the prodrug concept.



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Industria y Comercio
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**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [X]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- ◆ Descripción de la invención [X]
- ◆ Dibujos de ser estos pertinentes [X]
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- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
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- ◆ Representación gráfica del esquema trazado []
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COMPLETA []

INCOMPLETA []

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161

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
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REFERENCIA	Radicación No.	07 52636
	Solicitud internacional	PCT/CA2005/001652
	Fecha inicio fase nacional	01/06/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	8904

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

ALIX CARMENEA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 JUL 2007
adpall