

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "Los Países Miembros otorgarán Patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de Novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica". "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La Solicitud de Patente Colombiana No. 00043097 menciona un equipo para mejorar la salud de una mujer... el cual comprende una forma de dosis no oral de un esteroide androgénico en una cantidad suficiente para producir un efecto terapéutico en la presencia de niveles elevados o substancialmente elevados de SHGB.

El documento **WO 95/03764** (folios: 302 a 304) menciona parches y métodos para administrar testosterona (la cual es una hormona androgénica). En este documento la forma de administración también es no oral como en la presente solicitud.

El documento **US 5872114** (folios: 305 a 307) menciona seis esteroides andrógenos que se administran vía percutánea o transmucosal (son formas de administración no orales) para el tratamiento o prevención de enfermedades vaginales, cáncer de ovario, etc.

El documento **WO 98/02167** (folios: 308 y 309) menciona la aplicación transdérmica de hormonas esteroides androgénicas como terapia en la menopausia.

El documento **WO 97/03676** (folios: 310 a 312) menciona una formulación farmacéutica de un esteroide androgénico para aplicación tópica percutánea (administración no oral).

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en

el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 95/03764	1 a 12	Novedad
2	US 5872114	1 a 12	Novedad
3	WO 98/02167	1 a 12	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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 N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

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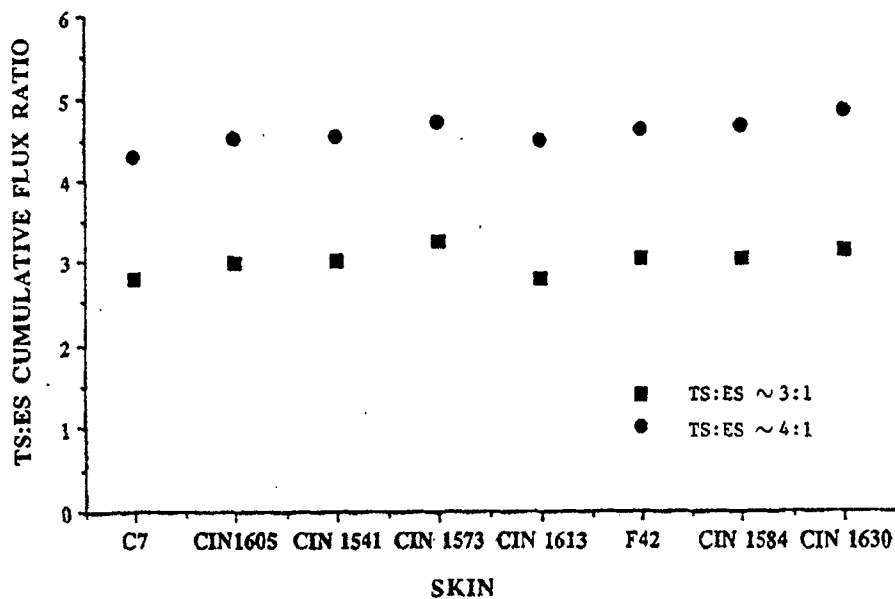
CONCEPTO TÉCNICO Nº: 576	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61F 13/00		(11) International Publication Number: WO 95/03764
A1		(43) International Publication Date: 9 February 1995 (09.02.95)
(21) International Application Number: PCT/US94/08637 (22) International Filing Date: 27 July 1994 (27.07.94) (30) Priority Data: 08/099,923 3 August 1993 (03.08.93) US (71) Applicant: THERATECH, INC. [US/US]; Suite 100, 417 Wakara Way, Salt Lake City, UT 84108 (US). (72) Inventors: EBERT, Charles, D.; 1515 S. Canterbury Drive, Salt Lake City, UT 84108 (US). PATEL, Dinesh, C.; 5839 S. Meadowcrest Drive, Murray, UT 84107 (US). MAZER, Norman, Alan; 4336 S. Pin Oak Street, Salt Lake City, UT 84124 (US). VENKATESHWARAN, Strinivasan; 2411 Emerson Avenue, Salt Lake City, UT 84108 (US). (74) Agents: CIOTTI, Thomas, E. et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).		(81) Designated States: AU, CA, CN, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>

(54) Title: SKIN PATCHES AND METHODS FOR PROVIDING TESTOSTERONE



(57) Abstract

A method of providing testosterone replacement therapy to a woman in need of such therapy comprising applying a testosterone-delivering patch to the skin of said woman which patch transdermally delivers 50 to 500 $\mu\text{g/day}$ of testosterone to the woman.

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297Claims

1. A method of providing testosterone
5 replacement therapy to a woman in need of such therapy
comprising administering testosterone transdermally to
the woman in an amount that provides blood levels of
testosterone in the woman that correspond substantially
10 to endogenous blood levels of testosterone in healthy
young adult women.
2. The method of claim 1 wherein said amount
is in the range of 50 to 500 $\mu\text{g/day}$.
- 15 3. A skin patch for providing testosterone
replacement therapy transdermally to a woman in need of
such therapy comprising a laminated compound of:
(a) a backing layer; and
(b) a matrix layer comprising a solution of
20 testosterone in a polymeric carrier, said
matrix layer providing a sufficient daily dose
of testosterone to provide such therapy.
4. The skin patch of claim 3 wherein the
25 polymeric carrier is a pressure sensitive adhesive and
the patch provides 50 to 500 μg testosterone/day.
5. A method of providing combined
testosterone and estrogen replacement therapy to a woman
30 in need of such therapy comprising coadministering
testosterone and estrogen transdermally to the woman in
respective amounts that provide blood levels of
testosterone and estrogen in the woman that correspond
substantially to endogenous blood levels of testosterone
35 and estrogen in a healthy young woman.

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6. The method of claim 5 wherein the amount of testosterone is 50 to 500 $\mu\text{g}/\text{day}$ and the estrogen is 17β -estradiol and the amount of estrogen is 25 to 200 $\mu\text{g}/\text{day}$.

7. A skin patch for providing testosterone and estrogen replacement therapy transdermally to a woman in need of such therapy comprising:

10 (a) a backing layer;

(b) a testosterone-and-estrogen-containing a layer that is adapted to be in diffusional communication with the skin of the woman and to transmit therapeutically effective

15 amounts of testosterone and estrogen through the skin of the woman.

8. The patch of claim 7 wherein the amount of testosterone is 50 to 500 $\mu\text{g}/\text{day}$, the estrogen is 17β -estradiol, and the amount of estrogen is 25 to 200 $\mu\text{g}/\text{day}$.

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United States Patent [19]**Labrie**[11] **Patent Number:****5,872,114**[45] **Date of Patent:****Feb. 16, 1999****[54] THERAPEUTIC METHODS AND DELIVERY SYSTEMS UTILIZING SEX STEROID PRECURSORS**[75] **Inventor:** **Fernand Labrie**, Quebec, Canada[73] **Assignee:** **Endorecherche, Inc.**, Quebec, Canada[21] **Appl. No.:** **481,668**[22] **Filed:** **Jun. 7, 1995****Related U.S. Application Data**

[60] Division of Ser. No. 180,361, Jan. 18, 1994, which is a continuation-in-part of Ser. No. 5,619, Jan. 19, 1993, abandoned.

[51] **Int. Cl.⁶** **A61K 31/56**[52] **U.S. Cl.** **514/178**[58] **Field of Search** **514/169, 178****[56] References Cited****U.S. PATENT DOCUMENTS**

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(List continued on next page.)

Primary Examiner—José G. Dees**Assistant Examiner**—Mary C. Cebulak**Attorney, Agent, or Firm**—Ostrolenk, Faber, Gerb & Soffen, LLP**[57] ABSTRACT**

Sex steroid precursors such as dehydroepiandrosterone and dehydroepiandrosterone sulphate, and compounds converted in vivo to either of the foregoing, are utilized for the treatment and/or prevention of vaginal atrophy, hypogonadism, diminished libido, osteoporosis, urinary incontinence, ovarian cancer, uterine cancer, skin atrophy, for contraception, and, in combination with an estrogen and/or progestin, for the treatment of menopause. The precursors may be formulated for percutaneous or transmucosal administration. Gels, solutions, lotions, creams, ointments and transdermal patches for the administration of these precursors are provided, as are certain pharmaceutical compositions and kits which can be used for the prevention and treatment of a wide variety of conditions related to decreased secretion of sex steroid precursors by the adrenals.

8 Claims, 9 Drawing Sheets

THERAPEUTIC METHODS AND DELIVERY SYSTEMS UTILIZING SEX STEROID PRECURSORS

RELATED APPLICATION

This patent application is a division of application Ser. No. 08/180,361, filed Jan. 18, 1994, which is in turn a continuation-in-part of U.S. patent application Ser. No. 08/005,619, filed Jan. 19, 1993, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to a method for preventing and/or treating vaginal atrophy, hypogonadism, diminished libido, osteoporosis, urinary incontinence, ovarian cancer, uterine cancer, and menopause or contraception in susceptible warm-blooded animals including humans involving administration of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S) or compounds converted in vivo to either and to pharmaceutical products, including kits and pharmaceutical compositions for delivery of active ingredient(s) useful to the invention.

Primates are unique in having adrenals that secrete large amounts of the precursor steroid dehydroepiandrosterone (DHEA) and especially DHEA-sulfate (DHEA-S), which are converted into androstenedione (Δ^4 dione) or androstenediol (Δ^5 -diol) and then into potent androgens and estrogens in peripheral tissues (Adams, *Mol. Cell. Endocrinol.* 41:1-17, 1985; Labrie et al., in *Important Advances in Oncology* (de Vita S, Hellman S, Rosenberg S A, eds), J B Lippincott, Philadelphia Pa., pp 193-200, 1985). DHEA-S, the major steroid present in blood of both men and women is converted into DHEA and Δ^5 -diol in peripheral tissues, thus maintaining a close correlation between the concentration of these three steroids in the blood (Adams, *Mol. Cell. Endocrinol.* 41:1-17, 1985). Depending upon the relative activities of 17β -hydroxysteroid dehydrogenase (17β -HSD), aromatase and 5α -reductase, DHEA or its derivatives will be preferentially converted into androgens and/or estrogens.

The low serum values of DHEA and DHEA-S found at birth persist up to six years of age. Usually, during the 7th year of age, serum levels of these two steroids increase and continue to rise until age 16 in both boys and girls (Orentreich et al., *J. Clin. Endocr. Metab.* 59:551-555, 1984). A further increase is then seen in males, who typically reach maximal levels between 20 and 24 years of age. In women, there is usually no further increase after 16 years. DHEA and DHEA-S decrease with aging in both men and women (Vermeulen and Verdoreck, *J. Steroid Biochem.* 7:1-10, 1976; Vermeulen et al., *J. Clin. Endocr. Metab.* 54:187-191, 1982). In fact, at 70 years of age, serum DHEA-S levels are at approximately 20% of their peak values while they decrease by up to 95% by the age of 85 to 90 years (Migeon et al., *J. Clin. Endocr. Metab.* 17:1051-1062, 1957). The 70% to 95% reduction in the formation of DHEA-S by the adrenals during aging results in a dramatic reduction in the formation of androgens and estrogens in peripheral target tissues, thus resulting in a marked decrease in the biochemical and cellular functions induced by sex steroids.

In addition to the decrease in DHEA-S formation, in men, a progressive decrease in the concentration of testosterone in the spermatic vein (Giusti et al., *Exp. Gerontol.* 10:241-245, 1975) as well as in plasma (Lewis et al., *Acta Endocrinol.* 82:444-448, 1976; Zumoff et al., *J. Clin. Endocr. Metab.* 54:534-538, 1982) has been observed after the age of 60-70 years. Such data, however, have been the subject of contro-

versy (Nieschlag et al., *J. Clin. Endocr. Metab.* 55:676-681, 1982). In postmenopausal women, serum testosterone levels are lower than during reproductive life (Forest MG, *Physiological changes in circulating androgens*, in *Androgens in Childhood* (Forest MG, ed), Karger Basel, p. 104-129, 1989).

The skin is an important site of sex steroid formation and its function is known to be regulated by sex steroids. Sex steroids can act directly in the skin or may stimulate growth hormone and prolactin secretion by the anterior pituitary gland. Skin atrophy is in fact known to occur in growth hormone deficiency, probably through a secondary decrease in insulin-like growth factor (IGF-1) secretion. Serum growth hormone (GH) and insulin-like growth factor (IGF-1) levels are known to be reduced in aging men and women.

Plasma DHEA-S concentration has been suggested as a predictor of osteoporosis (Nordin et al., *J. Clin. Endocr. Metab.* 60:651-657, 1985; Deutsch et al., *Int. J. Gynecol. Obstet.* 25:217-220, 1987). Serum DHEA has in fact been found to be significantly lower in osteoporotic compared to normal subjects (Nordin et al., *J. Clin. Endocr. Metab.* 60:651-657, 1985). Low tissue Δ^4 -dione is also likely to accompany low DHEA-S levels. Since Δ^4 -dione is the precursor of estrone which is a main source of estradiol in postmenopausal women (Marshall et al., *Clin. Endocrinol.* 9:407, 1978), such secondary low levels of estrogens are likely to be involved in osteoporosis (Nordin et al., *Lancet* 2:277, 1981).

As another mechanism, low serum DHEA-S levels resulting in low formation of androgens in peripheral tissues could also result in low bone formation, a characteristic of postmenopausal osteoporosis (Meunier et al., in *Histological heterogeneity of apparently idiopathic osteoporosis and treatment* (DeLuca H F, Frost H M, Jee W S S, Johnston Jr C C, Parfitt A M, eds), University Park Press, Baltimore, p. 293). In fact, Deutsch et al. (*Int. J. Gynecol. Obstet.* 25:217-222, 1987) have found a significant correlation between serum DHEA-S and androstenedione levels and osteoporosis in late postmenopausal women while no correlation was found between serum estrogens and bone density, thus suggesting a major importance of androgens in postmenopausal bone loss.

Studies in animals have shown that androgen deficiency leads to osteopenia while testosterone administration increases the overall quantity of bone (Silverberg and Silverberg, 1971; See Finkelstein et al., *Ann. Int. Med.* 106:354-361, 1987). Orchiectomy in rats can cause osteoporosis detectable within 2 months (Winks and Felts, *Calcif. Tissue. Res.* 32:77-82, 1980; Verhas et al., *Calcif. Tissue Res.* 39:74-77, 1986).

As mentioned earlier, adrenal androgen levels have been found to be reduced in osteoporosis (Nordin et al., *J. Clin. Endocr. Metab.* 60:651, 1985). Moreover, elevated androgens in postmenopausal women have been shown to protect against accelerated bone loss (Deutsch et al., *Int. J. Gynecol. Obstet.* 25:217-222, 1987; Aloia et al., *Arch. Int. Med.* 143:1700-1704, 1983). In agreement with such a role of androgens, urinary levels of androgen metabolites are lower in postmenopausal symptomatic menopause than in matched controls and a significant decrease in conjugated dehydroepiandrosterone (DHEA) was found in the plasma of osteoporotic patients (Hollo and Feher, *Acta Med. Hung.* 20:133, 1964; Urist and Vincent, *J. Clin. Orthop.* 18:199, 1961; Hollo et al., *Acta Med. Hung.* 27:155, 1970). It has been suggested that postmenopausal osteoporosis results from both hypoestrogenism and hypoandrogenism (Hollo et

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L-cysteine hexyl ester hydrochloride) are used instead of L-cysteine ethyl ester hydrochloride.

Example 10

3 β -hydroxy-5-androstene-17-spiro-2'-(1', 3'-oxazolidine-4'-ethyl carboxylate)

The same procedure as described in the Example 7 is used except the oxazolidine derivative is prepared using serine ethyl ester hydrochloride instead of L-cysteine ethyl ester hydrochloride.

Example 11

3 β -hydroxy-5-androstene-17-spiro-2'-(1', 3'-oxazolidine-4'-benzyl carboxylate)

Same procedure as described in example 10 except that serine benzyl ester hydrochloride is used instead of serine ethyl ester hydrochloride.

Example 12

3 β -hydroxy-5-androstene-17-spiro-2'-(1', 3'-oxazolidine-4'-alkyl carboxylate)

Same procedure as described in example 10 except that different serine alkyl esters hydrochloride (e.g. serine hexyl ester hydrochloride) are used instead of serine ethyl ester hydrochloride.

Example 13

3 β -hydroxymethoxy-5-androsten-17-one acetate

To a solution of dehydroepiandrosterone (2.88 g, 10 mmol) in THF (100 mL) is added sodium hydride (11 mmol, 60% in oil) at room temperature under an argon atmosphere. When all the sodium hydride has reacted, chloromethyl acetate (prepared from acetyl chloride and formaldehyde (or derivative) using ZnCl₂ as catalyst) is added and the mixture is heated for a few hours. After cooling, the mixture is poured into water and extracted with ethyl acetate. The organic phase is then washed with water, dried, filtered and evaporated to dryness to give the desired compound.

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS

In one aspect, the present invention involves applying DHEA (or its analogues) formulation to the skin or other epithelial tissue for a time period sufficient to permit sufficient penetration of the compound for systemic or topical action, as desired. The composition may be applied as a gel, a cream, an ointment, a lotion or the like or may involve use of a delivery system as described in U.S. Pat. Nos 3,742,951, 3,797,494 or 4,568,343. Devices as described in U.S. Pat. Nos 5,064,654, 5,071,644 or 5,071,657 can also be used to facilitate steroid absorption.

All the pharmaceutical compositions of the present invention may contain appropriate preservatives known in the art.

The following non-limiting examples describe the preparation of a typical cream, lotion, gel and ointment, respectively. In addition to these vehicles, one skilled in the art may choose other vehicles in order to adapt to specific dermatologic needs.

Example 14

A typical lotion contains (W/W) 10% DHEA, 15% propylene glycol and 70% ethanol and water 5%.

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Example 15

A typical gel contains (W/W) 10% DHEA, 5% propylene glycol, 0.2% Carbomer 940 (available as Carbopol 940^R from B. F. Goodrich), 40% water, 0.2% triethanolamine, 2% PPG-12-Buteh-16 (available as Ucon^R fluid 50 from Union Carbide), 1% hydroxypropyl and 41.6% ethanol (95% ethanol-5% water).

Example 16

A typical ointment contains (W/W) 10% DHEA, 13% propylene glycol, 74% petrolatum, 2.9% glycerylmonostearate and 0.1% polyparaben.

Example 17

A typical cream contains (W/W) 10% DHEA, 0.2% propylparaben, 5% lanolin oil, 7.5% sesame oil, 5% cetyl alcohol, 2% glyceryl monostearate, 1% triethanolamine, 5% propylene glycol, 0.1% Carbomer 940^R and 64.2% water.

In each of the foregoing Examples 14-17, a progestin and/or an estrogen may be added. For example 0.005 to 0.02% 17 β -estradiol and/or 0.2 to 2.0% medroxyprogesterone acetate may be added with corresponding reductions in water or ethanol or petrolatum. DHEA permeability can be enhanced by various techniques in order to reduce the dose used. Methods and compositions for enhancing permeability of an active compound can be found, for example, in U.S. Pat. Nos. 5,051,260, 4,006,218, 3,551,554, 3,472,931, 4,568,343, 3,989,816 and 4,405,616.

Although the present invention has been described in relation to particular embodiments thereof, many other variations and modifications and other uses will become apparent to those skilled in the art. It is preferred, therefore, that the present invention be limited not by the specific disclosure herein, but only by the appended claims.

What is claimed is:

1. A method for inhibiting the development and proliferation, or treatment, of uterine cancer comprising administering to a female patient in need thereof a therapeutically effective amount of a sex steroid precursor selected from the group consisting of DHEA, DHEA-S, and compounds converted in vivo to either.

2. The method of claim 1, wherein said precursor is administered at a dosage sufficient to maintain serum DHEA concentration of said female between 7 and 13 micrograms per liter.

3. The method of claim 1, wherein said precursor is DHEA.

4. The method of claim 1, further comprising administering a therapeutically effective amount of a progestin.

5. A method for inhibiting the development and proliferation, or treatment, of uterine cancer comprising administering to a female patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and a sex steroid precursor selected from the group consisting of DHEA, DHEA-S, and compounds converted in vivo to either.

6. The method of claim 5, wherein said composition is administered at a dosage sufficient to maintain serum DHEA concentration of said patient between 7 and 13 micrograms per liter.

7. The method of claim 5, wherein said precursor is DHEA.

8. The method of claim 5, wherein said pharmaceutical composition further comprises a therapeutically effective amount of a progestin.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/56	A1	(11) International Publication Number: WO 98/02167 (43) International Publication Date: 22 January 1998 (22.01.98)
(21) International Application Number: PCT/US97/11912 (22) International Filing Date: 10 July 1997 (10.07.97) (30) Priority Data: 60/021,894 12 July 1996 (12.07.96) US 08/889,529 8 July 1997 (08.07.97) US (71)(72) Applicant and Inventor: SHAAK, Carolyn, V. [US/US]; 1093 Beacon Street, Brookline, MA 02146 (US). (74) Agent: CLARK, Paul, T.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: TRANSDERMAL APPLICATION OF NATURALLY OCCURRING STERIOD HORMONES (57) Abstract The invention features a physiologically acceptable cream that contains estrogen, progesterone, and testosterone molecules that are identical to the estrogen, progesterone, and testosterone molecules naturally produced by the human body. The cream may be self-administered to the skin and is useful as a means of hormone replacement therapy, which may begin at around the time of menopause.		

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1. A method of hormone replacement therapy, said method comprising administering to the skin of a patient in need of said therapy a physiologically acceptable cream comprising native estrogen, native progesterone, and native testosterone in a ratio, by weight, of 1-5:10-500:1-5.

5 2. The method of claim 1, wherein said estrogen is estradiol, estrone, or estriol.

3. The method of claim 1, wherein said cream further comprises dehydroepiandrosterone.

4. The method of claim 1, wherein said administration is begun at around the time of menopause.

10 5. A physiologically acceptable cream comprising native estrogen, native progesterone, and native testosterone.

6. The cream of claim 5, wherein said estrogen, progesterone and testosterone are synthesized from compounds obtained from a plant source.

15 7. The cream of claim 5, wherein said cream further comprises dehydroepiandrosterone.

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(54) Title: NOVEL PHARMACEUTICAL FORMULATION OF DEHYDROEPIANDROSTERONE FOR PERCUTANEOUS TOPICAL APPLICATION (54) Título: NUEVA FORMULACION FARMACEUTICA DE DEHIDROEPIANDROSTERONA PARA APLICACION TOPICA PERCUTANEA (57) Abstract The disclosed formulation is comprised of: (a) 0.1-5 % by weight of dehydroepiandrosterone; (b) 0.5-3 % of acrylic gel, 1-3 % of guar gum or 1-3 % of a gel derived from cellulose; and optionally other ingredients such as hydrophilic gels, estradiol, vitamins, progesterone, minoxydil, xantic bases, hyaluronidase, vasoprotectors, plant extracts, etc. The formulation has various pharmacological applications, for example for treating troubles in the feminine menstruation, mammary and gynaecological neoplasia, lipodystrophy, paniculopathy and circulatory troubles, bruises, muscular pain, obesity, diabetes, osteoporosis, ageing, etc. (57) Resumen Comprende: (a) 0,1 a 5 % en peso de dehidroepiandrosterona; (b) 0,5-3 % de un gel acrílico, 1-3 % de goma-guar ó 1-3 % de un gel derivado de celulosa; y opcionalmente otros ingredientes tales como geles hidrófilos, estradiol, vitaminas, progesterona, minoxidil, bases xánticas, hialuronidasa, vasoprotectores, extractos vegetales, etc. La formulación tiene diversas aplicaciones farmacológicas, por ejemplo, en desarreglos del ciclo menstrual femenino, neoplasias de mamas y ginecológicas, lipodistrofias, paniculopatías y trastornos circulatorios, contusiones, dolores musculares, obesidad, diabetes, osteoporosis, envejecimiento, etc.		

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305**TITULO DE LA INVENCION**

**NUEVA FORMULACION FARMACEUTICA DE DEHIDROEPIANDROSTERONA
PARA APLICACION TOPICA PERCUTANEA.**

CAMPO TECNICO DE LA INVENCION

5 La presente invención se encuadra dentro del campo técnico de la terapia hormonal destinada al mantenimiento de ciertas funciones vitales que se van deteriorando con la edad o al tratamiento de diversas enfermedades metabólicas o degenerativas.

10 Más concretamente, la presente invención se refiere a una nueva forma de presentación de la dehidroepiandrosterona (DHEA) destinada a su aplicación tópica percutánea.

ESTADO DE LA TECNICA ANTERIOR A LA INVENCION

15 La Dehidroepiandrosterona (DHEA) es una hormona esteroidea de carácter androgénico, sintetizada por las glándulas suprarrenales y que se ha venido utilizando por vía oral en el mantenimiento de determinadas funciones, que van deteriorándose con la edad, y en el tratamiento de
20 diversas enfermedades metabólicas y degenerativas tales como la diabetes, la obesidad, la osteoporosis, ciertas neoplasias, artritis, artrosis y disminución de la actividad sexual, etc.

Se han efectuado numerosos estudios con esta
25 hormona y sus posibles aplicaciones. Burke, K.E. en Postgrad. Med., 85 (6), 52-58 y 67-73, expone un estudio sobre la pérdida del cabello y sus posibles causas, así como su posible tratamiento con progesterona a la que se puede asociar DHEA. Ishihara y col. en Horm.Metab.Res., 25
30 (1), 34-36, 1993, publica un estudio acerca del papel de la dehidroepiandrosterona y del sulfato de dehidroepiandrosterona para el mantenimiento del vello axilar en la mujer. Por su parte, Lufkin, E.G. y col. en Trends Endocrinol. Metab., 6, 50-54, 1995, hace un estudio acerca de la
35 terapia postmenopáusica con estrógenos.

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REIVINDICACIONES

1.- Nueva formulación farmacéutica de dehidroepiandrosterona para aplicación tópica percutánea, caracterizada porque comprende como ingredientes esenciales:

- 5 (a) 0,1 a 5 % en peso de dehidroepiandrosterona;
- (b) 0,5 -3% de un gel acrílico (carbopol), goma-guar (1-3%) o un gel derivado de celulosa (1-3%);
- 10 pudiendo comprender la formulación además de los ingredientes (a) y (b) otros geles de tipo hidrófilo, seleccionados entre glicólicos, hidroglicólicos, hidroglicerolatos, hidroalcohólicos e hidropopilenglicólicos en proporciones semejantes del 0,5-2% de carbopol y otros ingredientes
- 15 activos seleccionados entre 0,02-0,1% de estradiol, 0,05-1% de Vitamina E, 0,1-5% de Vitamina C, 2-5% de progesterona, 1-3% de minoxidil, 0,1-2% de tricosacáridos y tricopéptidos, 0,1-5% de bases xánticas, 0,1-20% de productos yodados, 100-2000 U% de hialuronidasa, 0,1-12% de agentes
- 20 vasoprotectores y capilarotropos, 0,1-2% de dinitrilosuccínico, 0,1-5% de extractos glicólicos e hidroalcohólicos de capsico y arnica, 0,1-0,75% de alcanfor, 0,01-0,5% de mentol y 0,1-5% de extractos de Centella Asiática y entre
- 25 lúpulo) ó del 0,1-5% de antiandrógenos sintéticos como el acetato de ciproterona.

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